Advances in the treatment of disseminated *Mycobacterium avium* complex in adults with AIDS

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CA KEMPER. Advances in the treatment of disseminated *Mycobacterium avium* complex in adults with AIDS. Can J Infect Dis 1994;5(Suppl B):14B-20B. Although the prospects for successful treatment of *Mycobacterium avium* complex (MAC) infection in AIDS recently seemed quite dismal, the introduction of the semisynthetic macrolides, clarithromycin and azithromycin, has altered this perspective. Several recent clinical studies have been key to our understanding of the successful management of these patients and are the basis of this review. Yet, some patients with disseminated MAC remain poorly responsive to therapy, intolerance often limits therapy, and recrudescent bacteremia often occurs. Though our understanding of this infection has been rapidly advanced in the past three years, much remains to be learned about its optimal therapeutic management.

Key Words: *AIDS, Azithromycin, Clarithromycin,* Mycobacterium avium *complex (MAC), Treatment regimens*

MUCH HAS BEEN GAINED IN THE BATTLE TO TREAT DISseminated infection due to organisms of the *Mycobacterium avium* complex (MAC) in patients with AIDS in the past three years. Most importantly, treatment of this infection has been greatly advanced by the introduction of the semisynthetic macrolide antibiotics, clarithromycin and azithromycin. Clarithromycin has now been approved by the United States Food and Drug Administration for use, in combination with other antimycobacterial agents, in the treatment of MAC bacteremia in patients with AIDS.

Early reports suggested that disseminated infection due to MAC in patients with AIDS could be ameliorated using multiple antimycobacterial agents in combination, but intolerance to therapy was frequent, and most patients continued to have clinical and microbiological evidence of infection (1-6). Subsequently, a raft of newer data (including at least 10 studies of combination therapy and eight of single-agent therapy), demonstrating the short term antibacterial effect of multidrug and single-drug regimens, have enhanced our ability to manage this infection. These data provide a rationale for the recent United States Public Health Service guidelines which advocate the use of a macrolide, either clarithromycin or azithromycin, in combination with at least one other antimycobacterial agent, in the treatment of MAC infection in adults with AIDS (7).

Highlights of several recent studies and a brief over-

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view of ongoing clinical trials are the subject of this discussion; two recent reviews provide additional information (8,9).

EARLY CLINICAL TRIALS

Recognizing elimination of mycobacteremia as the single tangible measure of antimycobacterial efficacy, Masur and colleagues (6) examined the effect of a combination of clofazimine (100 mg once daily) and rifabutin (150 to 300 mg once daily), in addition to a variety of other antimycobacterial agents, on MAC bacteremia in 13 patients for various durations (16 to 303 days). Although the authors were disappointed by their results (seven of 13 patients had at least two negative blood cultures, but two later developed recrudescent bacteremia), these data were an early signal that aggressive therapy with multiple agents could effect a microbiological response in some patients.

Hoy et al (4) identified 76 AIDS patients with MAC bacteremia. Twenty-two of 25 patients who tolerated a combination of isoniazid, clofazimine, ethambutol and rifabutin for more than 30 days had at least two consecutive negative blood cultures. Five subsequently relapsed. One of four patients who responded to the therapy, but subsequently died, had evidence of MAC at autopsy. However, no data were available on the other 51 patients. Similar results were demonstrated in another smaller study (1).

The results of these early studies provided a harbinger of a now well recognized fact: eradication of MAC in the blood stream is not equivalent to microbiological cure (tissue infection may be present in the absence of detectable bacteremia) and, despite initial sterilization of blood, recrudescence of mycobacteremia is frequent. For this reason, the relationship of mycobacteremia to tissue levels of infection in bone marrow is currently being examined in a longitudinal treatment study (Division of AIDS Treatment Research Initiative [DATRI] Protocol 007).

MULTIDRUG REGIMENS (WITHOUT A MACROLIDE)

Hawkins et al (3) and Wong et al (5) were the first investigators to recognize that quantitatively-determined mycobacteremia may be a useful measure of antibacterial activity in humans, and all studies discussed below employed this methodology.

