Recent Advances in the Management of AIDS-related Opportunistic Infections

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Secondary infections remain the leading cause of death in patients with the acquired immunodeficiency syndrome (AIDS). Dealing with the rapidly evolving spectrum of infectious problems seen in patients with AIDS requires knowledge of current therapeutic and prophylactic strategies. Through an extensive preclinical trials network supported by both industry and government, an increasing number of new agents are being identified and rapidly moved into clinical trials. Several agents are now available to treat diseases caused by *Pneumocystis carinii*, and corticosteroids have become a useful adjunct to antimicrobial agents in the treatment of *P. carinii* pneumonia. Although the treatment of toxoplasmosis remains a challenge, alternatives to sulfadiazine and pyrimethamine are now available. Mycobacterial infections, particularly with *Mycobacterium tuberculosis*, have become an increasing problem for patients with AIDS, and both old and new combination drug regimens are being used. Cytomegalovirus disease, until recently an untreatable problem, can now at least be partially managed with antiviral agents. The use of more complete prophylactic regimens may decrease the morbidity and mortality from opportunistic infections.


**Preclinical Evaluation of Candidate Therapeutic Agents**

Dr. Barbara E. Laughon (NIAID, NIH): New agents to treat AIDS-related opportunistic infections are needed because of the relatively high rate of toxic reactions to current drugs, the treatment failures in various settings, and the increased emergence of resistant strains. The development of new therapies is often hampered by a lack of information on the basic biology of most of these organisms. Many exhibit complex life cycles, and both in vitro and in vivo culture systems are either difficult or nonexistent.

The standard animal model for *Pneumocystis carinii* pneumonia is the corticosteroid-treated rat. In addition, molecular screens are now being established using enzymes purified from animal-derived organisms or derived by recombinant technology. Among the potential new drugs for treating *P. carinii* pneumonia are two compounds from Merck and Company that may be useful for long-term prophylaxis because they are potent inhibitors of cyst-wall formation; a dihydrofolate reductase inhibitor with less toxicity than trimetrexate; a group of primaquine-like drugs of the 8-aminoquinoline class that have been developed by the Walter Reed Institute of Army Research; and an oral version of pentamidine, a DMP-lactate being considered by Lyphomed (Rosemont, Illinois).

Drug discovery efforts directed toward the treatment of disease caused by *Toxoplasma gondii* have focused on the relatively easy-to-grow tachyzoite form of the organism. In addition, molecular screens targeting specific *T. gondii* enzymes search for compounds with selectivity for the metabolic processes of the parasite. Although reactivation of the tissue cyst is the principal mechanism of disease in patients with AIDS, convenient models of chronic infection are not available, and most in vivo drug screening uses the acute systemic infection of mice. Currently, no compounds other than atovaquone (see below) are showing promise in these models.

Mycobacterial infections present problems for rapid drug screening because the organisms routinely take 2 to 4 weeks to produce colonies. One alternative, using the Bactec technology to detect radiolabeled CO₂ release, has recently shortened this process to about a week. Unfortunately, until recently no molecular screens have been in place because little is known about the metabolism of these microbes. At present, all new drugs for mycobacterial infections were originally discovered and developed for other diseases. Among them are the newer macrolides clarithromycin and azithromycin; the rifampin derivatives rifapentine, rifabutin, and rifapentine; and the group of nonribosomal peptides of intermediate activity (INH, EMB, and RFP).
Table 1. Drugs Used for the Treatment of Acute Pneumocystis carinii Pneumonia*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Trimethoprim plus sulfamethoxazole</td>
<td>Trimethoprim, 15-20 mg/kg per day; sulfamethoxazole, 75-100 mg/kg per day, intravenous or oral</td>
<td>Fixed combination; avoid doses exceeding 960 mg of trimethoprim daily; administer in three divided doses</td>
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<tr>
<td>Peptamidine</td>
<td>4 mg/kg per day, intravenous</td>
<td>Infuse over 1 to 2 hours to prevent hypotension</td>
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<tr>
<td>Trimethoprim plus dapsone</td>
<td>Trimethoprim, 15-20 mg/kg per day, oral; dapsone, 100 mg/d, oral</td>
<td>Investigational but readily available</td>
</tr>
<tr>
<td>Atovaquone (566C80)</td>
<td>750 mg three times daily, oral</td>
<td>Administer with food; less effective and less toxic than trimethoprim-sulfamethoxazole; use in patients with mild to moderate Pneumocystis carinii pneumonia who cannot tolerate trimethoprim-sulfamethoxazole</td>
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<tr>
<td>Primaquine plus clindamycin</td>
<td>Primaquine, 15-30 mg base, oral; clindamycin, 600 mg every 6 h to 900 mg every 8 h, intravenous, or 300-450 mg every 6 h, oral</td>
<td>Investigational but readily available</td>
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<tr>
<td>Trimetrexate</td>
<td>45 mg/m² per day, intravenous</td>
<td>Use with leucovorin, 20 mg/m² orally or intravenously, four times daily</td>
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<tr>
<td>Adjunctive corticosteroids</td>
<td>Prednisone 40 mg, oral twice daily for 5 days followed by 20 mg twice daily for 5 days, then 20 mg/d until the end of antimicrobial therapy</td>
<td>Begin at the onset of antipneumocystis therapy (effective within 72 hours of the start of therapy); Use in patients with a PaO₂ of &lt;70 mm Hg or an alveolar-arterial gradient of &gt;35 mm Hg</td>
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</table>

* IND = investigational new drug.

butin, and rifamycin; and the newer fluoroquinolones sparflaxin, ofloxacin, levofloxacin, and WIN-57273.

