

**A COMPARISON OF TWO REGIMENS FOR THE TREATMENT  
OF *MYCOBACTERIUM AVIUM* COMPLEX BACTEREMIA IN AIDS:  
RIFABUTIN, ETHAMBUTOL, AND CLARITHROMYCIN VERSUS RIFAMPIN,  
ETHAMBUTOL, CLOFAZIMINE, AND CIPROFLOXACIN**

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**ABSTRACT**

**Background** Bacteremia with the *Mycobacterium avium* complex is common in patients with the acquired immunodeficiency syndrome (AIDS), but the most effective treatment for this infection remains unclear.

**Methods** We randomly assigned 229 patients with AIDS and *M. avium* complex bacteremia to receive either rifampin (600 mg daily), ethambutol (approximately 15 mg per kilogram of body weight daily), clofazimine (100 mg daily), and ciprofloxacin (750 mg twice daily) (the four-drug group) or rifabutin (600 mg daily), ethambutol (as above), and clarithromycin (1000 mg twice daily) (the three-drug group). In the three-drug group the dose of rifabutin was reduced by half after 125 patients were randomized, because 24 of 63 patients had uveitis.

**Results** Among 187 patients who could be evaluated, blood cultures became negative more often in the three-drug group than in the four-drug group (69 percent vs. 29 percent,  $P < 0.001$ ). Among patients treated for at least four weeks, the bacteremia resolved more frequently in the three-drug group (78 percent vs. 40 percent,  $P < 0.001$ ). In the three-drug group, bacteremia resolved more often with the 600-mg dose of rifabutin than with the 300-mg dose ( $P = 0.025$ ), but the latter regimen was more effective than the four-drug regimen ( $P < 0.05$ ). The median survival was 8.6 months in the three-drug group and 5.2 months in the four-drug group ( $P = 0.001$ ). The median Karnofsky performance score was higher in the three-drug group than in the four-drug group from week 2 to week 16 ( $P < 0.05$ ). Mild uveitis developed in 3 of the 53 patients receiving the 300-mg dose of rifabutin, an incidence about one quarter that observed with the 600-mg dose ( $P < 0.001$ ).

**Conclusions** In patients with AIDS and *M. avium* complex bacteremia, treatment with the three-drug regimen of rifabutin, ethambutol, and clarithromycin leads to resolution of the bacteremia more frequently and more rapidly than treatment with rifampin, ethambutol, clofazimine, and ciprofloxacin, and survival rates are better. (N Engl J Med 1996;335:377-83.)

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**D**ISSEMINATED *Mycobacterium avium* complex infection is the most common opportunistic bacterial infection in adults infected with the human immunodeficiency virus (HIV).<sup>1,2</sup> It has an annual incidence of approximately 20 percent after the occurrence of a first event defining the presence of the acquired immunodeficiency syndrome (AIDS).<sup>3</sup> Although disseminated *M. avium* complex disease appears late in the course of HIV disease,<sup>1,2</sup> it is an independent predictor of mortality, even after adjustment for the CD4 lymphocyte count.<sup>4,5</sup> Treating *M. avium* complex bacteremia can lead to both clinical and bacteriologic improvement.<sup>1,2,6-8</sup> Several retrospective studies<sup>9-12</sup> and one prospective, nonrandomized study<sup>13</sup> have shown increased survival with treatment.

Clarithromycin is the most active drug used to treat *M. avium* complex.<sup>14</sup> Despite initial clinical and bacteriologic improvement with clarithromycin monotherapy, relapses with resistant strains are frequent.<sup>14,15</sup> Accordingly, multidrug regimens have been proposed to lower the rate of relapse. A promising agent to consider in combination therapy is rifabutin, since it is effective in both the prophylaxis<sup>16</sup> and the treatment<sup>17,18</sup> of *M. avium* complex bacteremia. As monotherapy, ethambutol reduces the circulating load of *M. avium* complex bacteria somewhat, whereas clofazimine and rifampin are ineffective.<sup>19</sup>

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Hence, we chose the combination of clarithromycin, rifabutin, and ethambutol as a candidate regimen. When our study began in 1992, the recommended regimen was rifampin, ethambutol, clofazimine, and ciprofloxacin.<sup>8,20,21</sup> We conducted a randomized trial comparing rifabutin, ethambutol, and clarithromycin with the four-drug standard regimen to treat AIDS-associated *M. avium* complex bacteremia.

