

A RANDOMIZED TRIAL OF CLARITHROMYCIN AS PROPHYLAXIS AGAINST DISSEMINATED *MYCOBACTERIUM AVIUM* COMPLEX INFECTION IN PATIENTS WITH ADVANCED ACQUIRED IMMUNODEFICIENCY SYNDROME

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ABSTRACT

Background Disseminated infection with *Mycobacterium avium* complex is the most common opportunistic infection in patients with advanced stages of the acquired immunodeficiency syndrome (AIDS). We studied the efficacy and safety of prophylactic treatment with clarithromycin, a macrolide antibiotic.

Methods We conducted a randomized, placebo-controlled, double-blind study of clarithromycin in patients with AIDS in the United States and Europe. Entry criteria included blood cultures that were negative for *M. avium* complex, a Karnofsky performance score of 50 or higher, a CD4 cell count of 100 or less per cubic millimeter, and a life expectancy of at least six months.

Results After the first interim analysis, the study was stopped. *M. avium* complex infection developed in 19 of the 333 patients (6 percent) assigned to clarithromycin and in 53 of the 334 (16 percent) assigned to placebo (adjusted hazard ratio, 0.31; 95 percent confidence interval, 0.18 to 0.53; $P < 0.001$). During the follow-up period of about 10 months, 32 percent of the patients in the clarithromycin group died and 41 percent of those in the placebo group died (hazard ratio, 0.75; $P = 0.026$). In the clarithromycin group, isolates from 11 of the 19 patients with *M. avium* complex infection were resistant to clarithromycin. Prophylaxis with clarithromycin was associated with an increased incidence of taste perversion (11 percent in the clarithromycin group vs. 2 percent in the placebo group, $P < 0.001$) and rectal disorders (8 percent vs. 3 percent, $P = 0.007$); however, the frequency of more severe adverse events was similar in the two groups (7 percent and 6 percent, respectively).

Conclusions In patients with advanced AIDS, the prophylactic administration of clarithromycin is well tolerated, prevents *M. avium* complex infection, and reduces mortality. (N Engl J Med 1996;335:384-91.)

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DISSEMINATED infection with *Mycobacterium avium* complex is the most common systemic bacterial infection in advanced stages of the acquired immunodeficiency syndrome (AIDS), occurring in up to 40 percent of patients,¹ and its incidence appears to be increasing.^{2,3} Infection with *M. avium* complex pro-

duces night sweats, fever, weight loss, and diarrhea,^{1,3} and infected patients have a shorter survival than those without infection.^{4,5}

Clarithromycin is a macrolide antibiotic with demonstrated *in vitro*⁶ and *in vivo*^{7,8} activity against *M. avium* complex. Administered alone or in combination with other agents, clarithromycin reduces mycobacteremia and associated symptoms in patients with AIDS. The only drug approved by the Food and Drug Administration for the treatment of *M. avium* complex infection, clarithromycin is recommended as the main component of combination therapy.⁹

METHODS

The primary objective of this prospective, multicenter, double-blind investigation was to determine the efficacy and safety of clarithromycin in preventing disseminated infection with *M. avium* complex in patients with AIDS. A secondary objective was to examine the effect of clarithromycin on survival.

In a protocol-specified interim analysis performed when disseminated infection with *M. avium* complex had developed in 50 patients, the incidence of infection was significantly lower in the clarithromycin group than in the placebo group. Since the difference between the two groups met the predetermined criterion for terminating the trial, it was stopped.

Enrollment of Patients

Patients over 12 years of age who had human immunodeficiency virus (HIV) infection, with a positive enzyme-linked immunosorbent assay confirmed by another method, were eligible for enrollment. Women had to be nonpregnant and nonlactating. Other requirements for eligibility were an absolute CD4 T-lymphocyte count of 100 or less per cubic millimeter, at least one negative blood culture for *M. avium* complex within 30 days before randomization, a Karnofsky performance score of 50 or higher, and a life expectancy of at least six months.