Possible agents for the treatment of cytomegalovirus (CMV) infection are generally evaluated in tissue culture systems, which limit the rate at which new compounds can be screened. Several new compounds for treating CMV diseases are entering the pipeline. Among them are a series of nucleotide analogs, a ganciclovir prodrug, and a new series of heterocyclic benzimidazoles developed at the University of Michigan in collaboration with Burroughs-Wellcome.

We are only beginning to understand the biology of the agents responsible for most AIDS-related opportunistic infections. The development of new therapies requires continued improvement in the basic foundations of preclinical science, including predictive animal models, rapid culture systems, and improved molecular probes to clone, express, and identify new therapeutic targets. The Developmental Therapeutics Branch of the NIH Division of AIDS supports a comprehensive research program of grants and contracts focused on target drug discovery and animal model testing of new therapies to facilitate the transition from the laboratory to the clinic.

Treatment of Pneumocystis carinii Pneumonia

Dr. Judith Falloon (NIAID, NIH): Before effective antipneumocystis prophylaxis was routinely used, P. carinii pneumonia occurred at least once in approximately 80% of North American patients with AIDS. The lung is the most important target organ for P. carinii, although disseminated disease has been recognized more frequently in patients with AIDS than in other patients. Standard therapy with oral or intravenous trimethoprim-sulfamethoxazole or intravenous pentamidine is highly effective but often poorly tolerated (1).

Because of recent drug development, the list of treatment options for P. carinii pneumonia is growing (Table 1). Atovaquone, previously called 566C80, was approved by the Food and Drug Administration (FDA) in December 1992 for patients with mild to moderately severe P. carinii pneumonia (a PaO₂ of 60 mm Hg or greater or an alveolar-arterial gradient of 45 mm Hg or less) who cannot tolerate trimethoprim-sulfamethoxazole. In a preliminary uncontrolled trial, atovaquone was shown to be highly effective and safe (2). A large, double-blind controlled trial comparing trimethoprim-sulfamethoxazole with atovaquone in 322 patients was recently completed (3). Overall response rates were similar, and both drugs were effective; however, trimethoprim-sulfamethoxazole was associated with a lower failure rate and fewer deaths (7% and 0.6%, respectively) than atovaquone (20% and 7%, respectively). Atovaquone was better tolerated, however; treatment-limiting adverse effects occurred in 20% of patients treated with trimethoprim-sulfamethoxazole but in only 7% of patients treated with atovaquone. The efficacy of atovaquone was correlated with plasma concentrations, and those patients with higher concentrations (>15 μg/mL) were substantially more likely to have been successfully treated.

In its current tablet form, oral atovaquone is variably absorbed, and higher concentrations cannot be reliably achieved by increasing the daily dosage or altering the schedule of administration. A suspension formulation designed to be more consistently and completely absorbed is currently being evaluated and may be a notable improvement over the tablet. An intravenous preparation is also being assessed. Atovaquone is safe and
tolerable, but it is less effective than trimethoprim-sulfamethoxazole. Atovaquone is thus well suited for patients with mild to moderately severe *P. carinii* pneumonia who can be treated as outpatients and who cannot tolerate trimethoprim-sulfamethoxazole.

Although not licensed for treating *P. carinii* pneumonia, the oral combination of dapsone plus trimethoprim is widely used. Data from a 60-patient, double-blind trial suggested efficacy similar to that of trimethoprim-sulfamethoxazole with less toxicity (4). The study was too small to prove the equivalence or superiority of dapsone-trimethoprim. It is also not clear how many trimethoprim-sulfamethoxazole-intolerant patients can tolerate dapsone-trimethoprim. Nevertheless, it is proving to be a useful, well-tolerated alternative that is suited to the outpatient treatment of those with mild to moderately severe *P. carinii* pneumonia. Based on data from small, uncontrolled trials, clindamycin with primaquine is a highly effective regimen, regardless of whether clindamycin is given orally or intravenously (5, 6). Rash, diarrhea, or methemoglobinemia occurs in many patients, and this regimen should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency. This combination is also useful for the outpatient treatment of mild *P. carinii* pneumonia in trimethoprim-sulfamethoxazole-intolerant patients.

Other agents that have been studied in humans include trimetrexate, pirithrexin, inhalen pentamidine, dapsone alone, and efomithine (7–11). Intravenous trimetrexate and oral pirithrexin are antifolate agents so potent that they have been assessed as single agents for the treatment of *P. carinii* pneumonia, usually combined with folic acid to diminish hematologic toxicity. In a double-blind, randomized trial of 303 patients assigned to receive trimetrexate-leucovorin or trimethoprim-sulfamethoxazole, failure rates because of lack of efficacy were 20% for the patients treated with trimethoprim-sulfamethoxazole and 38% for patients treated with trimetrexate. Relapses occurred more often in patients treated with trimetrexate (12%) than in those treated with trimethoprim-sulfamethoxazole (0%). Trimetrexate was better tolerated than was trimethoprim-sulfamethoxazole: Nine percent of patients assigned to receive trimetrexate had the drug discontinued compared with 28% of patients assigned to receive trimethoprim-sulfamethoxazole (12). Trimetrexate has recently been licensed for the treatment of *P. carinii* pneumonia. It appears to have a role in the treatment of patients with severe *P. carinii* pneumonia who require parenteral therapy and who are either unresponsive to or intolerant of both parenteral pentamidine and trimethoprim-sulfamethoxazole.