## METHODS

### Study Patients

This study was conducted in 24 HIV clinics in 16 Canadian cities. The study was approved by the ethics committee at each center, and each participant gave informed consent. The study participants were at least 16 years old, were HIV-seropositive, and had mycobacteremia. Patients with non-*M. avium* complex mycobacteremia were excluded from the study. Other criteria for exclusion from the study were previous therapy for *M. avium* complex; the use of drugs active against *M. avium* complex during the preceding four weeks (excluding prophylaxis with rifabutin); the concomitant use of corticosteroids to treat symptoms of *M. avium* complex infection; a Karnofsky performance score below 20; the anticipation of death within six weeks; a creatinine level greater than 2.8 mg per deciliter (250  $\mu$ mol per liter); an aspartate aminotransferase level more than five times the upper limit of normal; a total bilirubin level greater than 2.9 mg per deciliter (50  $\mu$ mol per liter); allergy to a study drug; and pregnancy, lactation, or the nonuse of contraception (by a woman of childbearing potential). The principal investigator could authorize exemptions when there were minor deviations from the criteria for inclusion and exclusion.

### Base-Line Evaluation and Mycobacteriologic Cultures

Each patient had a medical history taken and a physical examination performed. Blood counts and a biochemical profile were obtained, and two blood samples were collected for quantitative mycobacterial culture. The patient's Karnofsky performance score<sup>22</sup> was assessed, and each patient completed a 45-item medical-outcome survey that was adapted for HIV (the MOS-HIV)<sup>23</sup> and modified for disseminated *M. avium* complex infection. Blood was collected in tubes containing sodium polyanetholesulfonate and transported by courier to the central laboratory, where it was lysed, centrifuged, resuspended in bovine serum albumin, inoculated on Middlebrook 7H11 agar, and incubated at 37°C in 5 percent carbon dioxide.<sup>24</sup> Blood was also cultured radiometrically in vials containing Bactec 12B medium (Becton Dickinson Diagnostic Instrument Systems, Sparks, Md.). The speciation of *M. avium* complex was confirmed by the DNA-RNA hybridization technique (AccuProbe, Gen-Probe, San Diego, Calif.).

### Study-Drug Therapy

At each institution, patients were randomized in permuted blocks, with variable blocks of two and four patients. The patients were stratified before randomization according to whether they had previously received prophylaxis with rifabutin for at least seven days.

The three-drug regimen included clarithromycin (1000 mg twice daily), rifabutin (600 mg daily), and ethambutol. Ethambutol was given once daily in a dose based on the patient's weight: 800 mg for patients weighing less than 60 kg, 1200 mg for patients weighing 60 to 80 kg, and 1600 mg for patients weighing more than 80 kg. On November 24, 1993, the dose of rifabutin was reduced to 300 mg daily because of the unexpected and frequent occurrence of uveitis in the three-drug group<sup>25</sup>; rifabutin was discontinued permanently in the patients with uveitis. The four-drug regimen included rifampin (600 mg daily), clofazimine

(100 mg daily), ciprofloxacin (750 mg twice daily), and ethambutol given as described above. All the study medications were given on an open-label basis.

The patients' conditions were reassessed at weeks 2, 4, 8, 12, and 16. They were permitted to continue taking the study medication indefinitely beyond week 16.