Patients were excluded if they had a history of allergy or hypersensitivity to macrolides, known or suspected infection with

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M. avium complex, a degree of anemia disproportionate to the severity of the underlying illness, an absolute neutrophil count of less than 500 per cubic millimeter, a hemoglobin level of less than 8.0 g per deciliter, a platelet count of less than 50,000 per cubic millimeter, a serum creatinine level that was more than twice the upper limit of the normal range, a total bilirubin level that was more than 2½ times the upper limit of the normal range, or aminotransferase levels that were more than 10 times the upper limit of the normal range. Patients receiving treatment with terfenadine, astemizole, any antimycobacterially active drug except prophylactic isoniazid, or any investigational agent were also excluded; patients receiving ciprofloxacin or clindamycin for non-mycobacterial infections were eligible if the duration of treatment was less than 21 days.

The protocol was approved by the institutional review committee at each participating center. All patients (or their guardians) gave written informed consent after the purposes and procedures of the study had been explained.

Protocol

Patients were randomly assigned to receive clarithromycin (500 mg) or an identical-appearing placebo twice daily. (The commercial names for clarithromycin are Biaxin in the United States, Klaricid in the United Kingdom, Mavid in Germany, and Zeclar in France.) The random assignments were made with the use of a computer-generated randomization schedule. Each center had a separate schedule, with blocks of four randomly assigned study numbers; within each block, two patients were assigned to the clarithromycin group and two to the placebo group. The study drug and placebo were prepared by Abbott Laboratories (North Chicago, Ill.) or the International Development Center (Queenborough, Kent, United Kingdom). All clinicians, research assistants, and data-management personnel were unaware of the treatment assignments.

During screening visits, which were scheduled 28 to 30 days before randomization and again on the day of randomization, the patients underwent a clinical evaluation for signs and symptoms of disseminated infection with *M. avium* complex. In addition, the Karnofsky performance score was determined, and a blood culture for *M. avium* complex, a CD4 T-lymphocyte count, a complete blood count, coagulation tests, and a blood-chemistry panel were performed. Eligible patients were given a supply of the study drug and were seen eight days later and then every four weeks after randomization. At each visit, the patients underwent a clinical evaluation, compliance with the protocol was determined by pill count, and the use of concurrent drugs and the patient's medication diary were reviewed. A complete blood count and a blood culture for *M. avium* complex were performed every four weeks, with a blood chemistry panel and CD4 T-lymphocyte count performed every eight weeks.

The primary end point was the time from randomization to the detection of disseminated infection with *M. avium* complex as evidenced by a positive culture from blood or another normally sterile site. Survival was defined as the time from randomization to death from any cause.

The analysis of safety included data from all patients who received a study medication. Adverse events that occurred after the start of treatment, excluding those considered to be related solely to HIV infection, were summarized with COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms)¹⁰ and categorized according to their severity and the strength of their association with the intervention.

Cultures and Drug-Sensitivity Testing

M. avium complex was isolated on 7H11 agar, in 7H12 broth by a radiometric method, or by a combination of the two methods.¹¹ Blood cultures were performed at a central laboratory in each of the four countries with centers participating in the study: the Public Health Laboratory Service, Dulwich Hospital, in London; the Mycobacteriology Laboratory, National Jewish Center

for Immunology and Respiratory Medicine, in Denver; the Institute for Experimental Biology and Medicine, in Borstel, Germany; and the Central Laboratory for Bacteriology and Virology, Groupe Hospitalier Pitié-Salpêtrière, in Paris. Positive cultures were shipped to the Mycobacteriology Laboratory in Denver for clarithromycin-sensitivity tests of isolates in 7H12 broth, by a previously described method.¹²

Withdrawal from the Study

Patients received the assigned study medication until any of the following occurred: disseminated infection with *M. avium* complex (confirmed by a positive culture), a concurrent illness requiring antimycobacterial treatment other than isoniazid alone, evidence of noncompliance with the drug regimen (discontinuation of the study drug for more than 35 consecutive days or for more than 90 days in a 12-month period), a request for withdrawal from the study (made by the patient or the patient's physician), one or more adverse events requiring discontinuation of the study drug, or death.

Statistical Analysis

Categorical demographic variables (sex and race) were compared with use of Fisher's exact test; base-line demographic and clinical variables were compared with use of the Wilcoxon rank-sum test.