Chiu and colleagues (10), through the California Collaborative Treatment Group (CCTG), were the first to examine the effect of multiple agents, in combination, on the numbers of circulating mycobacteria in a group of patients with AIDS. Seventeen patients with MAC bacteremia received parenterally administered amikacin (7.5 mg/kg/day) for four weeks in combination with orally administered ciprofloxacin (750 mg bid), rifampin (600 mg once daily), and ethambutol (1000 mg once daily) for 12 weeks. After four weeks, mean pretreatment colony counts fell from 537 colony forming units (cfu)/mL of blood to 14 cfu/mL in 15 patients (–1.5 $\log_{10}$ cfu/mL). Colony counts remained suppressed (mean, 15 cfu/mL) in 10 patients who completed the 12-week study, and three of these patients had clearance of bacteremia. Fevers, sweats and diarrhea improved in several patients who could tolerate the regimen, but three patients (18%) were withdrawn from study for gastrointestinal side effects. Colony counts remained suppressed (mean, 0.1 cfu/mL) in eight patients who continued the three oral agents for an average of 22 weeks of therapy.

This study was the first to demonstrate that reductions in quantitatively determined mycobacteremia were associated with improvement in clinical symptoms in patients who could tolerate therapy. However, intolerance to therapy was frequent and amikacin was difficult to administer.

Clofazimine (100 to 200 mg once daily) was therefore substituted for amikacin in a second phase of this study, resulting in a regimen of four drugs, all given per os (11). In order to evaluate the initial antibacterial effect of the oral agents in combination, the use of amikacin was restricted to the second four weeks of study at the discretion of the investigator. A total of 41 patients was enrolled, 31 of whom were evaluable with regard to the antibacterial effect of the regimen, but only 19 patients completed the 12-week study. Mean logarithmically determined colony counts fell from 2.1 $\log_{10}$ cfu/mL to 0.7 $\log_{10}$ cfu/mL after four weeks of therapy in 29 individuals, and to 0.1 $\log_{10}$ cfu/mL after 12 weeks of therapy in 19. Thirteen patients (42%) had at least one blood culture negative for MAC. Again, dramatic reductions in colony counts were seen within the first four weeks of therapy, often associated with improvement in clinical symptoms. The mean individual change in colony counts (–1.4 $\log_{10}$ cfu/mL) after four weeks of treatment was comparable with that of the previous regimen using amikacin. Although eight patients received amikacin after the first four weeks of study, there did not appear to be any additional significant impact on colony counts; unfortunately, two of these patients died before week 8, yielding a very small subset for analysis.

Preliminary data from the AIDS Clinical Trials Group (ACTG Protocol 135) also suggest that the addition of amikacin to the four-drug combination used by the CCTG does not result in any greater antibacterial activity than that of the four-drug regimen alone (9). Although its clinical efficacy has not been clearly demonstrated, amikacin remains one of the most active agents in vitro and in the animal model, and is likely to remain a useful agent, particularly in those patients who can not tolerate oral therapy, are severely ill or are hospitalized.

Jacobson and colleagues (12) at the University of California, San Francisco is one of two groups to have attempted a placebo-controlled treatment trial of MAC in AIDS. Twenty-four patients were randomized to receive ciprofloxacin (750 mg once daily), rifampin (600 mg

once daily), and ethambutol (25 mg/kg daily) or matching placebos; in addition, patients received ibuprofen as needed. While four of nine drug recipients had a microbiological response (defined as a 1.0 log or greater decrease in baseline colony counts), none of 10 placebo recipients did. Only one of 10 patients failed active drug treatment (defined as a 1.0 or greater increase in baseline colony counts), while seven of 10 placebo recipients had an increase in the level of mycobacteremia. While not a statistically significant difference, only one of 12 drug recipients versus four of 12 placebo recipients became moribund and were withdrawn from study. Originally intended as a crossover treatment trial, so few patients in the placebo arm remained after eight weeks that the investigators abandoned the original study design in favour of continued treatment. These were the first controlled data to support the long-held belief that, in the absence of therapy, colony counts increase in the majority of patients.

Rifabutin recently made its entrance as a useful agent in the prophylaxis of MAC. Although it has been used in a number of moderately successful multidrug treatment regimens, its contribution to these regimens has not been clear. In a recent treatment trial, 40 patients were randomized to clofazimine and ethambutol with or without rifabutin (13). After four weeks of therapy, seven of 11 patients who received the three-drug combination had a microbial response (six had clearance of mycobacteremia and one had more than a 2.0 $\log_{10}$ reduction in colony counts). In contrast, none of the 13 patients who received the two-drug combination responded. After 12 weeks of therapy, six of nine patients remaining on the three-drug arm had a microbial response versus only one of seven of those who received clofazimine and ethambutol. This study has since been terminated in favour of one using clarithromycin-containing regimens.

