

PROPHYLAXIS AGAINST DISSEMINATED *MYCOBACTERIUM AVIUM* COMPLEX WITH WEEKLY AZITHROMYCIN, DAILY RIFABUTIN, OR BOTH

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ABSTRACT

Background Azithromycin is active in treating *Mycobacterium avium* complex disease, but it has not been evaluated as primary prophylaxis in patients with human immunodeficiency virus (HIV) infection. Because the drug is concentrated in macrophages and has a long half-life in tissue, there is a rationale for once-weekly dosing.

Methods We compared three prophylactic regimens in a multicenter, double-blind, randomized trial involving 693 HIV-infected patients with fewer than 100 CD4 cells per cubic millimeter. The patients were assigned to receive rifabutin (300 mg daily), azithromycin (1200 mg weekly), or both drugs. They were monitored monthly with blood cultures for *M. avium* complex.

Results In an intention-to-treat analysis, the incidence of disseminated *M. avium* complex infection at one year was 15.3 percent with rifabutin, 7.6 percent with azithromycin, and 2.8 percent with both drugs. The risk of the infection in the azithromycin group was half that in the rifabutin group (hazard ratio, 0.53; $P=0.008$). The risk was even lower when two-drug prophylaxis was compared with rifabutin alone (hazard ratio, 0.28; $P<0.001$) or azithromycin alone (hazard ratio, 0.53; $P=0.03$). Among the patients in whom azithromycin prophylaxis was not successful, 11 percent of *M. avium* complex isolates were resistant to azithromycin. Dose-limiting toxic effects were more common with the two-drug combination than with azithromycin alone (hazard ratio, 1.67; $P=0.03$). Survival was similar in all three groups.

Conclusions For protection against disseminated *M. avium* complex infection, once-weekly azithromycin is more effective than daily rifabutin and infrequently selects for resistant isolates. Rifabutin plus azithromycin is even more effective but is not as well tolerated. (N Engl J Med 1996;335:392-8.)

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UNLESS they receive antimycobacterial prophylaxis in some form, up to 40 percent of patients have disseminated *Mycobacterium avium* complex infection within two years of the diagnosis of the acquired immunodeficiency syndrome (AIDS).^{1,2} Disseminated *M. avium* complex infection causes fever, night sweats, diarrhea, anorexia, abdominal pain, and wasting and is associated with shortened survival.^{3,4} Pro-

phylaxis against opportunistic infections is critical to the management of human immunodeficiency virus (HIV) disease as it progresses. The high incidence of disseminated *M. avium* complex infection, its considerable morbidity, and the limited response to therapy make it a logical target for prophylaxis.⁵⁻⁷ Because rifabutin halved the incidence of *M. avium* complex bacteremia in two large placebo-controlled trials, a task force of the Public Health Service endorsed it as prophylaxis against *M. avium* complex disease.^{8,9} Rifabutin is well tolerated but potentially interacts with numerous other drugs commonly used to treat HIV-infected patients.

Azithromycin is an azalide with activity in vitro against *M. avium* complex and limited efficacy in treating pulmonary disease in immunocompetent patients or disseminated disease in patients with AIDS.^{10,11} Azithromycin is concentrated and persists in phagocytic cells, with a three-day half-life in tonsillar tissue.^{12,13} These pharmacologic properties explain its effectiveness as intermittent treatment for disseminated *M. avium* complex infection in the beige-mouse model¹⁴ and provide the rationale for administering azithromycin weekly to prevent such infection.

To determine whether azithromycin could simplify or improve the effectiveness of prophylaxis against *M. avium* complex disease, we compared weekly

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prophylaxis with azithromycin alone, daily prophylaxis with rifabutin alone, and the combination of both drugs with regard to safety and efficacy in patients with HIV infection.