### Assessment of Efficacy

The patients were randomized and the data managed at the National Centre of the Canadian HIV Trials Network. The analysis of efficacy included patients who met the criteria for eligibility and whose base-line blood cultures grew *M. avium* complex at the central laboratory. In the primary analysis, the study regimens were compared with respect to the proportion of patients whose blood was sterilized — that is, the proportion with two or more consecutive negative blood cultures during the 16 weeks after randomization, provided that no drugs active against *M. avium* complex other than the study drugs were given. A blood culture positive for *M. avium* complex after sterilization constituted a relapse. Patients whose blood did not become sterilized were considered to have had treatment failure, even if they discontinued therapy before four weeks.

The principal secondary outcomes were survival and changes in symptoms, as assessed by the eight questions on the MOS-HIV most specific for *M. avium* complex infection: those about fever or chills, night sweats, fatigue or malaise, nausea or anorexia, diarrhea, bodily pain, abdominal pain, and red rash or itching. Each symptom was scored on a scale from 1 to 5. The median changes from base line in the sum of the eight symptoms were compared between groups at each follow-up assessment. If patients missed an assessment, their data were excluded from that follow-up, but if they died, the worst score possible was assigned. Because the dose of rifabutin was cut in half at approximately the midpoint of the study, it was possible to compare the two subgroups of patients initially receiving the two doses of rifabutin.

### Statistical Analysis

The chi-square test was used to compare the groups with respect to the clearance of bacteremia. A logistic-regression model was used to estimate the effect of treatment after adjustment for important base-line variables. The Breslow-Day statistic<sup>26</sup> was used to assess the homogeneity of the treatment effect before and after the reduction in the rifabutin dose. Survival rates were compared by the log-rank test. Scores on the MOS-HIV symptom subscales and Karnofsky performance scores were compared by Wilcoxon tests of the change in the score at each assessment.

The incidence of adverse events was compared between groups by the chi-square test. When the results were statistically significant (or close thereto), further comparisons were made with time-to-event methods, including log-rank tests.

An interim analysis of the primary outcome was conducted after approximately half the patients had been randomized. This analysis used an O'Brien-Fleming<sup>27</sup> approach in which significance was tested at the 0.005 level in the interim analysis and at the 0.048 level in the final analysis. The interim analysis was evaluated by the Safety and Efficacy Review Committee of the Canadian HIV Trials Network.

## RESULTS

### Characteristics of the Patients

Between November 1992 and January 1995, 229 patients were enrolled in the study. Eight patients were excluded: four had non-*M. avium* complex mycobacteremia, two received antimycobacterial therapy for at least two weeks during the month before randomization, one was allergic to ciprofloxacin, and one was receiving prednisone. Seven of the remain-

ing 221 patients, 4 of them in the four-drug group, were enrolled with minor exemptions from the criteria for exclusion: 3 had slight elevations of aspartate aminotransferase, 3 had received anti-*M. avium* complex therapy for less than three days in the month before enrollment, and 1 had received prednisone for seven days before enrollment. Of the 221 eligible patients whose blood cultures grew *M. avium* complex in a local laboratory, 34 (15 percent) had negative base-line cultures at the central laboratory. The 187 patients who could be evaluated bacteriologically are described here.

The patients' mean age was 38 years, and the median CD4 lymphocyte count in both groups was 10 cells per cubic millimeter (Table 1). Most patients were homosexual men, as was reflective of the demographics of Canadian patients with AIDS during the study period. The two groups were balanced with respect to sex, HIV-transmission category, mycobacterial load, hemoglobin level, alkaline phosphatase level, and Karnofsky performance score. A history of *Pneumocystis carinii* pneumonia was more common in the four-drug group (62 percent, vs. 47 percent in the three-drug group;  $P=0.05$ ), and more patients in the three-drug group were receiving concurrent prophylaxis against *P. carinii* (93 percent vs. 79 percent,  $P<0.01$ ).

Permanently stopping treatment with at least two of the assigned medications constituted a discontinuation of treatment. The median times to such a discontinuation were 127 days in the three-drug group and 68 days in the four-drug group ( $P<0.001$ ). The most common reason for the discontinuation of treatment was a request by the patient, and the next most common was a switch to palliative care when death was imminent. Drug toxicity necessitated a permanent discontinuation of treatment within 16 weeks in two patients in the three-drug group and six in the four-drug group.

