

Discontinuation of *Mycobacterium avium* Complex Prophylaxis in Patients with Antiretroviral Therapy–Induced Increases in CD4⁺ Cell Count

A Randomized, Double-Blind, Placebo-Controlled Trial

Judith S. Currier, MD, MSc; Paige L. Williams, PhD; Susan L. Koletar, MD; Susan E. Cohn, MD, MPH; Robert L. Murphy, MD; Alison E. Heald, MD; Richard Hafner, MD; Ehab L. Bassily, MSc; Howard M. Lederman, MD, PhD; Charles Knirsch, MD, MPH; Constance A. Benson, MD; Hernan Valdez, MD; Judith A. Aberg, MD; and J. Allen McCutchan, MD, for the AIDS Clinical Trials Group 362 Study Team

Background: Patients infected with HIV who experience increases in CD4⁺ cell counts are at reduced risk for opportunistic infections. However, the safety of discontinuing prophylaxis against *Mycobacterium avium* complex has been uncertain.

Objective: To compare the rate of *M. avium* complex infection in patients with increased CD4⁺ cell counts who receive azithromycin and those receiving placebo.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: 29 university-based clinical centers in the United States.

Participants: 643 HIV-1–infected patients with a previous CD4⁺ cell count less than 0.05×10^9 cells/L and a sustained increase to greater than 0.10×10^9 cells/L during antiretroviral therapy.

Intervention: Azithromycin, 1200 mg once weekly ($n = 321$), or matching placebo ($n = 322$).

Measurements: *Mycobacterium avium* complex cultures, CD4⁺ cell counts, and clinical evaluations for AIDS-defining illnesses and bacterial infections were done every 8 weeks. Plasma HIV-1 RNA levels were measured at 16-week intervals.

Results: During follow-up (median, 16 months), 2 cases of *M. avium* complex infection were reported among the 321 patients assigned to placebo (incidence rate, 0.5 event per 100 person-years [95% CI, 0.06 to 1.83 events per 100 person-years]) compared with no cases among the 322 patients assigned to azithromycin (CI, 0 to 0.92 events per 100 person-years), resulting in a treatment difference of 0.5 event per 100 person-years (CI, –0.20 to 1.21 events per 100 person-years) for placebo versus azithromycin. Both cases were atypical in that *M. avium* complex was localized to the vertebral spine. Patients receiving azithromycin were more likely than those receiving placebo to discontinue treatment with the study drug permanently because of adverse events (8% vs. 2%; hazard ratio, 0.24 [CI, 0.10 to 0.57]).

Conclusions: Prophylaxis against *Mycobacterium avium* complex can safely be withdrawn or withheld in adults with HIV infection who experience increases in CD4⁺ cell count while receiving antiretroviral therapy.

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For author affiliations, current addresses, and contributions, see end of text.

The routine use of chemoprophylaxis against *Mycobacterium avium* complex infection has been recommended for HIV-1–infected adults and adolescents if they have a CD4⁺ T-lymphocyte count less than 0.05×10^9 cells/L (1). Clarithromycin or azithromycin are the preferred prophylactic agents. The superiority of azithromycin or clarithromycin over rifabutin for prevention of infection with *M. avium* complex has been established by randomized clinical trials in patients with HIV infection and CD4⁺ cell counts less than 0.10×10^9 cells/L (2, 3). Earlier data have suggested that use of *M. avium* complex prophylaxis is associated with survival benefit (4).

The advent of potent combination antiretroviral therapy has been accompanied by marked declines in the rates of all opportunistic infections (5–8). Both observational

and randomized studies have suggested that the immunologic improvements seen with potent antiretroviral therapy, as measured by increases in CD4⁺ cell count, were accompanied by a reduction in clinical events (5–9). However, the available data are inadequate to guide decisions about the use of prophylaxis against *M. avium* complex for patients who experienced sustained increases in CD4⁺ cell count above thresholds of risk. For example, there is concern that patients with a CD4⁺ cell nadir less than 0.05×10^9 cells/L may have incomplete restoration of immune function with potent antiretroviral therapy (10).