METHODS

Study Design

This study was a double-blind, randomized trial of primary prophylaxis against multiple organisms conducted at 12 sites. As prophylaxis against *M. avium* complex disease, patients were randomly assigned to receive 300 mg of rifabutin daily, 1200 mg of azithromycin (given as two 600-mg lactose-free tablets) once weekly, or both drugs. As prophylaxis against fungal disease, patients were assigned (in an independent randomization) to receive either 200 mg of fluconazole daily or 400 mg of fluconazole once weekly. This study design permitted us to analyze the simultaneous effect of both interventions. The results of the portion of the study involving prophylaxis against fungal disease have been presented elsewhere.¹⁵

To be eligible for the study, patients had to be infected with HIV and at least 18 years old, with documented CD4 cell counts below 100 cells per cubic millimeter within one year before study entry. They also had to have an absolute neutrophil count of at least 500 cells per cubic millimeter, a platelet count of at least 50,000 cells per cubic millimeter, serum creatinine and bilirubin concentrations less than three times the upper limit of normal, serum aminotransferase concentrations less than five times the upper limit of normal, a chest radiograph showing no evidence of active disease, a Karnofsky score above 60 for performance status, an expected survival of more than six months, no evidence of an acute opportunistic infection, and no history of hypersensitivity reactions to clarithromycin, azithromycin, rifampin, or rifabutin. Patients with documented or suspected mycobacterial infection and pregnant or lactating women were excluded. The protocol was approved by the institutional review board at each participating site, and each patient gave written informed consent before enrollment.

Blood was collected and cultured for *M. avium* complex at base line and monthly thereafter. Five milliliters of blood was injected into bottles containing Bactec 13A (Becton Dickinson Diagnostic Instrument Systems, Sparks, Md.) and shipped overnight at ambient temperature to a central laboratory (Veterans Affairs Medical Center, La Jolla, Calif.).¹⁶ Positive cultures were identified as *M. avium*, *M. intracellulare*, and *M. avium* complex with hybridization probes (AccuProbe, Gen-Probe, San Diego). Cultures were considered to be negative if no growth was detected after eight weeks of incubation. Isolates of *M. avium* complex obtained either from sterile sites other than blood or from blood samples collected between the study visits were processed locally and then sent to the central laboratory for susceptibility testing.

Susceptibility to clarithromycin, azithromycin, and rifabutin was determined in vials containing Bactec 12B at pH 6.8 according to previously described methods at an independent laboratory (Children's Hospital, Los Angeles).¹⁷ Resistance was defined as a minimal inhibitory concentration exceeding 128 µg per milliliter of solution for azithromycin, 16 µg per milliliter for clarithromycin, and 4 µg per milliliter for rifabutin.

Symptoms of *M. avium* complex disease, intercurrent illness, adverse events, and compliance with medication were assessed monthly. The patients were asked to complete HIV-PARSE survey questionnaires at base line and every 16 weeks thereafter. This instrument includes questions on use of health care, disability, and symptoms as well as on health-related quality of life.^{18,19} Complete blood counts and chemistry panels were obtained bimonthly. The use of antiretroviral therapy and prophylaxis against *Pneumocystis carinii* pneumonia was encouraged. The study medications were discontinued when a patient required treatment for more than four consecutive weeks during the study with any of the following open-label medications: azithromycin, rifabutin, erythromycin, rifampin, ethambutol, clofazimine, clarithromycin,

amikacin, streptomycin, ciprofloxacin, norfloxacin, and ofloxacin. The study medications were also discontinued if *M. avium* complex disease or dose-limiting toxic effects developed. All patients in whom the study medications were discontinued prematurely were followed to assess survival and the development of disseminated *M. avium* complex infection.

End Points

The primary end point in the study was the time to the development of disseminated *M. avium* complex disease, which was diagnosed on the basis of a positive culture for *M. avium* complex from blood or another sterile body site. Bacterial infection was considered to be present when there was bacteremia (defined as a positive blood culture), soft-tissue infection (detected on clinical diagnosis), sinusitis (defined as radiographic evidence of disease plus a compatible clinical picture), or pneumonia (defined as radiographic signs of pneumonia with a compatible clinical picture).