Aerosol pentamidine is appealing because it could maximize delivery to the major target organ while minimizing systemic absorption and toxicity. Results of several trials suggest, however, that this approach is associated with numerous treatment failures and early relapses and thus cannot be advocated outside of organized trials (8, 9).

In addition to the development of new agents, another major advance in the treatment of *P. carinii* pneumonia has been the development of corticosteroids as adjunctive therapy. Corticosteroids clearly reduce mortality in patients with moderate or severe *P. carinii* pneumonia, as defined by arterial blood oxygenation (13). The exact mechanism is unclear, but corticosteroids blunt the deterioration that commonly occurs after therapy is initiated but before the 5 to 10 days generally required for improvement. In the largest randomized controlled trial of adjunctive corticosteroid therapy for AIDS-associated *P. carinii* pneumonia, the risk for death in corticosteroid-treated patients was approximately half that of those receiving antipneumocystis therapy alone, and the use of corticosteroids was not associated with adverse events other than the reactivation of localized herpetic lesions (13). These and other confirmatory data led to the formulation of recommendations for the appropriate use of corticosteroids in *P. carinii* pneumonia (14) (Table 1). All patients with moderate to severe impairment of oxygenation at presentation (PO2 < 70 or P(O2)/FIO2 > 35) should receive therapy with adjunctive corticosteroids, which should be started at the same time as antipneumocystis therapy. In the one study in which delayed corticosteroid therapy was permitted, the beneficial effects of corticosteroids were not observed in most patients treated after 72 hours of antipneumocystis therapy (13). The recommended dose shown in Table 1 is the one for which the most supporting data exist, but other doses and regimens may be equally effective.

In conclusion, because it is highly effective, trimethoprim-sulfamethoxazole remains the treatment of choice for mild, moderate, or severe *P. carinii* pneumonia. Dapsone-trimethoprim may be as effective as trimethoprim-sulfamethoxazole and is probably better tolerated. Atovaquone and clindamycin-primquine are alternative therapies for patients with mild to moderately severe *P. carinii* pneumonia who cannot tolerate trimethoprim-sulfamethoxazole and for whom oral therapy is appropriate. Intravenous pentamidine, despite its toxicity, remains the drug of choice for severe *P. carinii* pneumonia in patients who cannot tolerate trimethoprim-sulfamethoxazole. Adjunctive corticosteroid therapy results in a substantial decrease in mortality in patients with moderate to severe hypoxemia at presentation and is therefore now considered part of standard therapy. The relative roles of trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and pyrimethamine-clindamycin should be more clearly established after ongoing randomized trials are completed.

**Advances in the Therapy of Toxoplasmosis**

Dr. Joseph A. Kovacs (AIDS Section, Critical Care Medicine Department, Clinical Center, NIH): Toxoplasmosis, primarily *Toxoplasma gondii* encephalitis, develops in 5% to 10% of patients with AIDS in the United States, and in an even higher percentage of patients with AIDS in Europe, where the incidence of latent infection is greater (15–17). Currently, standard therapy for toxoplasmosis is the combination of pyrimethamine and sulfadiazine (16). This combination is effective in treating toxoplasmosis in patients with AIDS; an estimated 80% to 90% will have a radiographic or clinical response (15). However, adverse reactions to this combination, primarily to sulfadiazine, are common (20% to 40% of...
patients), and discontinuation of combination therapy results in a high relapse rate (40% to 80% of patients) (15–18).

Given this rate of relapse, it is recommended that patients with AIDS continue some form of effective anti-Toxoplasma therapy for life (16). Because many patients cannot continue standard therapy, an imperative need exists for the development of effective, well-tolerated alternative regimens to treat toxoplasmosis. Over the past few years, several such agents have been identified, primarily through in vitro and animal studies, with subsequent confirmation of potential clinical efficacy in anecdotal reports, uncontrolled clinical trials, and, rarely, controlled trials.

The best-studied alternative to pyrimethamine plus sulfadiazine is clindamycin and pyrimethamine (18–20). A randomized, open-label study in 56 evaluable patients compared clindamycin (1200 mg intravenously every 6 hours for 3 weeks, then 300 mg orally every 6 hours or 450 mg orally every 8 hours for an additional 3 weeks) plus pyrimethamine (200-mg load, then 75 mg/d orally) with oral sulfadiazine (25 mg/kg up to a maximum of 2 g every 6 hours) plus the same dose of pyrimethamine (20). All patients also received folinic acid (at least 10 mg/d). At 6 weeks, clinical and radiographic responses were similar, with approximately 75% of patients responding in each group. Adverse reactions requiring discontinuation of therapy were frequent in both groups: 23% of patients receiving pyrimethamine plus clindamycin and 33% of patients receiving pyrimethamine plus sulfadiazine. This study did not provide long-term follow-up, nor was it large enough to establish the true equivalence of the two regimens.