Compounding the interpretation of the results of these studies was the demonstration by Horsburgh et al (14) that absorption of many antimycobacterial agents is, at best, marginal in the majority of patients with AIDS. In a group of 27 patients with MAC bacteremia treated with clofazimine, ciprofloxacin, ethambutol and rifampin, 20 of whom tolerated at least three agents for eight weeks, only three patients had serum concentrations of a single-agent that fell within the expected range. Peak serum levels for 77 of the 80 assays ranged from borderline 'therapeutic' in two assays to undetectable in 29 (36%). Nevertheless, six patients had clearance of mycobacteremia. These observations have important implications for clinical practice and the conduct of treatment trials.

SINGLE-AGENT STUDIES

In an attempt to define the individual antibacterial activity of several agents used in the previous modestly successful CCTG regimens, 60 patients were randomized to receive either clofazimine (200 mg once daily), ethambutol (800 mg daily) or rifampin (600 mg daily) for four weeks (15). This short term efficacy trial yielded unexpected results; while colony counts were not significantly changed in response to the administration of either clofazimine or rifampin, they fell a median of 0.6 $\log_{10}$ cfu/mL in response to four weeks of ethambutol. These data proved that, in contrast to much in vitro data but confirming animal data, ethambutol has modest antibacterial activity in vivo, and supports its inclusion in combination regimens (7).

The lack of a significant decrement in mycobacteremia in response to either rifampin or clofazimine does not necessarily indicate a total lack of antibacterial effect. Based on limited data that colony counts increase in the absence of therapy (12,16), each of these agents may have prevented an increase in colony counts and could therefore be considered bacteriostatic in vivo.

While the individual activity of these three agents does not fully account for the observed bacteriological activity of the previous CCTG regimens, it is unlikely that this difference can be accounted for solely by the addition of ciprofloxacin in the earlier regimens. In a similar study, sparfloxacin (200 to 300 mg daily), a fluoroquinolone with slightly better in vitro activity than ciprofloxacin, had little effect on mycobacterial colony counts in blood when administered as a single-agent for four weeks (17). However, when ethambutol was added for another four to eight weeks, colony counts fell a mean of 0.95 $\log_{10}$ cfu/mL in 18 of 22 patients.

Nightingale and colleagues (18) administered lipid-associated gentamicin (TLC G-65) in three doses ranging from 1.7 mg/kg to 5.1 mg/kg once daily for approximately six weeks to 21 AIDS patients with MAC bacteremia (17). Mean pretreatment colony counts were reduced by over 90% at day 32; in 14 evaluable patients, individual colony counts fell a median of 0.45 $\log_{10}$ cfu/mL. No apparent difference in bacteriological efficacy between the three doses was detected, but the study was prematurely discontinued when one patient (who received the higher dose) developed reversible nonoliguric renal failure. No other adverse effects were identified.

No other single-agent or combination of agents to date has demonstrated the remarkable antimycobacterial effect of the semisynthetic macrolides, clarithromycin and azithromycin. In a placebo controlled crossover treatment trial, one group of eight patients received clarithromycin alone for six weeks, and then a combination of clofazimine, ethambutol, isoniazid and rifampin plus placebo for six weeks (16). A second group of seven patients received placebo for six weeks, and then a combination of clarithromycin plus the four other agents. Clearance of bacteremia was documented in six of eight patients after administration of clarithromycin alone. After discontinuation of clarithromycin,

TABLE 1
Commonly used antimycobacterial agents in the treatment of disseminated infection due to *Mycobacterium avium* complex in adults with AIDS