To determine the need for continued prophylaxis against *M. avium* complex, we conducted a multicenter clinical trial of azithromycin in patients with a previous CD4⁺ cell count less than 0.05×10^9 cells/L who experi-

enced an increase to greater than 0.10×10^9 cells/L. The primary objective was to compare the rate of *M. avium* complex infection in patients who were randomly assigned to azithromycin therapy and those assigned to placebo on the basis of a standard superiority hypothesis. Secondary objectives were to compare the rates of azithromycin-preventable diagnoses and AIDS-defining infections in these patients.

METHODS

Patients

Participants were recruited from AIDS Clinical Trials Group study sites located at university-based outpatient clinics. Patients were required to have documented HIV infection and CD4⁺ cell counts of 0.05×10^9 cells/L or less (either on two occasions at least 7 days apart or a single CD4⁺ cell count $\leq 0.05 \times 10^9$ cells/L with no documentation of a count $> 0.15 \times 10^9$ cells/L in the previous 3 months) followed by a documented increase in CD4⁺ cell count to 0.10×10^9 cells/L or more on two separate occasions at least 4 weeks apart, with no intervening values less than 0.10×10^9 cells/L. Further eligibility criteria were receipt of antiretroviral therapy, a Karnofsky score of at least 50, and no documented previous positive culture for *M. avium* complex from the blood or another usually sterile body site. Laboratory requirements were a hemoglobin level of 80 g/L or greater, alkaline phosphatase and total bilirubin levels less than 2.5 times the upper limit of normal, and serum aminotransferase concentrations less than five times the upper limit of normal. The protocol was approved by the institutional review board at the 29 participating sites, and each patient gave written informed consent before enrollment.

Patients were randomly assigned in a 1:1 ratio to receive 1200 mg of azithromycin once weekly or matching placebo. Both participants and staff were blinded to the treatment assignment throughout the study. Randomization was stratified by three categories of previous *M. avium* complex prophylaxis: no previous prophylaxis, previous prophylaxis containing azithromycin, and previous prophylaxis with agents other than azithromycin. Patients were randomly assigned in permuted blocks of four within each stratification level. Randomization was dynamically balanced within study center, with a maximum allowed imbalance between treatment groups of 2 patients. The study was designed to enroll 636 patients in the course of

1 year, with follow-up for 1.5 years after the last patient had been enrolled. Patients were required to have a culture for *M. avium* complex at baseline; patients with positive cultures were ineligible and were withdrawn from the study. Ten mL of blood was collected for mycobacterial cultures in acid citrate dextrose tubes and shipped overnight with refrigerant packs at -20°C to a central laboratory (Non-tuberculous Mycobacterial Reference Laboratory, Childrens Hospital, Los Angeles, California) (11).

Outcome Measures

At 8-week intervals, patients were evaluated for clinical end points and blood was collected for mycobacterial cultures and measurement of CD4⁺ cell counts. Information was also collected on clinical signs and symptoms, adverse events, and adherence to therapy with study drug and antiretroviral agents. Adverse events were classified by using the Division of AIDS Table for Grading the Severity of Adult Adverse Experiences. Plasma HIV-1 RNA levels were measured at entry and week 8 and then at 16-week intervals. Patients whose CD4⁺ cell count decreased to less than 0.05×10^9 cells/L on two consecutive occasions were switched to therapy with open-label azithromycin and remained in follow-up for *M. avium* complex and other infections. Infections considered preventable by azithromycin prophylaxis were bacterial infections (sinusitis, pneumonia, bacterial diarrheal diseases, sepsis, and deep-tissue infections), *Pneumocystis carinii* pneumonia, toxoplasmosis, and cryptosporidiosis (3, 12, 13). AIDS-defining clinical events (14) were reviewed in a blinded fashion by the study chair; only those that met the criteria defined in the study protocol were included as events in the analysis.