The times to the detection of *M. avium* complex infection (reported as the interval between randomization and the first positive blood culture) were compared with use of a Cox proportional-hazards model stratified according to center, with the treatment assignment as the only factor. The data from patients without infection were censored at the time of the last negative culture. Kaplan-Meier curves were also constructed with unstratified data. The assumption of a constant hazard ratio over time was assessed by calculating the logarithm of the negative logarithm of the Kaplan-Meier curves for intergroup parallelism. In the analysis of survival, all deaths were counted, including those of patients who were not receiving treatment at the time of death. The data from other patients were censored at the time of the last contact. The relation between *M. avium* complex infection and survival was analyzed with a Cox proportional-hazards model, with the base-line CD4 cell count as a fixed effect and the current CD4 cell count and positive or negative status of the most recent culture for *M. avium* complex as time-dependent effects. All computations were performed with SAS software.¹³

A sample size of 300 patients per group was planned, because calculations of the statistical power^{14,15} for the primary end point indicated that this size would yield at least an 80 percent probability of detecting a 67 percent reduction in the incidence of disseminated infection with *M. avium* complex in the clarithromycin group, as compared with the placebo group.

The protocol specified an interim analysis when the first 300 patients had completed one year of therapy or when *M. avium* complex infection had developed in 50 patients, whichever came first. Group sequential methods incorporating the Lan-DeMets use function¹⁶ corresponding to O'Brien-Fleming boundaries¹⁷ were used to preserve the statistical power.

For the analysis of adverse effects, the treatment groups were compared with use of the Mantel-Haenszel test, with the data stratified according to country (United States or other).

RESULTS

Patients

Patients were enrolled at 66 centers in the United States and Europe between November 1992 and July 1993. When the study was stopped, 111 patients were receiving clarithromycin, and 83 were receiving placebo; all were offered continued treatment in an open-label study (data not shown). Of the 682 en-

TABLE 1. BASE-LINE CHARACTERISTICS OF 682 PATIENTS WITH AIDS RANDOMLY ASSIGNED TO RECEIVE CLARITHROMYCIN OR PLACEBO.

CHARACTERISTIC	CLARITHROMYCIN GROUP (N=341)	PLACEBO GROUP (N=341)
Sex — M/F	310/31	311/30
Age — yr		
Mean	37.5	37.6
Range	22–66	20–65
Mean weight — kg	68.7	68.5
Race — white/nonwhite	290/51	295/46
Mean Karnofsky score	86.2	86.0
HIV risk factor — no. of patients (%)*		
Homosexual or bisexual	255 (75)	255 (75)
Heterosexual, engaging in unprotected sex	58 (17)	58 (17)
Intravenous drug user	54 (16)	44 (13)
Other or none	25 (7)	31 (9)
CD4 count — no. of patients		
0–10/mm ³	100	100
>10–50/mm ³	157	147
>50/mm ³	84	94
Median CD4 count/mm ³	30	25
Median CD8 count/mm ³	560	590
Mean years since diagnosis of HIV	3.9	3.8
Anemia or use of epoetin — no. of patients	30	34

*Some patients had more than one risk factor.

TABLE 2. PRIMARY REASONS FOR WITHDRAWAL FROM THE STUDY.

REASON FOR WITHDRAWAL	CLARITHROMYCIN (N=182)	PLACEBO (N=175)
	no. of patients	
Patient's request	48	53
Adverse event	51	41
Noncompliance		
Insufficient medication taken	23	23
Other	11	13
Nonprotocol medications required	9	16
Physician's request (in the best interest of the patient)	9	12
Loss to follow-up	13	8
Failure to meet enrollment criteria (noted after enrollment)	4*	0
Marked alteration in laboratory results	5	0
Other	9	9

*Two patients had CD4 cell counts above 100 per cubic millimeter at the time of screening, one took clindamycin for more than 21 days, and one was erroneously withdrawn from the study because of a contaminated blood sample. All four were included in the primary analysis.

rolled patients, 333 were from 22 U.S. centers, 175 were from 26 French centers, 138 were from 14 German centers, and 36 were from 4 English centers. Another 172 patients were ineligible: 46 had CD4 counts that were higher than 100 per cubic millimeter or undetermined, 45 withheld consent, 18 were unwilling to follow the protocol, 12 had positive cultures for *M. avium* complex at the time of screening, and 51 were ineligible for other reasons.