#### Efficacy of Bacteriologic Clearance

*M. avium* complex bacteremia was cleared in 69 percent of the patients in the three-drug group and 29 percent in the four-drug group ( $P<0.001$ ) (Fig. 1). Adjustment by logistic regression for important prognostic factors, including prior prophylaxis with rifabutin, did not alter the outcome. The rapidity of blood sterilization differed between treatment groups. Among patients whose blood was sterilized, 87 percent of those in the three-drug group reached this outcome by week 4, as compared with 54 percent of those in the four-drug group ( $P<0.001$ ).

Because sterilization required at least four weeks of treatment, we performed a secondary analysis of patients treated through week 4. It is noteworthy that 89 percent of the patients in the three-drug group remained in the study until this point, as compared with only 72 percent of those in the four-

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS WHO COULD BE EVALUATED.

VARIABLE*	THREE-DRUG GROUP (N=97)	FOUR-DRUG GROUP (N=90)
Mean ( $\pm$ SD) age (yr)	38 $\pm$ 7.9	38 $\pm$ 7.4
Male sex (%)	95	92
Men who have sex with men (%)	81	84
CD4 count (cells/mm <sup>3</sup> )		
Median	10	10
Interquartile range	2-14	2-14
$\leq$ 30 CD4 cells/mm <sup>3</sup> (%)	91	92
Hemoglobin (g/dl)		
Median	9.6	9.5
Interquartile range	8.4-11.0	8.8-10.6
MAC (CFU/ml of blood)		
Median	15	15
Interquartile range	3-80	4-125
MAC as an AIDS-defining event (%)	21	14
Karnofsky performance score		
Mean	67	67
Interquartile range	60-80	60-80
<i>P. carinii</i> pneumonia (%)		
Previous	47	62 <sup>†</sup>
Current prophylaxis	93	79 <sup>‡</sup>
Current antiretroviral therapy (%)	33	36
Prior rifabutin prophylaxis (%)§	22	24

\*MAC denotes *M. avium* complex, and CFU colony-forming units. Interquartile ranges are the ranges from the 25th to the 75th percentiles of the values obtained.

<sup>†</sup> $P=0.05$  for the comparison with the three-drug group.

<sup>‡</sup> $P<0.01$  for the comparison with the three-drug group.

§Prophylaxis with rifabutin for at least seven days before randomization was the criterion used in stratifying the study patients.

drug group ( $P=0.004$ ). This restricted analysis also showed the superior efficacy of the three-drug regimen, with sterilization of blood achieved in 78 percent of patients, as compared with 40 percent in the four-drug group ( $P<0.001$ ).

We compared the magnitude of the treatment effect before and after the adjustment of the rifabutin dose. Before the adjustment, 41 of 52 patients in the three-drug group (79 percent) had clearance of *M. avium* complex bacteremia, as compared with 10 of 46 patients in the four-drug group (22 percent) (Fig. 2). After the adjustment, 26 of 45 patients in the three-drug group (58 percent) had clearance, as compared with 16 of 44 patients in the four-drug group (36 percent) (Fig. 2). The effect of treatment was greater before the dose adjustment than after it ( $P=0.008$ ). We also directly compared the rates of clearance before and after the adjustment among patients in the three-drug group; there was significantly more clearance with the 600-mg dose ( $P=0.03$ ). A logistic-regression model adjusting for previous prophylaxis with rifabutin and the log count of bacteria in the blood at base line found a similar trend ( $P=0.05$ ). Among the patients with clearance of their bacteremia