Agent	Daily dose	Adverse effects
Amikacin	7.5 to 15.0 mg/kg	Ototoxicity, nephrotoxicity, rash
Azithromycin	500 to 600 mg	Nausea, diarrhea, abdominal pain, reversible hearing loss (less commonly, elevations in hepatic enzymes, leukopenia)
Clarithromycin	500 to 1000 mg bid	Nausea, diarrhea, abdominal pain, taste intolerance, reversible hearing loss (less commonly, elevations in hepatocellular enzymes, leukopenia)
Ciprofloxacin	500 to 750 mg bid	Nausea, diarrhea, abdominal pain, anorexia (less commonly, mental status changes and seizures)
Clofazimine	100 to 200 mg	Skin discoloration, icthyosis, nausea, abdominal pain (less commonly, peripheral neuropathy and retinopathy)
Ethambutol	800 to 1000 mg	Anorexia, nausea, diarrhea, rash (at higher doses, retrobulbar neuritis and loss of colour vision)
Rifampin	600 mg	Nausea, diarrhea, abdominal pain, neutropenia, thrombocytopenia, rash, myalgia (less commonly, elevations in hepatocellular enzymes, headache)
Rifabutin	300 to 600 mg	Rash, myalgia, neutropenia, uveitis, nausea, diarrhea, abdominal pain, orange discoloration of tears, urine and skin

mycobacteremia increased in three patients. Five of seven patients who received placebo alone had increasing levels of mycobacteremia (and the other two died). These were the first controlled data to support the long-held belief that, in the absence of therapy, colony counts increase in the majority of patients.

In a randomized, dose-ranging study of clarithromycin in the treatment of MAC bacteremia in AIDS (ACTG 157), 154 patients received either 500 mg, 1.0 g or 2.0 g bid for 12 weeks (19,20). Preliminary results showed eradication of mycobacteremia in more than 50% of the patients by four to six weeks; median times to sterilization of blood cultures were 27, 43 and 55 days, respectively. Pretreatment colony counts, ranging from 2.6 to 2.8 $\log_{10}$ cfu/mL, fell a mean of 1.5, 2.4 and 2.3 $\log_{10}$ cfu/mL, respectively. In addition, clinical symptoms and quality of life were improved in patients who received either 500 or 1000 mg bid. However, 15%, 16% and 40% of patients prematurely discontinued study, respectively, most due to gastrointestinal side effects.

Suppression of bacteremia proved to be short-lived in many patients; recrudescence associated with high level resistance (minimum inhibitory concentration [MIC] 128 µg/mL or greater) occurred in 61 patients a mean of 16 weeks after entry into the study. The MICs of 180 isolates obtained from patients who relapsed were examined: only 29 (16%) were 8 µg/mL or less and 151 (84%) were 128 µg/mL or greater. Thus the post-treatment microbial isolates demonstrated a clearly biphasic population consistent with a single mutation leading to high level resistance.

In a second similar study, 299 patients were randomized to receive clarithromycin either 500 mg or 1.0 g bid for four weeks (21). Preliminary data showed that mycobacteremia fell by 1.0 $\log_{10}$ or more in 72% of those who received the lower dose and 82% of those who received the higher dose; clinical improvement was noted in 75% and 82%, respectively.

Apparently comparable antibacterial activity has been demonstrated in response to azithromycin in two studies. The first, conducted by Young et al (22), included 21 patients who received 500 mg daily for 10, 20 and 30 days. Colony counts were reduced from 118 cfu/mL to 43 cfu/mL in three patients after only 10 days; after 20 to 30 days, colony counts fell from 2028 cfu/mL to 136 cfu/mL. Fifteen of 21 patients had resolution of fever and 12 of 18 had resolution of sweats, but the mean weight decreased slightly.

In the second study, azithromycin, either 600 mg or 1200 mg daily, was administered for six weeks to 89 patients with AIDS and MAC bacteremia, 65 of whom were evaluable with regard to antimicrobial efficacy (23). Similar reductions in MAC colony counts were demonstrated for both treatment arms; after six weeks of treatment, colony counts fell 2.0 $\log_{10}$ in those who received 600 mg daily and 1.55 $\log_{10}$ in those who received 1200 mg daily. Sterilization of blood cultures was achieved in 56% and 42%, respectively. While 10% of those at the lower dose experienced nausea and diarrhea (none of which was dose-limiting), approximately 40% of patients at the higher dose experienced gastrointestinal toxicity (11% of which was dose-limiting). MICs remained stable and low during the six-week study, but resistance, including cross-resistance to clarithromycin, was demonstrated in the post-study period.