Statistical Analysis

On the basis of a two-year incidence of 20 percent for *M. avium* complex disease among rifabutin recipients, we estimated that a sample containing 240 patients per group would provide at least 80 percent power to detect a reduction of 50 percent or more in the incidence of *M. avium* complex disease in any group at the 0.05 level of significance.

The cumulative risk of reaching the primary end point was estimated by the Kaplan-Meier method, and the treatments were compared by the log-rank test after stratification for study site and assigned treatment for fungal prophylaxis. Hazard ratios for *M. avium* complex disease were computed with Cox proportional-hazards models, which were stratified according to study site and treatment assignment for fungal prophylaxis and adjusted for the CD4 cell count. All the statistical tests were two-tailed. The proportions of patients in whom toxic effects developed were compared among treatment groups by the Cochran-Mantel-Haenszel test.

The efficacy of prophylaxis was determined in two analyses. In the first, the eligible patients were studied according to their treatment assignments at randomization (the intention-to-treat analysis). The second analysis was limited to the patients who continued to receive their assigned regimen (the on-treatment analysis). In the latter analysis, events occurring within 30 days of the start of the study, more than 30 days after the permanent discontinuation of the study medication, or after 30 days of interrupted therapy or treatment with disallowed medications were not considered failures of prophylaxis and were excluded as end points.

The incidence rates of *M. avium* complex disease and toxic effects in each group were reviewed quarterly by a Data and Safety Monitoring Board composed of a statistician and experts in *M. avium* complex disease, using guidelines specified in the study protocol. No changes were recommended by the monitoring board during the course of the study.

RESULTS

Study Population

Patients were enrolled in the study from December 1992 through April 1994 and were followed for a median of 514 days until April 1995 (total follow-up, 909 patient-years). Survival and the occurrence of *M. avium* complex disease were ascertained through April 1995 for 80 percent of the enrollees.

Of 723 patients enrolled in the study, 693 were randomized and received at least one dose of rifabutin (236 patients), azithromycin (233 patients), or the combination (224 patients). The mean number of days of treatment was similar in the three

groups — 296 days in the rifabutin group, 315 in the azithromycin group, and 344 in the combination-therapy group. The three groups were similar with respect to demographic characteristics and base-line laboratory values (Table 1), except that the median CD4 cell count at base line was higher in the combination group (45 cells per cubic millimeter) than in the azithromycin group (36 cells per cubic millimeter) or the rifabutin group (38 cells per cubic millimeter). Twenty-four patients with base-line blood cultures positive for *M. avium* complex and five patients in whom no assessments were made after base line were excluded from further analysis.

Disseminated *M. avium* Complex Infection

In the intention-to-treat analysis, the incidence of disseminated *M. avium* complex infection was 23.3 percent (52 of 223) in the patients assigned to rifabutin, 13.9 percent (31 of 223) in the patients assigned to azithromycin, and 8.3 percent (18 of 218) in the patients assigned to combination therapy. Of these 101 isolates of *M. avium* complex, 94 were from blood, 5 were from bone marrow, 1 was from lymph node, and 1 was from liver. At one year, the cumulative incidence of disseminated *M. avium* complex infection was 15.3 percent in the rifabutin group, 7.6 percent in the azithromycin group, and 2.8 percent in the combination-therapy group.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 693 STUDY PATIENTS ACCORDING TO TREATMENT GROUP.