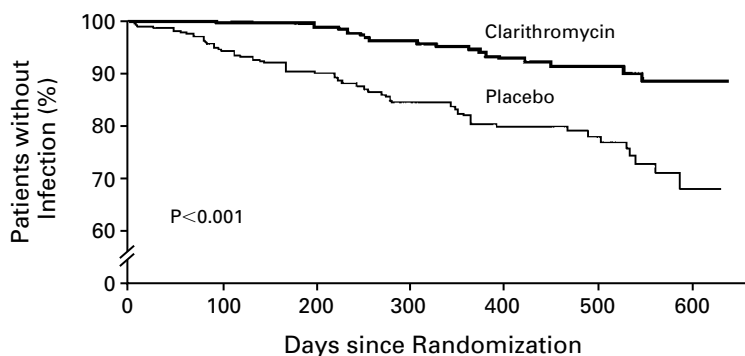
Base-line demographic characteristics and disease-related variables were similar in the two treatment groups (Table 1). At base line, the most common HIV-related conditions were oral candidiasis (in 68 percent of the patients), *Pneumocystis carinii* pneumonia (in 33 percent), hairy leukoplakia (in 24 percent), seborrheic dermatitis (in 21 percent), herpes zoster in a dermatomal distribution (in 18 percent), and other herpes simplex viral infections (in 18 percent). Other HIV-related conditions were Kaposi's sarcoma (in 10 percent of the patients), anemia (in 8 percent), cerebral toxoplasmosis (in 5 percent), and atypical mycobacteriosis (in 3 percent). There were no statistically significant differences in the incidence of HIV-related conditions in the two treatment groups. As compared with the patients in the United States, the European patients had a higher median CD8 count (630 vs. 525 per cubic millimeter), a lower incidence of intravenous drug use (12 percent vs. 17 percent), but a similar mean interval since HIV infection had been diagnosed (3.9 vs. 3.8 years).

Of the 682 patients enrolled in the study, 341 were randomly assigned to each treatment group; however, 14 were excluded from the analyses because of positive pretreatment cultures, and 1 was excluded because no pretreatment culture was available. Thus, the primary, intention-to-treat analysis included 667 patients: 333 in the clarithromycin group and 334 in the placebo group.

The mean duration of treatment was longer in the clarithromycin group than in the placebo group (10.5 vs. 9.5 months). Table 2 shows the reasons for withdrawal. The mean follow-up was 427 days in the clarithromycin group and 402 days in the placebo group. Equal proportions of patients in the two groups (12 percent in each) were lost to follow-up. On average, patients who withdrew from treatment were followed for 197 days afterward (maximal possible follow-up, 251 days).

Occurrence of *M. avium* Complex Infection

M. avium complex infections developed in 19 of the 333 patients in the clarithromycin group (6 percent) and in 53 of the 334 patients in the placebo group (16 percent) (Fig. 1). Blood cultures were positive in all but one of these patients, who had a positive bone marrow culture. Since the mean follow-up among the clarithromycin recipients was longer than that among the placebo recipients, the risk of un-



No. OF PATIENTS							
Clarithromycin	333	258	215	185	148	90	28
Placebo	334	254	199	145	111	79	20

Figure 1. Kaplan–Meier Curves for the Development of *M. avium* Complex Infection in Patients with AIDS Receiving Clarithromycin or Placebo.

The number of patients remaining in each treatment group who were free of infection at each 100-day interval is shown at the bottom of the figure.

detected *M. avium* complex infection in the placebo recipients was increased. The proportional-hazards model for the risk of *M. avium* complex infection includes adjustments for such differences.

In the clarithromycin group, the adjusted hazard ratio was 0.31 (95 percent confidence interval, 0.18 to 0.53; $P < 0.001$), representing an estimated 69 percent reduction in the risk of disseminated infection with *M. avium* complex. The risk reduction was smaller among the clarithromycin recipients in the United States than among their European counterparts (60 percent vs. 89 percent). Disseminated infection with *M. avium* complex developed in 21 percent of the U.S. placebo recipients, as compared with 11 percent of the European placebo recipients.