TABLE 2
Ongoing and future clinical treatment trials of *Mycobacterium avium* complex in adults with AIDS

Lead or sponsoring organization	Total number of patients (number enrolled)*	Treatment arms
Ongoing studies		
Abbott Laboratories (M93-069)	100 (7)	Clarithromycin (500 mg bid), ethambutol (800 to 1000 mg daily) ± clofazimine (100 mg daily)
AIDS Community Research Consortium	20 (9)	Azithromycin (600 mg daily) ± GM-CSF (250 μg daily)
California Collaborative Treatment Group (549)	100 (60)	Clarithromycin (1000 mg bid), clofazimine (100 mg daily), ± ethambutol (800 mg daily)
Canadian Network Trial	200 (144)	Clarithromycin (1000 mg bid), ethambutol (800 mg daily) and rifabutin (600 mg daily) versus ciprofloxacin (750 mg bid), clofazimine (100 mg daily), ethambutol (800 mg daily), and rifampin (600 mg daily)
National Institutes of Health (DATRI 007)	30 (9)	Clarithromycin (1000 mg bid) and ethambutol (15 mg/kg daily)
National Institutes of Health†	36 (10)	Azithromycin (1200 mg daily) versus sparfloxacin (300 mg daily) versus the combination
Pharmacia (Adria 087250)	320 (5)	Clarithromycin (500 mg bid), ethambutol (800 mg daily) ± rifabutin (300 or 450 mg daily) (three arms)
US Veterans Administration Cooperative Group	100 (17)	Clarithromycin (1000 mg bid) and ethambutol (800 mg daily) versus azithromycin (600 mg daily) and ethambutol (800 mg daily)
Future studies		
Pfizer Central Research	100	Clarithromycin (1000 mg bid) and ethambutol (800 mg daily) versus azithromycin (600 mg daily) and ethambutol (800 mg) daily
AIDS Clinical Trials Group (ACTG 223)		Three clarithromycin-containing arms
Community Programs for Clinical Research in AIDS (CPCRA 0287)		Four clarithromycin-containing arms

**Approximate number of patients enrolled as of March 1993. †Prematurely terminated as of January 1994. GM-CSF Granulocyte-macrophage-colony stimulating factor*

MULTIDRUG REGIMENS (WITH A MACROLIDE)

Several studies are available by which to gauge the efficacy of clarithromycin in combination with other antimycobacterial agents. De Lalla et al (24) used amikacin (7.5 mg/kg bid) for the first three weeks in combination with clarithromycin (1.0 g bid) and ciprofloxacin (500 mg tid) for 10 to 44 weeks in 12 patients with AIDS and MAC bacteremia. Sterilization of blood cultures was achieved in all 12 patients within two to six weeks of therapy. Three of four patients who died 12 to 44 weeks after entry into study had no histological or microbiological evidence of MAC at autopsy. Similar results were obtained using a combination of clarithromycin and clofazimine in 18 patients (25). An open multicentre trial of clarithromycin in combination with one or more additional antimycobacterial agents showed that mycobacteremia was eliminated in 11 of 16 evaluable patients who received 500 to 1000 mg daily, and 45 of 46 of those who received 1500 to 2000 mg daily (26). Acquired resistance to therapy was observed within two to seven months of study entry.

Recognition that the monocyte/macrophage is the dominant site at which MAC reside has led to a novel attempt at immunomodulatory therapy using granulocyte-macrophage colony stimulating factor (GM-CSF). Preliminary results from a controlled, randomized trial of azithromycin (600 mg daily) with or without GM-CSF indicate that this cytokine enhanced superoxide production and intracellular killing of mycobacteria in one patient with disseminated MAC relative to an untreated control (27).

SUMMARY TREATMENT GUIDELINES

Based on these data, the United States Public Health Service has recommended that adults with human immunodeficiency virus (HIV) infection and disseminated MAC receive one of the macrolide agents in combination with at least one other antimycobacterial (7) (Table 1). Which agent or agents will provide the optimal bacteriological activity in combination with the macrolides has not been determined, but most experts start with a combination of clarithromycin and ethambutol. While

the relative efficacy of the two macrolides has not yet been determined, clarithromycin and azithromycin appear to have, at least in preliminary trials, comparable efficacy. While many clinicians add a third agent (usually clofazimine), the value of this practice vis-à-vis tolerability and long term effectiveness remains uncertain, but is being addressed by several groups (Table 2). Monitoring of the serum concentrations of administered drugs may prove useful, but further data are needed.

Initial treatment is often complicated by gastrointestinal symptoms, which may be the result of drug administration, MAC involvement of the gastrointestinal tract, or both. While a chosen therapy may be initially poorly tolerated, once the infection is under some control, reintroduction of that agent may be successfully attempted.