CHARACTERISTIC	RIFABUTIN (N=236)	AZITHROMYCIN (N=233)	COMBINATION THERAPY (N=224)
Male sex (%)	95	96	94
Race or ethnic group (%)			
White	60	60	61
Black	19	23	21
Hispanic	15	15	12
Asian	0	0	1
Other	6	2	5
Mean age (yr)	38.0	38.2	38.5
CD4 cells/mm ³			
Mean	47	49	57
Median	38	36	45
CD4 count <50 cells/mm ³ (% of patients)	60	59	50
Prior opportunistic infection (%)	40.0	41.6	40.2
Mean hemoglobin (g/dl)	12.5	12.7	12.6
Mean serum alkaline phosphatase (units/liter)*	91.3	99.6	90.6
Prior rifabutin prophylaxis (%)	8.5	5.6	5.4
Prior azithromycin (%)	1.7	2.6	1.8
Prior clarithromycin	4.2	6.4	3.1
Fluconazole prophylaxis (%)	92.4	90.5	92.4
200 mg daily	46.2	45.5	46.0
400 mg weekly	46.2	45.0	46.4

*To convert values to microkatal per liter, multiply by 0.01667.

There were similar trends in the on-treatment analysis. Disseminated *M. avium* complex disease occurred in 24 of 204 patients taking rifabutin (11.8 percent), 18 of 204 patients taking azithromycin (8.8 percent), and 5 of 199 patients taking the combination of drugs (2.5 percent). The one-year cumulative incidence of disseminated *M. avium* complex infection was 9.3 percent in the rifabutin group, 5.4 percent in the azithromycin group, and 0.5 percent in the combination-therapy group in the on-treatment analysis.

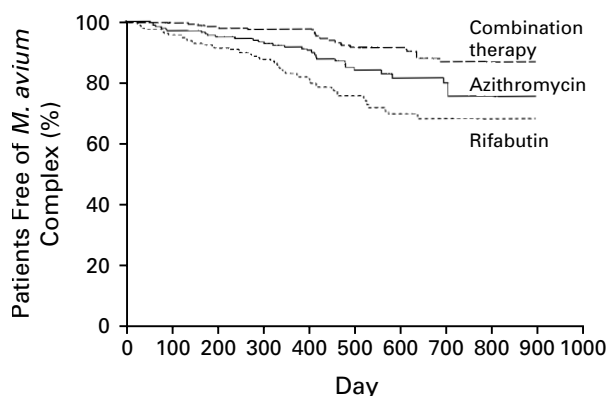
In the intention-to-treat Kaplan–Meier analysis (Fig. 1), the risk of disseminated *M. avium* complex infection after adjustment for CD4 cell counts at entry was 72 percent lower (hazard ratio, 0.28; $P < 0.001$) with combination therapy than with rifabutin alone and 47 percent lower (hazard ratio, 0.53; $P = 0.03$) than with azithromycin alone (Table 2). The risk in the patients taking azithromycin was 47 percent lower (hazard ratio, 0.53; $P = 0.008$) than the risk in patients taking rifabutin.

Patients in whom disseminated *M. avium* complex developed had the symptoms and laboratory abnormalities typical of the disease. Fever was reported in 70 percent, weight loss (a reduction of more than 5 percent from base line) in 49 percent, anemia (a reduction in hemoglobin of more than 1.0 g per deciliter from base line) in 53 percent, and elevated serum alkaline phosphatase (to a value more than three times the upper limit of normal) in 4 percent. All the patients in whom azithromycin prophylaxis failed, 77 percent of those in whom rifabutin failed, and 56 percent of those in whom the combination therapy failed were symptomatic at the time of diagnosis.

Fluconazole, which may increase serum concentrations of rifabutin,²⁰ had similar effects on the rates of disseminated *M. avium* complex disease in all groups, whether it was administered daily or weekly. In the rifabutin group, *M. avium* complex disease developed in 22 percent of the patients randomly assigned to receive 200 mg of fluconazole daily and in 25 percent of the patients randomly assigned to receive 400 mg of fluconazole once weekly. The mean duration of treatment with daily or weekly fluconazole did not differ significantly, either within or among the study groups (336 vs. 329 days, respectively).