Based on currently available data, the recommended dosage for this combination is clindamycin, 600 mg every 6 hours either orally or intravenously, plus pyrimethamine and folinic acid for at least 3 weeks (longer for more severely ill patients); for maintenance therapy, data are scant, but the recommendation is to administer at least 1200 mg/d of clindamycin in three to four divided doses combined with pyrimethamine and folinic acid (18).

Atovaquone, a drug recently licensed for the treatment of P. carinii pneumonia, is also an excellent candidate for treating toxoplasmosis. Preclinical studies have shown it to be active against both tachyzoites and intracytic bradyzoites, the form of the organism that presumably allows reactivation of latent disease (21, 22). In contrast, sulfadiazine and pyrimethamine are not active against bradyzoites (22). In a study done at NIH, eight patients with Toxoplasma encephalitis who were intolerant of or had failed therapy with pyrimethamine combined with either sulfadiazine or clindamycin received atovaquone, 750 mg orally 4 times a day (23). At the week 6 evaluation, seven patients had improved radiographically, and one remained stable (Figure 1). Five patients died from other AIDS-related complications at weeks 16 to 60 with no clinical or autopsy (two patients) evidence of toxoplasmosis. Two patients who had responded relapsed at weeks 10 and 32. Thus, atovaquone as a single agent is effective in treating toxoplasmosis. Additional studies are needed with atovaquone alone or in combination with pyrimethamine to determine where this agent will be most useful.

Azithromycin is a macrolide antibiotic that is related to erythromycin and is also effective against T. gondii in vitro and in animal models (24, 25). The results of early clinical trials with this agent used alone for treating toxoplasmosis have been disappointing. In our experience, two patients receiving oral azithromycin, 1200 mg daily, showed radiographic progression at the week 2 evaluation and were removed from the study. Although azithromycin has been anecdotally reported to be effective, we believe that it should be used cautiously as a single agent. However, in combination with pyrimethamine it may have a role in the management of toxoplasmosis.

Clarithromycin is another macrolide that has been effective against T. gondii in preclinical studies (25). In a recent study, 13 patients with AIDS who were presumed to have toxoplasmosis received oral clarithromycin (1 g twice a day) plus pyrimethamine (75 mg/d) and folinic acid (20 mg/d) for 6 weeks; 8 patients (62%) showed a radiographic and clinical response, whereas 3 (23%) were withdrawn from the study because of serious toxicity, and two withdrew voluntarily (26). Two patients died during the study period. Thus, the combination of clarithromycin and pyrimethamine is also effective over the short term but is associated with frequent adverse reactions. Long-term responses are not

Figure 1. Sequential magnetic resonance imaging scans showing resolution of multiple lesions of central nervous system toxoplasmosis during therapy with atovaquone. Nearly complete resolution of the contrast-enhancing lesions is seen by week 10, and this improvement was sustained through 30 weeks of therapy (23). Reprinted with permission from The Lancet Ltd., 1992.
well studied, and thus the role of clarithromycin needs further evaluation.

A potential approach for treating toxoplasmosis is using cytokines as adjuvant therapy. Interferon-γ and interleukin-2 have both been shown to be important in controlling toxoplasmosis in preclinical studies. Interferon-γ inhibits the replication of T. gondii in vitro; it prevents death in animals with acute toxoplasmosis; anti–interferon-γ antibodies increase mortality in such animals (27, 28). Further, interferon-γ and antimicrobial agents have been shown to be synergistic in animal models (29). It is thus logical to combine this cytokine with specific anti-Toxoplasma therapy, and such a trial is currently under way. Interleukin-2 has also been shown to be protective in animal models (30) and is a candidate for study. Whether immunotherapy will be a useful addition to specific therapy remains to be determined.

In summary, pyrimethamine plus sulfadiazine remains the treatment of choice for toxoplasmosis. Clindamycin plus pyrimethamine is clearly an effective alternative, but whether it is as safe or effective as pyrimethamine plus sulfadiazine has not been determined. Atovaquone, clarithromycin plus pyrimethamine, and azithromycin plus pyrimethamine are promising new agents, but their optimal use requires additional investigation.

**Mycobacterial Disease in HIV-1 Infection: Recent Therapeutic Advances**

Dr. Richard T. Davey, Jr. (NIAID, NIH): The list of mycobacterial species found to cause serious and sometimes life-threatening diseases in the HIV-1-infected person continues to grow steadily (Table 2). By far, however, on both a regional and global basis, two members of this group account for most infections in this population: *Mycobacterium tuberculosis* and the *M. avium-intracellulare* complex.

**Mycobacterium tuberculosis** Infection

Earlier projections that tuberculosis might be eliminated within the first decade of the new millennium have been replaced by an increasing concern that this disease has the potential to become the new plague of the 1990s. These fears have been fueled by data documenting the potential for rapid spread of tuberculosis within susceptible populations, the ineffectiveness of many standard control measures when they are not rigorously applied, and, in particular, the emergence of multidrug-resistant strains.

Over the past 2 years, an appreciation has grown of the rapidity with which tuberculosis can spread in the HIV-1-infected population (31–36). In one communal home for such patients in San Francisco, 37% of exposed residents subsequently developed tuberculosis after the arrival of an infected patient (35). In some cases, the time between exposure and the development of the disease has been only a matter of weeks. In this regard, the health care worker infected with HIV-1 is at particularly high risk because of the frequency and duration of exposure to potentially infectious patients (35).