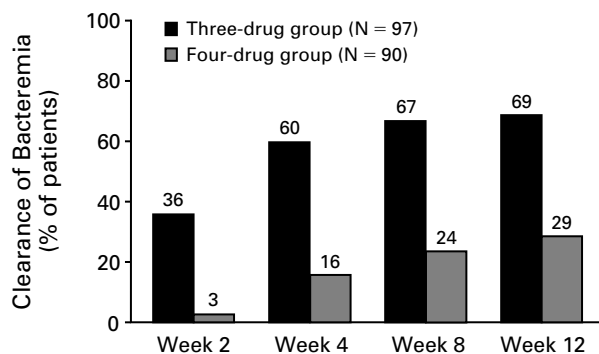
mia, the proportions whose blood was sterilized were 61 percent with the high dose of rifabutin and 38 percent with the low dose ( $P=0.07$ ) at two weeks; after four weeks, these proportions were 95 percent and 73 percent, respectively ( $P=0.01$ ). The only relapse during the 16-week period occurred at week 12 in a patient in the four-drug group whose blood was sterilized at week 4.

**Survival**

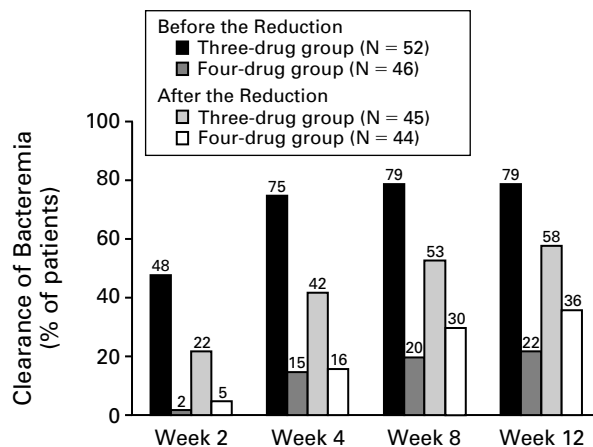
Kaplan–Meier curves for survival are shown in Figure 3. The median survival of the patients in the three-drug group was 8.6 months, as compared with 5.2 months for the patients in the four-drug group ( $P=0.001$ ). A proportional-hazards model with adjustment for important base-line covariates (including prior prophylaxis with rifabutin) yielded similar results. Of the 187 patients who could be evaluated, only 4 were lost to follow up with respect to survival — 3 in the three-drug group and 1 in the four-drug group. The magnitude of the effect of treatment with regard to survival was essentially the same in the patients randomized before the dose adjustment and those randomized after it, with median advantages for survival in the three-drug group of 90 and 92 days, respectively. Furthermore, an intention-to-treat analysis of all 229 randomized patients also demonstrated a survival advantage in the three-drug group ( $P=0.002$ ).

**Symptoms**

When the eight MOS-HIV symptom scores were totaled, there was a significantly greater median change from base line in the three-drug group at week 12 ( $P=0.03$ ), and there were trends favoring that group at weeks 2 and 16 ( $P<0.10$ ). The magnitude of the effect ranged from three to five points on the survey. There was no apparent difference be-



**Figure 1.** Clearance of *M. avium* Complex Bacteremia over Time. The bars show the percentages of patients in each treatment group in whom the blood culture was sterile at each time point. The numbers above the bars are percentages of patients.



**Figure 2.** Clearance of *M. avium* Complex Bacteremia over Time, before and after November 24, 1993, When the Rifabutin Dose in the Three-Drug Group Was Reduced by Half.

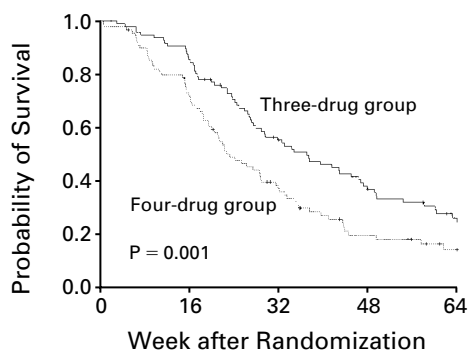
The bars show the percentages of patients in each treatment group in whom the blood culture was sterile at each time point according to treatment group, before and after the reduction of the daily dose of rifabutin from 600 mg to 300 mg. Treatment remained the same in the four-drug group. The numbers above the bars are percentages of patients.

tween the high and low doses of rifabutin with regard to these trends. There was no significant difference between treatment groups with respect to the resolution of fever or diarrhea, but there was significantly less weight loss in the three-drug group by week 8 (0.5 kg, vs. 2.5 kg in the four-drug group;  $P=0.005$ ). There was no significant difference between groups in the normalization of hemoglobin or alkaline phosphatase levels.