Susceptibility of *M. avium* Complex Isolates

Of the 47 isolates of *M. avium* complex obtained from patients who reached primary end points in the on-treatment analysis, 44 (94 percent) were tested for susceptibility to antibiotics. Isolates from 2 of 18 patients (11 percent) receiving azithromycin alone were resistant to both azithromycin (minimal inhibitory concentration, $>256 \mu\text{g}$ per milliliter) and clarithromycin (minimal inhibitory concentration, $>16 \mu\text{g}$ per milliliter). Patients receiving azithromycin



NO. AT RISK

Azithromycin	223	207	183	158	125	92	58	31	5	0	0
Rifabutin	223	202	172	154	121	82	59	30	3	1	0
Combination	218	205	190	170	141	96	69	36	9	1	0

Figure 1. Kaplan-Meier Estimates of the Cumulative Risk of Disseminated *M. avium* Complex Infection According to Treatment Group.

The number of patients in each group who were at risk for disseminated *M. avium* complex infection at each time point is shown below the figure. The risk of infection was lower in the combination-therapy group than in the azithromycin group ($P=0.039$) or the rifabutin group ($P<0.001$). Azithromycin was more effective than rifabutin ($P=0.002$) in protecting against disseminated *M. avium* complex infection.

and those receiving rifabutin had similar distributions of the minimal inhibitory concentrations to clarithromycin and azithromycin in the remaining isolates. Azithromycin-resistant isolates of *M. avium* complex were detected after 282 to 421 days of prophylaxis. Overall, 1 percent of the patients initially assigned to azithromycin were found to have an isolate of *M. avium* complex from blood or another sterile site that was resistant to azithromycin.

None of the 21 isolates from the patients receiving rifabutin were resistant to rifabutin. None of the five isolates from patients assigned to combination-drug prophylaxis were resistant to either azithromycin or rifabutin. The proportions of resistant isolates of *M. avium* complex did not differ significantly among the three groups.

Infections with Bacteria Other Than *M. Avium* Complex

Respiratory tract infections (pneumonia and sinusitis) developed in the rifabutin recipients twice as frequently as in the azithromycin recipients (Table 3). The overall rates of bacterial infection were 37 percent lower in the combination-therapy group than in the rifabutin group. Rates of soft-tissue infection were similar, and the 29 episodes of bacteremia were distributed equally among the groups. Five patients were treated for *M. tuberculosis* infection,

two in each single-drug group and one in the combination-therapy group. Four of these cases were diagnosed empirically on the basis of abnormal chest radiographs; the sputum cultures did not grow *M. tuberculosis*. The fifth patient was taking azithromycin and had *M. tuberculosis* cultured from a bronchoscopy specimen.

Quality of Life and Survival

At base line and before the development of disseminated *M. avium* complex disease, there was no difference among the three groups in overall quality of life as assessed by the HIV-PARSE survey. The power of the study to detect differences between treatment groups after the occurrence of disseminated *M. avium* complex infection was limited, because patients in whom disease developed did not always return their surveys.

Two hundred forty-nine patients died during the study period: 83 patients in the azithromycin group, 85 in the rifabutin group, and 81 in the combination-therapy group. In a Cox regression analysis, the time to death did not differ significantly among the three groups.

Adverse Effects

More patients assigned to azithromycin (88 percent) or to combination therapy (90 percent) had adverse events than did those assigned to rifabutin (76 percent), largely because they had more gastrointestinal toxic effects (Table 4). Most gastrointestinal symptoms in the azithromycin-containing regimens were mild to moderate, were limited to the day the study medication was given, and did not result in discontinuation of the medication. The permanent discontinuation of study medications due to gastrointestinal symptoms was similarly frequent in these groups (azithromycin, 8 percent; rifabutin, 8 percent; combination therapy, 9 percent). Overall dose-limiting toxic effects were most common in the patients randomly assigned to combination therapy (21 percent).