Statistical Analysis

The sample size of 318 per group was calculated by using the method of Rubinstein and colleagues (15) to provide 90% power for detecting a twofold difference in the rate of *M. avium* complex disease (5% yearly rate in the azithromycin group vs. 10% in the placebo group, or a corresponding hazard ratio of 2.05). The sample size calculations assumed a 1-year accrual period and 1.5 years of additional follow-up and accounted for loss to follow-up from death and other causes.

The primary end point of the study was time to development of *M. avium* complex disease, defined by growth from a usually sterile site, such as blood, lymph

node, liver, or bone marrow. An intention-to-treat approach was used to compare the strategies of randomly assigning patients to azithromycin therapy or placebo. The protocol analysis plan specified that a stratified log-rank test would be used to compare the time to *M. avium* complex infection between the two treatment groups, with stratification by levels of previous *M. avium* complex prophylaxis. However, because of the rarity of this end point during follow-up, exact confidence intervals for the incidence rate within each study group for the difference between treatment groups were instead calculated on the basis of the Poisson distribution.

Baseline characteristics were compared between treatment groups by using the Fisher exact test for discrete variables or the Wilcoxon rank-sum test for continuous variables. Standard survival methods—Kaplan–Meier survival estimates, estimated hazard ratios (with 95% CIs), and log-rank tests—were used to compare time to other events (permanent treatment discontinuation, death, and clinical end points) between the two study groups. All hazard ratios are reported for placebo versus azithromycin, so that estimates greater than 1 suggest a protective benefit of azithromycin.

Multivariate Cox proportional hazards models were fit to evaluate the time to first AIDS-defining illness or diagnosis that was potentially preventable by azithromycin therapy, both to adjust the treatment effect for possible confounders and to identify other important risk factors. Separate Cox models were fit for each end point of interest. The potential confounders considered were sex, ethnicity (white or nonwhite), previous prophylaxis against *M. avium* complex (yes or no), previous *P. carinii* prophylaxis with trimethoprim–sulfamethoxazole (yes or no), previous AIDS-defining illness (≥ 1 or none), Karnofsky score (≤ 80 or > 80), intravenous drug use (current or previous vs. none), age, lowest preentry CD4⁺ cell count, number of weeks receiving combination therapy before study entry, time since nadir CD4⁺ cell count, and baseline plasma HIV-1 RNA levels. The latter six covariates were considered to be continuous predictors. The CD4⁺ cell count was divided by 50 so that the hazard ratio represents the change in hazard for each 50-cell increase in CD4⁺ cell count.

A generalized estimating equation approach was used to compare trajectories of CD4⁺ cell counts over time between treatment groups while accounting for correlation between CD4⁺ cell measurements from the same patient

(16). A similar approach was used to compare plasma HIV-1 RNA trajectories between treatment groups with respect to the percentage below the limit of quantification (500 copies/mL) over the study period. The Stata statistical software package (Stata Corp., College Station, Texas) was used to obtain exact confidence intervals for incidence of *M. avium* complex infection; the SAS statistical package (SAS Institute, Inc., Cary, North Carolina) was used for all other statistical analyses.

Safety Monitoring

Plans for interim monitoring included two reviews of safety and efficacy data by an independent Data and Safety Monitoring Board. Two stopping guidelines were specified at each review. The first was based on identification of a significant treatment difference between azithromycin and placebo, and the second was based on detecting a yearly rate of *M. avium* complex infection of less than 5% in the placebo group. Significance levels at interim analyses were adjusted for multiple looks by using O'Brien–Fleming bounds. At the second interim review by the Data and Safety Monitoring Board (in July 1999), the yearly rate of *M. avium* complex infection in the placebo group was significantly less than 5%; the second stopping guideline was therefore met. Data presented include those obtained during follow-up through October 1999, at which time sites were notified that blinded administration of study drugs would be discontinued.

Role of the Study Sponsor

Pfizer, Inc., supplied azithromycin and matching placebo and funding for the *M. avium* complex cultures and viral load testing. The sponsor had no role in the collection or analysis of the data or in the decision to submit the paper for publication. Dr. Knirsch, a representative of Pfizer, Inc., was a member of the study team and reviewed the protocol and protocol amendments, reviewed the statistical reports, and reviewed the manuscript after preparation by the study team.