Susceptibility studies on the baseline isolate are not believed to be of benefit in the initial selection of therapy. All pretreatment isolates have been susceptible to the macrolides and in vitro studies of susceptibility to clofazimine, ethambutol or rifampin are of questionable value (28,29). No evidence of emergent resistance has been demonstrated in patients who receive rifabutin as preventative therapy in patients who develop mycobacteremia while receiving this drug (30).

Susceptibility studies may, however, be of value in directing therapy in a patient who has received a macrolide-containing regimen and who develops recrudescent bacteremia. Based on data from ACTG 157, resistance to the macrolides is likely, and continued administration of either macrolide, even at higher doses, is not likely to be of benefit in a case of proven resistance.

Additional data defining the relationship of in vitro susceptibility studies to clinical response, and the optimal management of patients who fail a macrolide-containing regimen, are needed. The results of ongoing clinical trials, including comparative studies of the relative efficacy of clarithromycin and azithromycin, studies involving newer agents such as lipid-associated gentamicin, as well as studies of immunomodulatory therapy using agents such as GM-CSF, may subsequently lead to appropriate alterations in current treatment recommendations.

ACKNOWLEDGEMENTS: This work was supported in part by funds provided by the State of California's University-wide AIDS Research Program (R91-CC86SD) through the CCTG. The author also thanks Dr Stan Deresinski for his review of the original manuscript.

REFERENCES

1. Agins BD, Berman DS, Spicehandler D, El-Sadr W, Simberkoff MS, Rahal JJ. Effect of combined therapy with ansamycin, clofazimine, ethambutol, and isoniazid for *Mycobacterium avium* infection in patients with AIDS. J Infect Dis 1989;159:784-7.
2. Bach MC. Treating disseminated *Mycobacterium avium-intracellulare* infection. Ann Intern Med 1989;110:169-70. (Lett)
3. 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.
4. Hoy J, Mijch A, Sandland M, Grayson L, Lucas R, Dwyer B. Quadruple-drug therapy for *Mycobacterium avium-intracellulare* bacteremia in AIDS patients. J Infect Dis 1990;161:801-5.
5. Wong B, Edwards FF, Kiehn TE, et al. Continuous high-grade *Mycobacterium avium-intracellulare* bacteremia in patients with the acquired immune deficiency syndrome. Am J Med 1985;78:35-40.
6. 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.
7. Masur H. Recommendations on prophylaxis and therapy for disseminated *Mycobacterium avium* complex disease in patients infected with the human immunodeficiency virus. Public Health Service Task Force on prophylaxis and therapy for *Mycobacterium avium* complex. N Engl J Med 1993;329:898-904.
8. Inderlied C, Kemper CA, Bermudez LE. The *Mycobacterium avium* complex. Clin Micro Review 1993;6:266-310.
9. Benson CA, Ellner JJ. *Mycobacterium avium* complex infection and AIDS: Advances in theory and practice. Clin Infect Dis 1993;17:7-20.
10. 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.
11. Kemper CA, Meng TC, Nussbaum J, et al. Treatment of *Mycobacterium avium* complex bacteremia in AIDS with a four-drug oral regimen: rifampin, ethambutol, clofazimine and ciprofloxacin. Ann Intern Med 1992;116:466-72.
12. Jacobson MA, Yajko D, Northfelt D, et al. Randomized, placebo-controlled trial of rifampin, ethambutol, and ciprofloxacin for AIDS patients with disseminated *Mycobacterium avium* complex infection. J Infect Dis 1993;168:112-9.
13. Sullam PM, Gordin FM, Wynne BA, and the Rifabutin Study Group. Efficacy of rifabutin in the treatment of disseminated *Mycobacterium avium* complex infection. Clin Infect Dis 1994. (In press)
14. Gordon SM, Horsburgh CR Jr, Peloquin CA, et al. Low serum levels of oral antimycobacterial agents in patients with disseminated *Mycobacterium avium* complex disease. J Infect Dis 1993;168:1559-62.
15. Kemper CA, Havlir D, Haghighat D, et al. The microbiologic effect of three antimycobacterial agents, clofazimine, ethambutol, or rifampin, on *Mycobacterium avium* complex bacteremia in patients with AIDS. J Infect Dis 1994. (In press)
16. Dautzenberg B, Truffot C, Legris S, et al. Activity of clarithromycin against *Mycobacterium avium* infection in patients with the acquired immune deficiency syndrome: A controlled clinical trial. Am Rev Respir Dis 1991;144:564-9.
17. Young LS, Wu M, Bender J. Pilot study of sparfloxacin for *M avium* complex (MAC) bacteremia complicating AIDS. In: Program and Abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Anaheim: American Society of Microbiology.