TABLE 2. RISK OF *M. AVIUM* COMPLEX INFECTION AMONG THE STUDY PATIENTS ACCORDING TO TREATMENT GROUP.*

COMPARISON	ON-TREATMENT ANALYSIS	INTENTION-TO-TREAT ANALYSIS
	hazard ratio (95% confidence interval)	
Azithromycin vs. rifabutin	0.63 (0.33–1.21)	0.53 (0.34–0.85)
Combination therapy vs. rifabutin	0.17 (0.06–0.46)	0.28 (0.16–0.49)
Combination therapy vs. azithromycin	0.27 (0.10–0.74)	0.53 (0.29–0.95)

*After stratification according to center and prophylaxis against fungal infection and adjustment for base-line CD4 cell count.

In a Cox model, the cumulative risk of discontinuation attributed to drug toxicity was significantly higher in the combination-therapy group than in the azithromycin group (hazard ratio, 1.67; 95 percent confidence interval, 1.10 to 2.60; $P=0.03$). Uveitis, a complication of rifabutin, was a dose-limiting toxic effect in five patients in the two rifabutin-containing regimens (1 percent in each). Hematologic abnormalities (leukopenia and anemia) and elevated results of liver-function tests were the predominant laboratory abnormalities that resulted in the permanent discontinuation of the study medication.

DISCUSSION

A task force of the Public Health Service and the Infectious Disease Society of America has endorsed rifabutin as prophylaxis against disseminated *M. avium* complex infection, a strategy expected to reduce the development of disease by about 50 percent.²¹ We tested the hypothesis that azithromycin, administered intermittently either alone or with rifabutin, would be more effective than standard prophylaxis with rifabutin alone. We found both azithromycin strategies to be more effective than rifabutin. As compared with rifabutin, azithromycin halved the risk of *M. avium* complex disease. In this study, the combination of azithromycin and rifabutin was the most effective regimen, reducing the risk of *M. avium* complex disease by 72 percent as compared with rifabutin alone.

Azithromycin can be administered once weekly, unlike clarithromycin and rifabutin, the other two drugs approved for prophylaxis against disseminated *M. avium* complex infection, both of which require daily dosing.^{22,23} The efficacy of azithromycin may be enhanced by the high and persistent concentrations of the drug in macrophages, the primary cells infected by *M. avium* complex.²⁴ Because of these

TABLE 3. INCIDENCE OF BACTERIAL INFECTION ACCORDING TO TREATMENT GROUP.

TYPE OF INFECTION	RIFABUTIN	AZITHROMYCIN	COMBINATION
			THERAPY
			episodes/100 patient-yr
Sinusitis or pneumonia*	20.5	10.0	4.9
Soft-tissue infection	11.0	14.5	13.1
Bacteremia	5.3	4.5	4.9
All†	36.8	29.0	22.9

*The incidence of sinusitis and pneumonia was significantly higher in the rifabutin group than in the azithromycin group (risk ratio, 2.00; 95 percent confidence interval, 1.17 to 3.45) or the combination-therapy group (risk ratio, 3.60; 95 percent confidence interval, 1.72 to 7.41).

†There were more bacterial infections overall in the rifabutin group than in the combination-therapy group (risk ratio, 1.58; 95 percent confidence interval, 1.10 to 2.30).

TABLE 4. INCIDENCE OF ADVERSE EVENTS AND DOSE-LIMITING TOXIC EFFECTS IN THE STUDY PATIENTS ACCORDING TO TREATMENT GROUP.

VARIABLE	RIFABUTIN (N=236)	AZITHROMYCIN (N=233)	COMBINATION
			THERAPY (N=224)
			% of patients
Any adverse event*	76	88	90
Gastrointestinal toxic effects†	56	84	74
Abdominal pain	18	36	35
Diarrhea	26	56	58
Nausea	25	37	36
Vomiting	9	12	10
Dose-limiting toxic effects‡	16	13	23
Gastrointestinal	8	8	9
Cutaneous	3	3	4
Musculoskeletal	1	0	3
Uveitis	1	0	1
Other	0	1	1
Laboratory abnormality§	3	1	4

*A significantly higher proportion of patients had adverse events in the combination-therapy group than in the rifabutin group and in the azithromycin group than in the rifabutin group ($P<0.001$ for both comparisons).