Most of the patients in whom *M. avium* complex infections developed had base-line CD4 counts well below the median value (Table 3). Incorporating the most recent CD4 cell count into the primary analysis reduced the hazard ratio to 0.23 (95 percent confidence interval, 0.14 to 0.44; $P < 0.001$).

Resistance to Clarithromycin

Among the 19 positive isolates from patients in the clarithromycin group, the minimal inhibitory concentration of clarithromycin was 1 μg per milliliter or less in 7 isolates, 4 μg per milliliter in 1, and 512 μg per milliliter or more in 11. In the placebo group, the minimal inhibitory concentration of clarithromycin was 1 μg per milliliter or less in 27 isolates, 2 μg per milliliter in 23, and 4 μg per milliliter in 1; 2 isolates were unavailable for testing.

All the clarithromycin recipients with drug-resistant positive isolates (minimal inhibitory concentration, $\geq 512 \mu\text{g}$ per milliliter) had base-line CD4 cell

counts of 25 per cubic millimeter or less (median, 10). Among the clarithromycin recipients with drug-sensitive positive isolates, the median base-line CD4 cell count was 25 per cubic millimeter ($P = 0.006$). The median time to the detection of disseminated infection with *M. avium* complex was 385 days among the clarithromycin recipients with drug-resistant isolates and 217 days among those with drug-sensitive isolates ($P = 0.003$). The median duration of treatment in these two groups was 12.8 and 5.5 months, respectively.

Mortality

During the treatment and follow-up periods, there were 107 deaths in the clarithromycin group (32 percent) and 137 in the placebo group (41 percent). The estimated hazard ratio was 0.75 (95 percent confidence interval, 0.58 to 0.97; $P = 0.026$), a 26 percent difference in mortality favoring the clarithromycin group. The difference in mortality between the two groups was most pronounced during the first 12 months of the study (Fig. 2). The clarithromycin-treated patients had a lower mortality rate than the placebo-treated patients in both the United States (38 percent vs. 47 percent) and Europe (26 percent vs. 35 percent). Approximately two thirds of the deaths occurred more than 30 days after the study medication had been withdrawn. The survival distributions among infected patients did not differ significantly between the two treatment groups.

The overall mortality rate among the patients with cultures that were positive for *M. avium* complex was more than double the rate among the patients with negative cultures. The hazard ratio among the

TABLE 3. RELATIVE RISK OF A POSITIVE CULTURE FOR *M. AVIUM* COMPLEX, ACCORDING TO THE MOST RECENT CD4 CELL COUNT.

CD4 COUNT (cells/mm ³)	POSITIVE CULTURE		RELATIVE RISK (95% CONFIDENCE INTERVAL)*	P VALUE
	CLARITHROMYCIN (N=19)	PLACEBO (N=53)		
	no. of patients			
0-9	11	25	3.63 (1.96-6.74)	<0.001
10-19	2	13	1.83 (0.86-3.89)	0.12
20-29	2	7		
30-39	2	6		
40-50	2	2		

*The relative risk was calculated with the Cox proportional-hazards model. The data shown are the relative risks of a positive culture, as compared with the risk among patients with CD4 counts of 20 or more per cubic millimeter.

clarithromycin recipients with positive cultures, as compared with those whose cultures remained negative, was 1.46 (95 percent confidence interval, 0.67 to 3.20; $P=0.10$); among the placebo recipients, the hazard ratio associated with a positive culture was 2.52 (95 percent confidence interval, 1.66 to 3.82; $P<0.001$). Deaths with no identifiable cause were reported as due to AIDS. There were no significant differences in the causes of death between the two treatment groups.

HIV-Related Conditions

The incidence of HIV-related conditions was similar in the two treatment groups; 283 clarithromycin recipients (85 percent) and 295 placebo recipients (89 percent) for whom data were available reported one or more such conditions. Only specific HIV-related conditions in which the P value for the difference between groups was 0.011 or less are reported here. The clarithromycin groups had significantly lower incidences of recurrent bacterial chest infections (2 percent vs. 6 percent, $P=0.002$) and giardiasis (1 percent vs. 3 percent, $P=0.011$).