1992:260(897). (Abst)
18. Nightingale S, Saletan S, Swenson C, et al. Phase I/II study of TLC G-65 (liposome encapsulated gentamicin) for treatment of *Mycobacterium avium* complex (MAC) disease. In: Program and Abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim: American Society for Microbiology, 1992:260(898). (Abst)
19. Chaisson RE, Benson C, Dubé M, et al. Clarithromycin therapy for disseminated *Mycobacterium avium* complex (MAC) in AIDS. In: Program and abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Anaheim: American Society of Microbiology, 1992:259(891). (Abst)
20. Chaisson RE, Benson CA, Dubé M, et al. Clarithromycin for disseminated *Mycobacterium avium* complex in AIDS patients. In: Abstracts of the VIIIth International Conference on AIDS/III STD World Congress. Amsterdam: Harvard University/Dutch Foundation, 1992:We54(WeB 1052). (Abst)
21. Gupta S, Blahunka K, Dellerson M, Craft JC, Smith T. Interim results of safety and efficacy of clarithromycin (C) in the treatment of disseminated *Mycobacterium avium* complex (MAC) infection in patients (Pts) with AIDS. In: Program and Abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Anaheim: American Society of Microbiology, 1992:259(892). (Abst)
22. Young LS, Wiviott L, Wu M, Kolonoski P, Bolan R, Inderlied CB. Azithromycin for treatment of *Mycobacterium avium*-intracellulare complex infection in patients with AIDS. Lancet 1991;338:1107-9.
23. Berry A, Koletar S, Williams D. Azithromycin therapy for disseminated *Mycobacterium avium*-intracellulare in AIDS patients. In: The First National Conference on Human Retroviruses and Related Infections. Washington DC: Centers for Diseases Control and Prevention/National Institutes of Health, 1993(292). (Abst)
24. de Lalla F, Maserati R, Scarpellini P, et al. Clarithromycin-ciprofloxacin-amikacin for therapy of *Mycobacterium avium-Mycobacterium intracellulare* bacteremia in patients with AIDS. Antimicrob Agents Chemother 1992;36:1567-9.
25. Saint-Marc T, Touraine JL. *Mycobacterium avium-intracellulare*: Treatment with the clarithromycin-clofazimine combination. Presse Med 1993;22:38.
26. Dautzenberg B, Saint-Marc T, Meyohas MC, et al. Clarithromycin and other antimicrobial agents in the treatment of disseminated *Mycobacterium avium* infections in patients with acquired immunodeficiency syndrome. Arch Intern Med 1993;153:368-72.
27. Kemper CA, Bermudez LE, Agosti J, Deresinski SC. Recombinant granulocyte macrophage colony stimulating factor (rhuGM-CSF) primes activation of monocytes (MO) in vivo in a patient with AIDS and *M avium* (MAC) bacteremia. In: Abstracts of the IXth International Conference on AIDS/IVth STD World Congress. Berlin: International AIDS Society/World Health Organization, 1993:497(PoB28 2170). (Abst)
28. Sison JP, Kemper CA, Yao Y, et al. Comparison of in vitro susceptibilities with quantitative *Mycobacterium avium* cultures. In: Abstracts and Program of the Frontiers in Mycobacteriology: *M avium*; the Modern Epidemic. Vail: National Jewish Center for Immunology and Respiratory Diseases, 1992(47). (Abst)
29. Yao Y, Hamilton J, Sison JP, et al. Correlation of *Mycobacterium avium* susceptibility to rifampin (R), ethambutol (EMB), or clofazimine (CLF) in various dilution testing methods, treatment of human macrophages (MP), and treatment of infection in an animal model. In: Abstracts and Program of the Frontiers in Mycobacteriology: *M. avium*; the Modern Epidemic. Vail: National Jewish Center for Immunology and Respiratory Diseases, 1992(65). (Abst)
30. Nightingale SD, Cameron DW, Gordin FM, et al. Two controlled trials of rifabutin prophylaxis against *Mycobacterium avium* complex infection in AIDS. N Engl J Med 1993;329:828-33.