†A significantly higher proportion of patients had gastrointestinal toxic effects in the combination-therapy group than in the rifabutin group and in the azithromycin group than in the rifabutin group ($P<0.001$ for both comparisons).

‡A significantly higher proportion of patients had dose-limiting toxic effects in the combination-therapy group than in the azithromycin group ($P=0.011$).

§Laboratory abnormalities included leukopenia, anemia, thrombocytopenia, and elevated values on liver-function testing.

pharmacologic properties, intermittent azithromycin therapy may provide a more constant effect than the daily administration of other prophylactic drugs.

Azithromycin-resistant isolates were detected infrequently (in 11 percent of patients) in the patients treated unsuccessfully in the azithromycin group and were not detected in the isolates from patients randomly assigned to combination therapy. In the present trial, disseminated *M. avium* complex infection developed in only 1 percent of patients randomly assigned to azithromycin who had an isolate resistant to that drug.

All the azithromycin-resistant isolates were also resistant to clarithromycin. Such cross-resistance is probably due to point mutations in the variable domain of the 23S ribosomal RNA gene that confer high-level resistance to both drugs.^{25,26} The low frequency of resistance in the patients in whom azithromycin prophylaxis failed is important, because there are no highly effective drugs other than clarithromycin and azithromycin with which to treat disseminated *M. avium* complex infection. Either noncompliance or the malabsorption of azithromycin may explain the failure of prophylaxis due to clarithromycin-sensitive isolates of *M. avium* complex.

In two trials of prophylaxis with clarithromycin, 29 percent and 58 percent of the breakthrough isolates were resistant to that drug.^{21,22} Among patients in whom treatment failed, the higher proportion of resistance to clarithromycin than to azithromycin is unexplained, but the prolonged high intracellular concentrations achieved with azithromycin may provide more consistent levels of drug than are achieved with clarithromycin. Alternatively, in one clarithromycin trial, a longer period of follow-up and less frequent monitoring with blood cultures may have provided more opportunity to select for resistance in the breakthrough isolates.²³ However, the overall risk of disseminated infection with an *M. avium* complex isolate resistant to clarithromycin was low with either of these drugs, because of their similarly high efficacy.

Rates of bacterial infections of the respiratory tract (pneumonia and sinusitis) were significantly lower in the azithromycin-containing groups than in the rifabutin-alone group, as is consistent with the activity of azithromycin against common respiratory tract pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*. This effect is corroborated by the results of another trial of prophylaxis against disseminated *M. avium* complex in which the rates of all bacterial infections were halved with azithromycin as compared with placebo.²⁷

Both study medications were generally well tolerated, particularly in view of the advanced stage of HIV disease in these patients and the often complicated accompanying treatment regimens. The 1200-mg dose of azithromycin was associated with gastrointestinal side effects in the majority of patients, but these were dose-limiting in only 8 percent. The overall incidence of adverse events was similar among the three groups. The addition of rifabutin improved the efficacy of the azithromycin regimen in preventing disseminated *M. avium* complex infection, but dose-limiting toxic effects were more frequent in the combination-therapy group. However, before the development of disseminated *M. avium* complex infection, the groups did not differ with respect to quality-of-life measures, suggesting that the overall disadvantage of combination therapy was small. Uveitis was a dose-limiting toxic effect in only five patients receiving rifabutin, suggesting that this complication is infrequent, occurring in less than 1 percent of patients.²⁸

In a previous report, patients receiving fluconazole and rifabutin had lower rates of *M. avium* complex disease than patients receiving rifabutin alone, presumably because of the inhibition of cytochrome P-450 by fluconazole, which results in an 80 percent increase in serum concentrations of rifabutin and its desacetyl metabolite.²⁰ Since nearly all the patients in our trial received fluconazole, we could not deter-

mine the effectiveness of the prophylactic regimens in patients not receiving fluconazole; however, the concomitant administration of 200 mg of fluconazole daily or 400 mg of fluconazole once weekly affected the efficacy and toxicity of rifabutin similarly. No interactions between azithromycin and fluconazole were observed in this study.