During the study, 49 percent of the clarithromycin recipients and 57 percent of the placebo recipients were hospitalized, representing a risk reduction of 23 percent in the clarithromycin group (hazard ratio, 0.77; 95 percent confidence interval, 0.61 to 0.96; $P=0.020$).

Adverse Events

All patients who received study medication were included in the analysis of adverse events. Of the patients in the clarithromycin group, 91 percent reported adverse events, as compared with 88 percent of the patients in the placebo group ($P=0.59$). Ad-

verse events that were more common in the clarithromycin group were taste perversion (11 percent, vs. 2 percent in the placebo group; $P<0.001$) and rectal disorders (8 percent vs. 3 percent, $P=0.007$). The overall incidence of severe adverse events was 32 percent in both groups.

Significantly more clarithromycin recipients (42 percent) than placebo recipients (26 percent) had adverse events that were possibly, probably, or definitely related to the administration of the study drug and unrelated to any concurrent condition ($P<0.001$). Within this category of adverse events, the clarithromycin group, as compared with the placebo group, had significantly higher incidences of digestive disturbances (28 percent vs. 18 percent, $P=0.004$) and taste perversion (8 percent vs. 0.3 percent, $P<0.001$). The incidence of severe treatment-related adverse events was similar in the two groups: 7 and 6 percent, respectively.

Eighteen percent of the clarithromycin recipients withdrew from the study because of adverse events, as compared with 17 percent of the placebo recipients. In 8 percent of the clarithromycin group and in 6 percent of the placebo group, the study medication was discontinued because of adverse events considered to be possibly, probably, or definitely related to the administration of the study drug ($P=0.45$). Similar proportions of patients in the two groups withdrew from the study because of adverse events from any cause, whether or not it was related to administration of the study drug.

DISCUSSION

Our results indicate that prophylactic treatment with clarithromycin reduces the incidence of disseminated infection with *M. avium* complex in patients with advanced AIDS. Such treatment is also associated with a reduced rate of hospitalization and a reduced incidence of certain complications of HIV infection. This randomized, double-blind trial shows that the prevention of *M. avium* complex infection can prolong survival in patients with AIDS.

Nightingale and colleagues¹⁸ reported that the administration of rifabutin reduced the incidence of *M. avium* complex infection and concomitant symptoms in patients with AIDS but did not appear to prolong survival. A Public Health Service task force⁹ subsequently recommended rifabutin prophylaxis in patients with CD4 counts below 100 per cubic millimeter. The task force expressed concern, however, about the efficacy, cost, and potential toxicity of such treatment, as well as the risk of drug interactions. As a result, many physicians have not routinely used rifabutin prophylaxis. In a post hoc analysis of the two controlled trials reported by Nightingale et al., Moore and Chaisson¹⁹ combined these results with those of the subsequent open-label trial. Although the patients who received open-label rifabu-

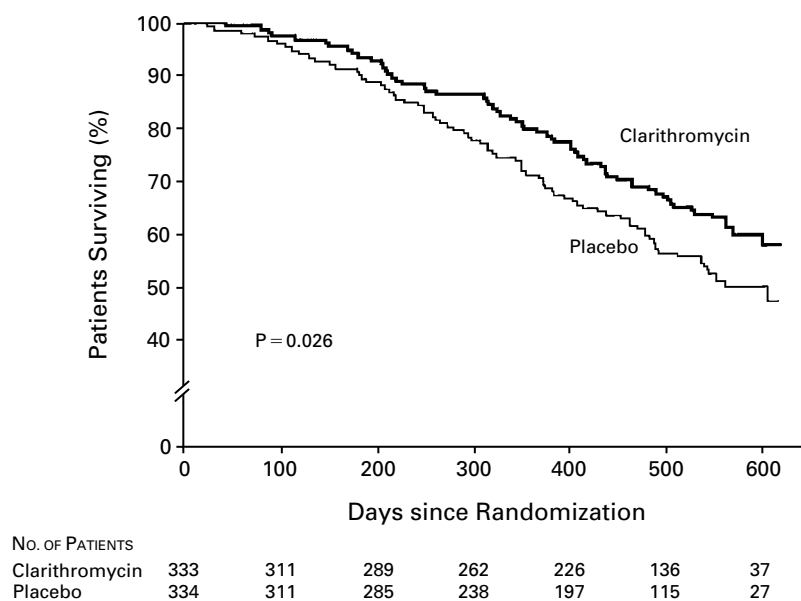


Figure 2. Kaplan-Meier Survival Curves for the Clarithromycin and Placebo Groups.