A second troubling development has been the increasing incidence of multidrug-resistant tuberculosis in the HIV-1-infected population (37). Multidrug-resistant *M. tuberculosis* strains are defined as those that are resistant in vitro to at least two first-line antituberculosis medications, usually isoniazid and rifampin. Resistance to other agents has also been documented. Affected areas of the country to date have included New York, Florida, Mississippi, Missouri, and Michigan, although the likelihood that these strains will spread to other areas is high.

In patients with HIV, the diagnosis of tuberculosis in general and multidrug-resistant tuberculosis in particular is often delayed because of atypical presentations, negative screening sputum cultures, and anergy on skin testing. The failure to promptly diagnose and treat infected persons leads to an increased period of infectiousness and thus increases the risk for transmission to susceptible persons. This is particularly true in many crowded health care settings, where it is difficult to ensure adequate respiratory isolation to prevent transmission to others. The period between diagnosis and the detection of drug resistance is usually several weeks. This delay has lengthened the period during which some persons with multidrug-resistant tuberculosis have been treated ineffectively with first-line agents. Because of this, the mortality associated with outbreaks of multidrug-resistant tuberculosis has been high, up to 72% to 89% in some instances.

The increasingly frequent reports of multidrug-resistant tuberculosis have identified weaknesses in our current therapeutic strategies for controlling this infection. For the initial treatment of tuberculosis in the era of multidrug resistance, the Centers for Disease Control and Prevention recommend a four-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin (37). Yet, in areas with a high prevalence of multidrug-resistant strains or in clinical circumstances in which the likelihood of exposure to resistant organisms appears high, such a regimen may be inadequate even as initial therapy. In such circumstances, others have proposed that an initial five- or six-drug regimen (including at least two drugs to which the *M. tuberculosis* isolate is likely to be susceptible based on local patterns of identified drug resistance) may be preferable, at least until the susceptibility profile of the tuberculosis isolate becomes known (38, 39). Nonetheless, no controlled clinical trials have been done to validate this approach. The activity of newer agents such as the fluoroquinolones and the newer macrolides, clarithromycin and azithromycin, are now being evaluated.

**Mycobacterium avium-intracellulare** Complex Infection

Midway through the first decade of the AIDS epidemic in this country, several discouraging reports of clinical treatment failures using multidrug regimens against *M. avium-intracellulare* complex infections in this patient population led to recommendations that, in some instances, the disease remain untreated. However, the introduction of new drugs with enhanced anti-*M. avium-intracellulare* complex potency (Table 2)...
Table 2. Mycobacterial Pathogens in HIV-1 Infected Persons*

<table>
<thead>
<tr>
<th>Mycobacterial Species</th>
<th>Clinical Manifestations</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Mycobacterium tuberculosis†</td>
<td>May present with an accelerated course of typical or atypical pulmonary disease; extrapulmonary spread to multiple organs can occur; constitutional symptoms of fever, weight loss, and night sweats are common</td>
<td>Sensitive strains: PPD+: isoniazid, 5 mg/kg per day (maximum, 300 mg/d), plus pyridoxine, 25 mg every day for 6 to 12 months. Active disease: 9-month regimen (for at least 6 months after culture conversion). First 2 months: isoniazid, 5 mg/kg per day (maximum, 300 mg/d), plus rifampin, 10 mg/kg per day (maximum, 600 mg/d), plus pyrazinamide, 15-25 mg/kg per day (maximum, 2.5 g/d). If isoniazid resistance is likely, add ethambutol, 15-25 mg/kg per day (maximum, 2.5 g/d), then switch to isoniazid plus rifampin daily as above, or twice weekly at isoniazid, 15 mg/kg per day (maximum, 900 mg/d), plus rifampin, 10 mg/kg per day (maximum, 600 mg/d). Likely exposure to multidrug-resistant strains: PPD+: efficacy data lacking; regimens such as 6 to 12 months of isoniazid plus rifampin plus ethambutol, ethambutol plus rifampin, or pyrazinamide plus rifampin have been proposed. Active disease: No clinically effective regimen yet established; institute directly observed therapy with a multidrug regimen usually including second-line agents, preferably including two or more drugs to which the organism has in vitro sensitivity. One alternative approach is to use ethambutol, 15 mg/kg per day, plus ciprofloxacin, 750 mg twice a day, plus rifampin, 10 mg/kg per day, plus amikacin, 7.5 mg/kg twice a day.</td>
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<tr>
<td>M. bovis†</td>
<td>Suppurative lymphadenitis; pulmonary and extrapulmonary dissemination after BCG vaccination</td>
<td>No consensus regimen established; sensitivity testing of isolates recommended as a guide to antimycobacterial drug selection. Multidrug regimens recommended, usually to include ethambutol plus 3 to 4 of the following drugs (based on sensitivities and if available): clarithromycin, 500-1000 mg twice a day, or azithromycin, 300-1000 mg every day, rifampin, 10 mg/kg per day (maximum, 600 mg/d), ciprofloxacin, 750 mg twice a day, or ofloxacin, 400 mg twice a day; clofazimine, 100 mg every day, amikacin, 7.5 mg/kg intravenously every day.</td>
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<tr>
<td>M. avium-intracellulare complex</td>
<td>Extrapulmonary manifestations are typical, with bone marrow and multorgan involvement common; mycobacteremia and constitutional symptoms of fever, right sweats, and weight loss are frequently present</td>
<td>Pulmonary and extrapulmonary disease, with multorgan dissemination described; clinical manifestations variable depending on mycobacterial species and organ involvement; constitutional symptoms may be similar to those seen in M. avium-intracellulare-complex infection. No consensus regimens established with many species; testing of isolates recommended as the best guide to appropriate antimycobacterial drug selections, for example, M. kansasii: INH, 5 mg/kg per day (maximum, 300 mg/d) plus rifampin, 10 mg/kg per day (maximum, 600 mg/d), plus ethambutol, 15-25 g/d (maximum, 2.5 g/d) for 15 to 18 months.</td>
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<tr>
<td>Other atypical mycobacteria</td>
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<td>Photochromogens (Runyon Group I)</td>
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<td>M. kansasi†, M. simiae†, M. asiaticum†, M. marium</td>
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<td>Scotochromogens (Runyon Group II)</td>
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<tr>
<td>M. gordonae†, M. scrofulaceum†, M. floccogenes†, M. szulgai†</td>
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<tr>
<td>Nonchromogens (Runyon Group II) other than M. avium-intracellulare complex:</td>
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<tr>
<td>M. xenopi†, M. malmoense†, M. triviale, M. terrae, M. ulcerans, M. gastri</td>
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<tr>
<td>Rapid growers (Runyon Group IV)</td>
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<td>M. fortuitum†, M. chelonii†, M. smegmatis</td>
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* PPD = purified protein derivative.
† Organisms that have been identified as causing infection in HIV-infected persons. Adapted and modified from MacDonell and Glassroth (31).