RESULTS

The study opened to accrual in October 1997 and closed to accrual in April 1999. During that time, 644 patients were enrolled from 29 centers over 19 months. One patient was mistakenly enrolled and was excluded from all analyses.

Table 1. Baseline Characteristics of the Study Patients by Treatment Group*

| Characteristic | All Patients (n = 643) | Azithromycin Recipients (n = 322) | Placebo Recipients (n = 321) |
|--|---------------------------|--------------------------------------|---------------------------------|
| Sex, n (%) | | | |
| Male | 561 (87) | 283 (88) | 278 (87) |
| Female | 82 (13) | 39 (12) | 43 (13) |
| Ethnicity, n (%) | | | |
| White | 370 (58) | 187 (58) | 183 (57) |
| Black | 131 (20) | 57 (18) | 74 (23) |
| Hispanic | 117 (18) | 61 (19) | 56 (17) |
| Asian | 20 (3) | 13 (4) | 7 (2) |
| American Indian | 5 (1) | 4 (1) | 1 (0) |
| Intravenous drug use at baseline, n (%) | | | |
| Never | 546 (85) | 274 (85) | 272 (85) |
| Current | 5 (1) | 2 (1) | 3 (1) |
| Previous | 92 (14) | 46 (14) | 46 (14) |
| Median age at baseline, y | 40 | 40 | 39 |
| CD4 ⁺ cell count | | | |
| Median count, cells × 10 ⁹ /L | 0.226 | 0.235 | 0.219 |
| Latest preentry value, n (%) | | | |
| <0.1 cells × 10 ⁹ /L | 1 (0) | 0 (0) | 1 (1) |
| 0.1–0.199 cells × 10 ⁹ /L | 239 (37) | 111 (34) | 128 (40) |
| 0.2–0.299 cells × 10 ⁹ /L | 208 (32) | 107 (33) | 101 (31) |
| 0.3–0.5 cells × 10 ⁹ /L | 152 (23) | 79 (25) | 73 (22) |
| >0.5 cells × 10 ⁹ /L | 43 (7) | 25 (8) | 18 (6) |
| Median weeks since preentry CD4 ⁺ cell count was <0.05 cells × 10 ⁹ /L | 96.9 | 95.5 | 99.4 |
| Baseline HIV-1 RNA level, n (%) | | | |
| ≤500 copies/mL (undetectable) | 407 (63) | 202 (62) | 205 (64) |
| 500 to <20 000 copies/mL | 110 (17) | 62 (19) | 48 (15) |
| ≥20 000 copies/mL | 96 (15) | 39 (12) | 57 (18) |
| Missing/unknown | 30 (5) | 19 (7) | 11 (3) |
| MAC prophylaxis status, n (%) | | | |
| No prophylaxis | 235 (37) | 117 (36) | 118 (37) |
| Previous prophylaxis with azithromycin | 288 (45) | 145 (45) | 143 (45) |
| Other MAC prophylaxis | 120 (19) | 60 (19) | 60 (19) |

* MAC = *Mycobacterium avium* complex.

The demographic characteristics of the 643 patients were well balanced across treatment groups (Table 1). The median time receiving potent combination antiretroviral therapy at study entry was 42 weeks. Thirty-seven percent of the patients had no record of previous prophylaxis against *M. avium* complex. Azithromycin prophylaxis had been used in the past by 288 patients (45%), and 120 patients (19%) had received some other form of prophylaxis against *M. avium* complex. All 643 patients had documented sterile blood cultures at entry.

The median duration of follow-up was 69 weeks (range, 8 to 114 weeks). The length of follow-up and the percentage of patients lost to follow-up were similar in both treatment groups. Eight patients experienced a decline in CD4⁺ cell count to less than 0.05 × 10⁹ cells/L and were switched to open-label therapy azithromycin (2 in the azithromycin group and 6 in the placebo group; *P* = 0.147). Seventy-three patients discontinued participa-

tion in the study. Sixty-three patients (9.8% [30 in the azithromycin group and 33 in the placebo group]) were lost to follow-up (they declined to have further contact, were unable to be followed, or specified another reason), and 10 patients died. The median follow-up time for patients who had discontinued participation in the study at the time of the final analysis was 10.8 months for azithromycin recipients and 11.4 months for placebo recipients. The baseline characteristics of the patients who discontinued follow-up were similar between the two treatment groups (data not shown) and were similar to those shown in Table 1 for all patients.