The number of patients remaining in each treatment group at each 100-day interval is shown at the bottom of the figure.

tin may have had a better initial prognosis than those who did not, on the basis of adjusted analyses, the authors concluded that rifabutin did confer a statistically significant survival advantage.

In our analysis, prophylaxis with clarithromycin was associated with prolonged survival in all CD4-count strata and in both American and European patients. One could argue that prophylaxis may be a less effective approach than active surveillance combined with aggressive therapy. Our data, however, do not support this position. Even with active surveillance in both treatment groups, including regular follow-up visits and cultures, as well as treatment at the discretion of the patient's physician, the clarithromycin group still had a markedly better outcome. Why prophylaxis is more effective than surveillance and treatment of emergent disease is unclear. Activated cytokines and an increased viral load, which have been demonstrated in HIV-infected patients with *M. avium* complex infection,²⁰ may adversely affect survival, thus favoring the preventive strategy. Although the median survival among patients with effectively treated *M. avium* complex infections is longer than that among untreated patients,^{4,5} no one has demonstrated that patients with treated infections survive as long as those without infections. *M. avium* complex infection is now recognized as a predictor of mortality in patients with AIDS.^{21,22}

The results of our study suggest that clarithromy-

cin also suppresses other common infections in patients with AIDS, such as pneumonia and giardiasis. This may be due either to the direct effect of clarithromycin or to its ability to improve general health by preventing disseminated infection with *M. avium* complex.

One concern about clarithromycin prophylaxis is the possible development of resistance to the antibiotic in positive isolates. Eleven of the 19 clarithromycin recipients who contracted *M. avium* complex infections had drug-resistant isolates. The patients with drug-resistant isolates tended to have very low base-line CD4 counts (<30 cells per cubic millimeter) and were likely to have a positive culture later than the patients with drug-sensitive isolates. Despite the resistance to clarithromycin that developed in some patients, mortality was still lower in the clarithromycin group than in the placebo group. Survival after the emergence of disseminated infection with *M. avium* complex was similar in the two groups. Because *M. avium* complex is acquired from environmental sources and not spread from person to person,²³ resistance to clarithromycin is a potential problem only among patients currently being treated with the drug; drug resistance is not transmitted from one patient with AIDS to another.

Our study shows that clarithromycin is well tolerated in patients with advanced AIDS. Although the incidence of adverse events thought to be related to the administration of the study drug was higher in

the clarithromycin group than in the placebo group, most of the events were those that would be expected with the use of any macrolide antibiotic: digestive problems and taste perversion. The clarithromycin recipients were no more likely to have severe adverse events or to withdraw from the study than the placebo recipients.

A task force recently formed to evaluate pharmacotherapy in patients with AIDS has recommended that the threshold for prophylactic treatment be lowered to a CD4 cell count of 50 to 75 per cubic millimeter and that clarithromycin be considered as an alternative to rifabutin.²⁴ Our data suggest that clarithromycin should be viewed as at least an equivalent therapeutic choice, since it confers a clear survival benefit and reduces the risk of disseminated infection with *M. avium* complex.