has brightened the prospects for successfully controlling this infection.
Rifabutin, also known as ansamycin LM427, is a semi-synthetic spiropepridyl derivative of rifamycin S with a half-life of approximately 16 hours in humans (38). In tissues, it is concentrated 5- to 10-fold relative to serum and exhibits only about 25% of the protein binding of rifampin. It also does not appear to induce
hepatic microsomal enzymes to the degree that rifampin does, and thus its effect on metabolism of concomitant medications may be less. The selective activity of rifabutin may be caused by its lipophilic nature, which results in increased penetration of the mycobacterial cell wall. In general, achievable serum concentrations of rifabutin exceed the minimal inhibitory concentration (MIC) levels of as much as 70% of M. avium-intracellularare complex strains. Based on its ability to delay the initial appearance of mycobacteremia in patients with HIV infection, it has recently been licensed for M. avium-intracellularare complex prophylaxis (see below). Interest in this compound for the treatment of established infection also continues, particularly when it is combined with other agents (39).

The new macrolides clarithromycin and azithromycin are recently licensed agents characterized by a broad spectrum of antibacterial activity, high oral bioavailability, excellent tissue penetration, and strong activity against many strains of M. avium-intracellularare complex (40-42). Clarithromycin is an acid-stable analog of erythromycin with a methoxy substitution at the C6 position of the erythronolide ring. Its resistance to acid degradation gives this agent high oral bioavailability. In a recent randomized, double-blind, placebo-controlled trial, quantitative blood cultures of M. avium-intracellularare complex were found to decrease in patients treated with clarithromycin-containing regimens. In six of eight patients who received initial therapy with clarithromycin alone, blood cultures became sterile. In view of these and other favorable findings, additional clinical trials of this macrolide both as a single agent and as part of a combination regimen are under way. Extended therapy with clarithromycin has been associated with the emergence of resistant strains of M. avium-intracellularare complex, however, and these findings cast doubt on its long-range treatment utility when administered as a single agent (43).

Azithromycin differs from erythromycin because of a methyl-substituted nitrogen at position 9a of the macrolide ring. This change results in both enhanced potency and acid stability. While the in vitro MICs for azithromycin are higher than those for clarithromycin, this may be compensated for by the 100- to 200-fold concentration of azithromycin in tissues relative to plasma. The half-life of azithromycin is up to seven times longer than that of erythromycin, and tissue levels are maintained with daily dosing (44). In an uncontrolled phase I trial (44), azithromycin was given at a dose of 500 mg/d to patients with AIDS for variable lengths of time. Quantitative blood levels of M. avium-intracellularare decreased for patients who had 5, 20, or 30 days of azithromycin therapy. In addition, most patients treated for 2 days or more reported resolution of both fever and night sweats, although fatigue, weight loss, and decreased appetite continued unabated (44). In view of its favorable pharmacokinetic profile, as well as proven activity against M. avium-intracellularare complex, azithromycin has entered additional phase I and II studies of its role in treating this infection.

In addition to the known antimycobacterial activities of both ciprofloxacin and ofloxacin, a new member of the fluoroquinolone family, sparfloxacin, has also been found to exhibit substantial activity against M. avium-intracellularare complex (45). In in vitro models of M. avium-intracellularare complex growth, the MICs of sparfloxacin have generally been substantially lower than those of ciprofloxacin. This agent is concentrated up to 11-fold in tissues relative to plasma and also shows synergistic activity when combined with ethambutol and rifampin. Trials of this compound in M. avium-intracellularare complex infection are under way.