An additional 67 patients discontinued study treatment but continued to be followed for all study end points without receiving treatment. Seven patients (6 in the azithromycin group and 1 in the placebo group) stopped taking the study medication because of protocol-defined toxicities and 24 patients (19 in the azithromycin group

and 5 in the placebo group) stopped therapy because of milder toxicities (Table 2). Overall, the rate of treatment discontinuation due to toxicity was significantly higher in the azithromycin group (8%) than in the placebo group (2%) (hazard ratio, 4.2 [95% CI, 1.7 to 10.3]; $P < 0.001$). The remainder of the reasons for treatment discontinuation were unrelated to toxicity.

Development of *M. avium* Complex Infection

After a median follow-up of 69 weeks, two cases of *M. avium* complex infection were reported among the 321 patients assigned to placebo (incidence rate, 0.5 event per 100 person-years [CI, 0.06 to 1.83 events per 100 person-years]) and none were reported among the 322 patients assigned to azithromycin therapy (incidence rate, 0 events per 100 person-years [CI, 0 to 0.92 events per 100 person-years]), for a treatment difference of 0.5 event per 100 person-years (CI, -0.20 to 1.21 events per 100 person-years) for placebo versus azithromycin. Although the treatment groups did not significantly differ in the rate of *M. avium* complex infection, the upper confidence limit of the rate in the placebo group was less than 5% at the second interim analysis, thus meeting one of the criteria for early stopping.

Both cases were atypical for *M. avium* infection without systemic signs or symptoms. *Mycobacterium avium* complex was isolated from vertebral bone and paraspinal masses causing localized neurologic symptoms and not from

blood. Both cases occurred in men who had a history of *P. carinii* pneumonia and had previously received *M. avium* complex prophylaxis. At the study visit before the clinical event (weeks 32 and 20), the two patients had plasma HIV-1 RNA levels less than 500 copies/mL and CD4⁺ cell counts of 0.306×10^9 cells/L and 0.203×10^9 cells/L.

Diagnoses Potentially Preventable by Azithromycin Prophylaxis

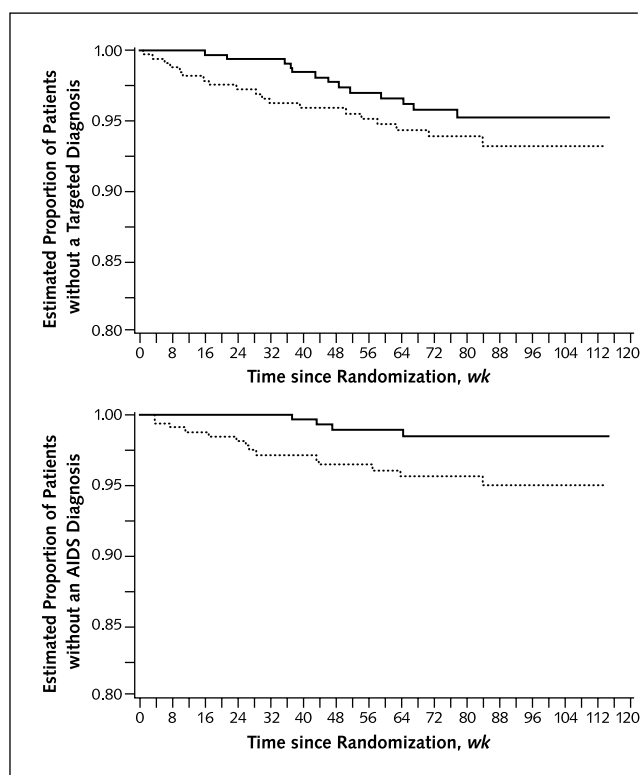
The rate of infections that may be prevented by azithromycin prophylaxis was slightly lower among patients assigned to azithromycin (13 events among 13 patients) than those assigned to placebo (21 events among 19 patients); however, this difference did not reach statistical significance (hazard ratio, 1.51 [CI, 0.75 to 3.70]) (Table 3 and Figure). Overall, the rate of such infections was 4.3 events per 100 person-years of follow-up (CI, 2.97 to 5.98 events per 100 person-years). In a Cox proportional hazards model that controlled for ethnicity, previous *M. avium* complex prophylaxis, previous *P. carinii* pneumonia prophylaxis, previous AIDS-defining illness, age, Karnofsky score, intravenous drug use, and lowest preentry CD4⁺ cell count, only weeks receiving previous combination antiretroviral therapy and female sex were significant predictors of time to first azithromycin-preventable infection. Of the 82 enrolled women, 8 (9.8%) developed one or more of these infections, whereas only 24 of the 561 men (4.3%) developed an infection.