There were significant differences in the Karnofsky performance score that favored the three-drug group at all weeks after base line ( $P<0.05$ ; median difference at week 16, 20 points). The proportions of patients whose changes in this variable exceeded the median change at 16 weeks were compared according to treatment assignment and rifabutin dose. The magnitude of the effect did not differ significantly according to the rifabutin dose ( $P=0.15$ ).

**Adverse Events**

The most noteworthy adverse event was the development of uveitis, which occurred exclusively in the three-drug group. In addition to the uveitis that developed in 23 of 63 patients in the group that received 600 mg of rifabutin daily,<sup>25</sup> a 24th patient was found to have uveitis on further review. The onset of uveitis occurred a median of 42 days after the start of treatment and first appeared on day 25. Among the 53 patients randomly assigned to receive 300 mg of rifabutin daily, only 3 had uveitis, with the earliest case appearing on day 77. The Kaplan–



NO. OF PATIENTS AT RISK/NO. OF EVENTS  
IN NEXT 16-WEEK PERIOD

Three-drug group	14/97	28/82	16/48	9/30	10/15
Four-drug group	25/90	31/63	12/29	3/13	5/6

**Figure 3.** Kaplan-Meier Survival Curves for the Study Patients. The curves show the survival of the 187 patients who could be evaluated, according to treatment group. The patients in the three-drug group had a 65 percent longer median survival (8.6 vs. 5.2 months,  $P=0.001$  by the log-rank test).

Meier estimates of the cumulative risk of uveitis at seven months were 48 percent with high-dose rifabutin and 13 percent with the low dose ( $P<0.001$  by the log-rank test).

Since the relation between the study treatments and uveitis was not understood early in the study, most patients who had uveitis with 600 mg of rifabutin daily continued to take that dose for a considerable time. Only 4 of the 24 patients discontinued rifabutin treatment within two weeks after the onset of symptoms, and 15 patients continued to take the drug for at least seven more weeks. The median duration of uveitis in these 24 patients was 6.5 weeks, as compared with 6 days in the 3 patients receiving 300 mg of rifabutin daily who had uveitis, all of whom discontinued the drug when the uveitis was diagnosed.

There was no significant difference between treatment groups in the incidence of other clinical adverse effects, except for alterations in taste, which occurred in nine patients in the three-drug group as compared with one patient in the four-drug group ( $P=0.02$ ). Elevations of serum lactate dehydrogenase levels were significantly more frequent in the four-drug group ( $P=0.02$ ), with 24 cases of grade 1 or 2 toxicity (as defined by the National Institute of Allergy and Infectious Diseases) and 2 cases of grade 3 or 4 toxicity, as compared with 16 cases and no cases, respectively, in the three-drug group.

## DISCUSSION

In this randomized trial comparing treatments for AIDS-associated *M. avium* complex bacteremia, blood was sterilized significantly more often and

more rapidly with the three-drug regimen of rifabutin, ethambutol, and clarithromycin than with the four-drug regimen of rifampin, ethambutol, clofazimine, and ciprofloxacin, and the three-drug regimen improved median survival by 65 percent. The patients in the three-drug group also had significantly better Karnofsky performance scores and reductions in the severity of *M. avium* complex symptoms. The patients in the three-drug group were treated significantly longer than those in the four-drug group. Nevertheless, among patients treated for at least four weeks, those in the three-drug group were significantly more likely to have sterile blood cultures.