Weekly azithromycin therapy can be recommended as prophylaxis against disseminated *M. avium* complex infection on the basis of the results of this trial and a placebo-controlled trial showing a 60 percent reduction in risk with azithromycin as compared with placebo.²⁷ Azithromycin is more effective than rifabutin, can be given once weekly, and does not interact with other medications commonly administered to patients with AIDS. Since few patients in whom prophylaxis with azithromycin failed had isolates resistant to both clarithromycin and azithromycin, the widespread use of weekly azithromycin as prophylaxis should not seriously compromise the treatment of those in whom that prophylaxis fails.

Adding rifabutin to weekly azithromycin further reduces the risk of *M. avium* complex disease. Factors that weigh against this benefit include the increases in toxicity, cost, and potential drug interactions associated with combination therapy. In addition, the need to take 16 capsules or tablets per week with combination therapy rather than 2 tablets per week with azithromycin alone increases the already complicated drug regimens of those with advanced AIDS. This means that using combination therapy instead of azithromycin alone would entail prescribing more than 15,000 capsules (or more than 6500 daily doses of medication) annually for each additional infection prevented. The metabolism of rifabutin is influenced by several drugs commonly used to treat patients with AIDS, including fluconazole, ritonavir, and indinavir. Ritonavir and indinavir increase the area under the serum-concentration curve of rifabutin (and its desacetyl metabolite), resulting in a composite increase in exposure to rifabutin by factors of 6.8 and 2.2, respectively (Chodakewitz J, Sun E: personal communication). The induction of the P-450 enzyme system by rifabutin can also reduce the serum concentrations of drugs metabolized through this pathway, producing subtherapeutic levels of essential drugs.²⁹

In summary, the results of this trial support two new strategies for preventing *M. avium* complex infection. Weekly azithromycin is a simple, highly effective prophylactic regimen. The combination of azithromycin and rifabutin is more efficacious, but its use may be limited by its tolerability and cost and by potential drug interactions.

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APPENDIX

In addition to the authors, the following institutions and investigators participated in this trial. The numbers in parentheses are the numbers of patients enrolled in each center. University of California, San Diego (112): K. Nuffer and A. Fraser; University of Southern California, Los Angeles (94): J. Leedom, S. Codina, and I. Teran; Santa Clara Valley Medical Center, San Jose, Calif., and the AIDS Community Research Consortium, Redwood City, Calif. (56): S.C. Deresinski, S. Burton, C.A. Kane, R. Schnell-Smith, and B. Cayme; University of California, Irvine (35): J. Tilles and B. Keenan; George Washington University, Washington, D.C. (84): G.L. Simon, S.F. LeLacheur, J.L. Courtless, and B.R. Lewis; Georgetown University, Washington, D.C. (85): J. Trembeth, P. Barrett; Baylor College of Medicine, Houston (76): S. Miller, J. Garner, W. Ace, S. Von Blon, and J. Simmons; Harbor–UCLA Medical Center, Torrance, Calif. (64): S. Houston and C. Alder; University of Texas Southwestern Medical Center, Dallas (29): J. Lawrence; New York Hospital–Cornell Medical Center, New York (23): T. Sarracco; University of Pennsylvania, Philadelphia (20): A.L. Graziani; and the University of Massachusetts, Worcester (15): C. Vola and J. Avato. Quality of Life Analysis: RAND, Santa Monica, Calif.: D.E. Kanouse, S. Berry, and C. Edwards; and the University of California, San Diego: B.C. Wright.

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