Liposome encapsulation of drugs, a therapeutic strategy used against other infectious processes, has also been studied in animal models for its utility in treating M. avium-intracellularare complex infection. Such encapsulation results in increased penetration into phagocytes, prolonged retention in tissues, and possibly decreased systemic toxicity. Agents such as kanamycin, amikacin, and other aminoglycosides have been tested in vitro models of M. avium-intracellularare complex infection. In patients treated for 2 days or more reported resolution of both fever and night sweats, although fatigue, weight loss, and decreased appetite continued unabated (44). In view of its favorable pharmacokinetic profile, as well as proven activity against M. avium-intracellularare complex, azithromycin has entered additional phase I and II studies of its role in treating this infection.

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formulation has been proved effective, and daily intravenous therapy through an indwelling catheter is required. In a series of clinical trials, treatment with ganciclovir resulted in the improvement or stabilization of CMV retinitis in 80% to 90% of patients (49). The median time to progression of disease after completion of induction therapy was approximately 50 to 56 days (53, 54). The most common toxicities noted were neutropenia and thrombocytopenia.

With the increasing incidence of CMV disease, ganciclovir has been used more often, and with the improved survival of persons with AIDS who receive the drug for longer periods, ganciclovir-resistant CMV infection has been reported with increasing frequency (55). The mechanism of resistance is similar to that for acyclovir and usually involves a change in the ability of the virus to phosphorylate the drug (56). Because ganciclovir and zidovudine are both myelosuppressive, it is difficult to administer them concurrently (57). In treating HIV-infected persons with CMV retinitis, physicians may feel that they must choose between using ganciclovir to preserve vision and zidovudine to prolong life. This conflict has been ameliorated to some extent by the increased use of cytokines such as granulocyte-colony stimulating factor (G-CSF) and nonmyelosuppressive antiretroviral agents such as didanosine and zalcitabine. However, for patients whose disease has progressed despite ganciclovir therapy and for those who cannot tolerate ganciclovir, a need exists for better anti-CMV agents.

Foscarnet, or trisodium phosphonoformate, at least partially meets this need and was licensed in September 1991 to treat CMV retinitis. Foscarnet inhibits DNA polymerases and is active against herpesviruses. Unlike ganciclovir, foscarnet does not require phosphorylation within virally infected cells (58). Foscarnet also inhibits the reverse transcriptase of HIV and, correspondingly, the replication of HIV (59). Cytomegalovirus resistance to foscarnet is not well characterized, and treatment with foscarnet has been successful for treatment of ganciclovir-resistant strains of the virus (60). This fact suggests that little cross-resistance exists between these two agents. Like ganciclovir, foscarnet is virustatic; in addition, no oral formulation is currently licensed, and lifelong treatment of the disease is required. Foscarnet affects renal function and serum minerals and electrolytes. Because of the need for previous or concurrent administration of a saline solution to minimize renal dysfunction, a longer infusion period is required for foscarnet therapy than for ganciclovir (61). Frequent monitoring of renal function and serum electrolytes, particularly Ca++, PO₄−, Mg++, and K+, is also required (62).

Approval of foscarnet was based on the results of a randomized clinical trial showing that treatment substantially delayed the time to progression of CMV retinitis (50). A subsequent comparative trial has shown foscarnet to be as effective as ganciclovir for treatment of retinitis (54). In addition, patients treated with foscarnet have been reported to show a decrease in serum HIV-1 p24 antigen levels, thereby suggesting that foscarnet has antiretroviral activity in vivo (50). In the comparative randomized trial, which compared ganciclovir with foscarnet, the survival of persons randomly

Figure 2. Characteristic features of cytomegalovirus disease. Top. Fundoscopic examination of the retina shows perivascular hemorrhage and exudate. Bottom. Biopsy specimen of the lung shows characteristic cytoplasmic and intranuclear inclusions that give the "owl's eye" appearance.

erally progresses relentlessly to blindness. Either ganciclovir or foscarnet can effectively treat retinitis. Treatment for the other CMV diseases has been less well studied. Cytomegalovirus retinitis has an initial response rate of between 80% and 90%, but relapse is predictable (49-51). The precise contribution of CMV infection to mortality in persons with HIV infection is unknown, but by hastening the progression towards AIDS it may be substantial.

The clinical manifestations of CMV usually occur in persons with CD4 counts lower than 100 cells/µL (50, 52). Cytomegalovirus retinitis is usually associated with the presence of CMV in the urine and blood (50). From preliminary analyses of data we have compiled at NIH, at least 35% of HIV-infected, CMV-viremic persons with CD4 counts lower than 100 cells/µL will develop disease caused by CMV within 6 months (51).

The first major advance in treating CMV disease was the use of ganciclovir, an agent highly specific for human herpesviruses. Ganciclovir, approved by the FDA for the treatment of CMV disease in June 1989, is a selective inhibitor of viral DNA polymerases. The drug is virustatic against CMV; that is, when treatment is stopped, viral spread and progression of the disease resume (49). Lifelong maintenance intravenous treatment is required to delay reactivation. Thus far, no oral formulation has been proved effective, and daily intravenous therapy through an indwelling catheter is required. In a series of clinical trials, treatment with ganciclovir resulted in the improvement or stabilization of CMV retinitis in 80% to 90% of patients (49). The median time to progression of disease after completion of induction therapy was approximately 50 to 56 days (53, 54). The most common toxicities noted were neutropenia and thrombocytopenia.