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APPENDIX

The following investigators enrolled patients in the clinical trial: H. Albrecht, Universitätsklinikum Eppendorf, Hamburg, Germany; T. Allegre, Centre Hospitalier General, Aix-en-Provence, France; K. Arasteh, Auguste-Victoria-Krankenhaus, Berlin, Germany; J.-C. Auvergnat, Hôpital Purpan, Toulouse, France; P. Balmes, Centre Hospitalier Universitaire, Nîmes, France; G. Bauer, Berlin, Germany; A. Berry, Audie Murphy Memorial Veterans Hospital, San Antonio, Tex.; E. Bouvet, Groupe Hospitalier Bichat-Claude Bernard, Paris; J.-P. Breux, Hôpital Jean Bernard, Poitiers, France; J.-P. Bru, Centre Hospitalier d'Annecy, Annecy, France; P. Canton, Hôpital de Brabois, Vandoeuvre-lès-Nancy, France; P. Chavanet, Hôpital du Bocage, Dijon, France; T. Chew, St. Francis Memorial Hospital, San Francisco; C. Chouaïd, Hôpital Saint-Antoine, Paris; J.J. Cocheton, Hôpital Tenon, Paris; C. D'Hiver, Hôpital Sainte-Marguerite, Marseille, France; B. Dautzenberg, Groupe Hospitalier Pitié-Salpêtrière, Paris; J. Desrués, Centre Hospitalier de Gonesse, Gonesse, France; C. Drobacheff, Centre Hospitalier Régional Saint-Jacques, Besançon, France; C. Duvivier, Hôpital Saint-Antoine, Paris; M. Eliaszewicz, Hôpital de l'Institut Pasteur, Paris; G. Fätkenheuer, Universitätsklinikum Köln, Cologne, Germany; W.J. Fessel, Kaiser Permanente Medical Center, San Francisco; K. Fife, Indiana University Hospital, Indianapolis; G. Force, Hôpital du Perpétuel Secours, Levallois-Perret, France; D. Garner, Veterans Affairs Medical Center, Salem, Va.; B. Gazzard, Chelsea and Westminster Hospital, London; M. Goos, Universitätsklinikum Essen, Essen, Germany; H.D. Heil, Berlin, Germany; H. Jäger, Munich, Germany; M. Johnson, Royal Free Hospital, London; J.R. Kalden, Universitätsklinikum Erlangen, Erlangen, Germany; C. Kemper, Santa Clara Valley Hospital and Medical Center, San Jose, Calif.; H. Knechten, Aachen, Germany; A. Lafeuillade, Hôpital Chalucet, Toulon, France; C.J. Lahart, Veterans Affairs Medical Center, Houston; C. Lee, Royal Free Hospital, London; G. Leoung, St. Francis Memorial Hospital, San Francisco; S. Loss, University of Texas Southwestern Medical Center, Dallas; M. Loveless, Westover Heights Clinic, Portland, Oreg.; T. May, Hôpital de Brabois, Vandoeuvre-lès-Nancy, France; J.M. McCarty, California Medice

search Group, Fresno; J.-L. Meynard, Hôpital Saint-Antoine, Paris; D. Pearce, HIV Research Group, San Diego, Calif.; E. Petersen, University of Arizona Health Science Center, Tucson; D. Peterson, University of Texas Southwestern Medical Center, Dallas; A. Pozniak, King's College Hospital, London; P. Puchot, Fondation L.J. Engelmaier, Saint-Paul-sur-Save, France; D. Quinsat, Centre Hospitalier Général de la Fontonne, Antibes, France; F. Raffi, Centre Hospitalier Universitaire Hôtel-Dieu, Nantes, France; B. Ruf, Universitätsklinikum Rudolf Virchow, Berlin, Germany; T. Saint-Marc, Hôpital Edouard-Herriot, Lyon, France; D. Salmon, Hôpital Cochin, Paris; S. Sargent, Regional Medical Center at Memphis, Memphis, Tenn.; M. Sheran, St. Vincent's Hospital and Medical Center, New York; A.D. Tice, Infections Limited, Tacoma, Wash.; R. Torres, St. Vincent's Hospital and Medical Center, New York; C. Trepo, Hôpital Hôtel-Dieu, Lyon, France; A. Trylesinski, Centre Hospitalier de Gonesse, Gonesse, France; A. Ullmann, St. Josef's Hospital, Bochum, Germany; A. Ulmer, Stuttgart, Germany; P. Veysier, Centre Hospitalier de Compiègne, Compiègne, France; N. Zide, Hollywood, Fla.; and W. Zidek, Universitätsklinikum Münster, Münster, Germany.

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