The initial rifabutin dose of 600 mg was associated with an unacceptably high incidence of uveitis. Because the association was not recognized at first, most patients continued to receive rifabutin after the onset of uveitis. Once the association was seen, the dose of rifabutin was halved to 300 mg daily, and the incidence of uveitis decreased significantly. The three cases of uveitis that developed after the dose reduction occurred relatively late and were mild, probably because rifabutin therapy was discontinued as soon as they were diagnosed. The incidence of rifabutin-associated uveitis depends on the dose and the patient's weight,<sup>28</sup> and the condition is easily treated by discontinuing the rifabutin and administering a short course of corticosteroid eye drops, usually supplemented with mydriatic eye drops.

To our knowledge, no results of randomized, comparative trials of multidrug therapy for *M. avium* complex disease have been reported. In 1991, two major reviews recommended the four-drug regimen we used.<sup>20,21</sup> In 1993, one year after our study began, several authorities recommended clarithromycin plus at least one other drug,<sup>1,2,29</sup> in the hope that the additional drug or drugs would improve the rate of blood sterilization and reduce the rate of resistance by mycobacteria.

In our study, no patient in the three-drug group had a relapse of *M. avium* complex bacteremia within 16 weeks. In contrast, Chaisson et al. reported that among patients receiving clarithromycin monotherapy, resistance to that drug developed within 12 weeks in 21 percent and developed eventually in 46 percent.<sup>14</sup> Our data suggest that adding rifabutin and ethambutol to clarithromycin therapy reduces the incidence of clarithromycin resistance in patients with *M. avium* complex disease, as is consistent with the findings of May et al., who reported significantly less acquired resistance to clarithromycin in patients receiving clarithromycin, rifabutin, and ethambutol than in those receiving clarithromycin and clofazimine.<sup>30</sup> Alternatively, the low rate of relapse in our patients could be explained by low base-line mycobacterial loads. Previous studies have shown an inverse relation between the mycobacterial load before

treatment and the time to relapse in patients receiving clarithromycin monotherapy.<sup>14,15</sup> The median base-line mycobacterial blood load reported by Chaisson et al.<sup>14</sup> ranged from 456 to 610 colony-forming units per milliliter, but in our study it was only 15 colony-forming units per milliliter.

The relative contributions of clarithromycin, rifabutin, and ethambutol in our study cannot be determined from our data. The higher dose of rifabutin in the first half of the study was associated with improved bacteriologic outcomes, but median survival was unaffected. Although the initial three-drug regimen was associated with an unacceptable incidence of uveitis, the rapid blood sterilization associated with the higher dose of rifabutin suggests a strategy of giving 600 mg of rifabutin daily for two to four weeks and then reducing the dose to 300 mg daily.

The optimal dose of clarithromycin to treat *M. avium* complex infection is unknown. We evaluated a dose of 1000 mg twice daily on the basis of the preliminary results reported by Chaisson et al.,<sup>31</sup> who compared three doses of clarithromycin monotherapy. These results indicated that a dose of 2000 mg twice daily was associated with unacceptable gastrointestinal effects and that 1000 mg twice daily sterilized the blood more rapidly than 500 mg twice daily, whereas the tolerability of those regimens was similar. We were unaware of subsequent data that showed lower mortality during the first 12 weeks with a dose of 500 mg twice daily.<sup>14</sup> More recently, a randomized trial of combination therapy for *M. avium* complex bacteremia was modified when an interim analysis showed better survival with 500 mg of clarithromycin twice daily than with 1000 mg twice daily.<sup>32</sup> The dose of clarithromycin currently approved for the treatment of *M. avium* complex infection in the United States and Canada is 500 mg twice daily. Recently, two-way interactions between clarithromycin and rifabutin have been demonstrated.<sup>33-35</sup> Rifabutin reduces serum clarithromycin concentrations by about half.<sup>33-35</sup> Thus, a dose of 1000 mg of clarithromycin twice daily combined with rifabutin could be expected to achieve a serum clarithromycin concentration similar to that obtained with 500 mg of clarithromycin twice daily but no rifabutin. With clarithromycin treatment, the area under the plasma concentration–time curve of rifabutin is increased by 77 percent, and that of LM 565, the active metabolite of rifabutin, is increased by 236 percent.<sup>34</sup> The increased serum concentrations of rifabutin, LM 565, or both in the presence of clarithromycin may account for the higher risk of uveitis when rifabutin and clarithromycin are given together.