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assigned to receive foscarnet was substantially longer than the survival of those randomly assigned to receive ganciclovir: 12.6 months compared with 8.5 months (Figure 3) (54). This increase could not be entirely attributed to the concurrent use of the specific antiretroviral agents zidovudine, didanosine, or zalcitabine. A subgroup analysis found this increase in survival only among persons with a relatively normal creatinine clearance. The result is somewhat controversial given the few patients followed for more than 9 months. Both drugs were found to be equally efficacious in delaying the time to progression of CMV retinitis, with a median time to progression of 59 days for patients receiving foscarnet and 56 days for patients receiving ganciclovir.

What does the future hold? Preliminary in vitro and in vivo data suggest that CMV disease refractory to single-agent ganciclovir and single-agent foscarnet may respond to a combination of these drugs (63–65). In addition, trials are under way using an oral ganciclovir preparation to attempt to prevent relapse in persons with CMV retinitis after high-dose intravenous ganciclovir is administered. The oral preparation appears to be well tolerated, but bioavailability is less than 10%. Oral foscarnet has similar problems with bioavailability, and clinical trials in humans have just begun. The compound BW256U, an acyclovir precursor, is in early clinical trials for prophylaxis against CMV. A ganciclovir precursor, 3′ nor-cyclic ganciclovir monophosphate, is active in vitro, but animal trials have not yet been concluded. Cytomegalovirus-specific immunoglobulin has been shown to be useful in preventing primary CMV disease in CMV-antibody-negative persons who receive renal transplants from CMV-antibody-positive donors (66). It has been used with ganciclovir with some success in treating CMV pneumonitis in transplant recipients, but its utility in preventing or treating CMV disease in patients with AIDS has not been shown (67).

HPMPC, a phosphoryl nucleotide analog with broad-spectrum activity against herpesviruses, has recently entered phase II clinical trials and appears to have sufficient prolonged anti-CMV activity to warrant further clinical trials with once-weekly or semi-weekly dosing (68).

Prevention and Future Directions in the Management of Opportunistic Infections

Dr. Henry Masur (Critical Care Medicine Department, Clinical Center, NIH): Patients infected with HIV have benefited from important advances in the diagnosis and treatment of opportunistic infections. However, the most productive approach toward reducing the morbidity associated with these infections is to reduce their frequency. This approach uses three basic strategies: 1) intervening in the natural history of HIV-associated immunodeficiency; 2) preventing the acquisition of new opportunistic pathogens; and 3) suppressing or eliminating latent infections.

Antiretroviral therapy with zidovudine or didanosine has been shown to slow the immunologic decline associated with HIV infection. Several large randomized trials have convincingly shown that zidovudine can reduce the frequency of opportunistic infections (especially P. carinii pneumonia) in patients with CD4+ lymphocyte counts lower than 700 cells/μL (69–72). This effect was independent of the effects of specific antipneumocystis prophylaxis that some patients received concurrently (73). The recent Concorde study does not support these findings (74); this discrepancy is the subject of considerable controversy. Didanosine appears to provide similar benefits (75). Other strategies to boost or preserve immune function, such as transfer of bone marrow or peripheral cells, therapy with interleukin-2, interferon-α, or interferon-γ, and HIV vaccines, show some promise but have not yet been proved to provide clinical benefit.

Preventing the acquisition of pathogens is easier to achieve in theory than in fact. Persons with HIV infection who practice unsafe sexual behavior are at risk for acquiring pathogens such as Treponema pallidum, herpes simplex virus, CMV, cryptococcosis, and salmonellosis. Persons with HIV infection who ingest contaminated food or water may also acquire cryptococcosis, salmonellosis, or other enteric organisms. Cats may pose a risk for transmitting Rochalimaea henselae infection. More practically, HIV-infected health care practitioners who are exposed to tuberculosis have a greater likelihood of acquiring infection and developing active disease. Limiting their exposure by avoiding bronchoscopy suites, aerosol pentamidine facilities, or pulmonary wards may be helpful in reducing the likelihood that they will develop tuberculosis.

Pneumocystis carinii, CMV, herpes simplex virus, varicella zoster virus, Candida species, and T. gondii are prime examples of opportunistic pathogens that persist latently in normal hosts and may become active and cause disease when immune function is qualitatively and quantitatively impaired by HIV. Natural history studies have shown that circulating CD4+ lymphocyte counts in HIV-infected persons are excellent predictors...
of the risk for developing these opportunistic infections (76). Thus, it is logical to monitor CD4+ lymphocyte counts regularly and to initiate prophylaxis against an opportunistic pathogen if a safe, convenient, and reasonably economical agent is available and the infection will probably occur and cause serious morbidity.

This decade is also likely to provide an expanding list of attractive oral agents such as quinolones, macrolides, azoles, and rifamycins, which have specific and sometimes broad activity against opportunistic pathogens. When combined with improved antiretroviral and immunomodulating agents, antimicrobials could reduce the effect of these pathogens on the duration and quality of life of HIV-infected persons. However, these regimens will not be panaceas because of difficulties in patient compliance, high cost, drug intolerance and interactions, and development of pathogen resistance. Moreover, as highly immunosuppressed patients live longer and survive the opportunistic pathogens we currently recognize, new problems such as microsporidiosis and *Rochaillarinea* infection will probably emerge. The 1990s will require continued efforts to develop new antimicrobial agents with new mechanisms of action for patients who cannot tolerate current agents or for patients who need more effective therapies.

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