An important limitation of our study is the lack of double blinding. Because we evaluated six drugs, double blinding would have required using a placebo to correspond to each of the five medications

other than ethambutol. We thought this would be impractical, because of the many drugs these patients were receiving. Since the laboratory personnel were unaware of the treatment assignments, it is unlikely that double blinding would have affected the primary outcome. Nevertheless, the lack of blinding could have introduced bias at both the level of the patient and that of the investigator, possibly accounting for the more rapid discontinuation of therapy in the four-drug group. However, after discontinuation, the patients and their physicians could select any regimen to treat *M. avium* complex infection. Therefore, it is likely that patients in the four-drug group who discontinued treatment early would receive alternate therapy that would reduce the true survival advantage in the three-drug group.

Another limitation of the study is the fact that no centrally processed blood cultures were collected beyond 16 weeks. At the outset of the study, acquired drug resistance was largely a theoretical problem. By the time acquired resistance to clarithromycin was demonstrated, our study was well under way, and it was impossible to collect enough samples to characterize the incidence of late relapse.

Finally, the comparison between the two doses of rifabutin must be interpreted cautiously, because the patients were not randomly assigned to receive one dose or the other, and the doses were given about one year apart. Conceivably, there are subtle differences between these groups that could contribute to different bacteriologic outcomes.

Our study has important implications for the care of patients with AIDS who have *M. avium* complex infection. It demonstrates a bacteriologic advantage of one multidrug regimen over another and shows that the three-drug regimen confers a survival advantage. In addition, we have reported the syndrome of uveitis that is induced by the combination of high-dose rifabutin and clarithromycin and have described a regimen combining rifabutin and clarithromycin that is efficacious and associated with an acceptably low incidence of uveitis that is easily managed. In summary, a regimen of rifabutin, ethambutol, and clarithromycin should be considered the standard treatment for *M. avium* complex infection in patients with AIDS until another regimen is found to be either more efficacious or equally efficacious with fewer toxic effects.

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## APPENDIX

In addition to the study authors, the members of the Canadian HIV Trials Network Protocol 010 Study Group included F. Turgeon (Hôpital Saint-Luc, Montreal); F.Y. Aoki (University of Manitoba, Winnipeg); E. Toma (Hôtel-Dieu de Montréal, Montreal); M. Miller (Sir Mortimer B. Davis-Jewish General Hospital, Montreal); R. Duperval (Centre Hospitalier de l'Université de Sherbrooke, Sherbrooke, Que.); C. Lemieux (Hôpital Notre-Dame, Montreal); F.M. Smail (McMaster University, Hamilton, Ont.); B. Romanowski (Alberta Health and the University of Alberta, Edmonton); D.W. Cameron (University of Ottawa, Ottawa, Ont.); W.F. Schlech III (Dalhousie University, Halifax, N.S.); I.D. Mackie (University of Western Ontario, London, Ont.); H. Senay (Centre Hospitalier de l'Université Laval, Ste-Foy, Que.); D.K. MacFadden (Toronto Hospital, Toronto); K.E. Williams (University of Saskatchewan, Saskatoon); G.W. Thompson (Moncton Hospital, Moncton, N.B.); M.I. Bowmer (Memorial University, St. John's, Newf.); J.A. Talbot, S. Chomyc, and E. Davison (Provincial Laboratory of Public Health for Northern Alberta, Edmonton); N. McGillivray, K. Grant, S. Khorasheh, J. Raboud, A. Thorne, and B. Savage (Canadian HIV Trials Network, Vancouver, B.C.); and J. Deschênes (McGill University, Montreal).

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