Table 2. Treatment Discontinuation, Adverse Events, and Death

| Variable | All Patients (n = 643) | Azithromycin Recipients (n = 322) | Placebo Recipients (n = 321) | Hazard Ratio (95% CI)* | Log-Rank P Value |
|---|---------------------------|---|------------------------------------|---------------------------|---------------------|
| | | | | | |
| Any permanent treatment discontinuation | 140 (22) | 74 (23) | 66 (21) | 0.88 (0.63–1.23) | >0.2 |
| Any discontinuation of study follow-up | 73 (11) | 33 (10) | 40 (12) | 1.25 (0.79–1.98) | >0.2 |
| Lost to follow-up | 63 (10) | 30 (9) | 33 (10) | 1.14 (0.69–1.87) | >0.2 |
| Death | 10 (1.6) | 3 (0.9) | 7 (2.2) | 2.36 (0.61–9.13) | 0.2 |
| Permanent treatment discontinuation due to adverse events | 31 (5) | 25 (8) | 6 (2) | 0.24 (0.10–0.57) | <0.001 |
| Adverse events | | | | | |
| Severe adverse events (grade 3 toxicity) | | | | | |
| Signs/symptoms | 8 (18) | 53 (16) | 65 (20) | 1.28 (0.89–1.83) | 0.188 |
| Laboratory toxicities | 118 (20) | 59 (18) | 68 (21) | 1.19 (0.84–1.69) | >0.2 |
| Either | 212 (33) | 100 (31) | 112 (35) | 1.18 (0.90–1.55) | >0.2 |
| Life-threatening adverse events (grade 4 toxicity) | | | | | |
| Signs/symptoms | 10 (2) | 5 (2) | 5 (2) | 1.02 (0.29–3.52) | >0.2 |
| Laboratory toxicities | 59 (9) | 23 (7) | 36 (11) | 1.60 (0.95–2.71) | 0.074 |
| Either | 67 (10) | 26 (8) | 41 (13) | 1.62 (0.99–2.65) | 0.051 |

* Hazard ratio calculated from Cox proportional hazards model comparing placebo with azithromycin.

Figure. Time to first azithromycin-preventable diagnosis (top) and first AIDS-defining illness (bottom) in patients receiving azithromycin prophylaxis (solid line) or placebo (dotted line).



Log-rank *P* values comparing azithromycin with placebo were 0.25 (13 of 322 patients receiving azithromycin and 19 of 321 patients receiving placebo) for time to first azithromycin-preventable diagnosis and 0.016 (4 of 322 patients and 14 of 321 patients) for time to first AIDS-defining diagnosis.

AIDS-Defining Illnesses

Nineteen AIDS-defining events developed in 18 patients during follow-up. These events are summarized by treatment group in Table 3. The overall incidence rate of AIDS-defining events was 2.4 events per 100 person-years (CI, 1.44 to 3.74 events per 100 person-years). The median CD4⁺ cell count at the last visit before an AIDS-defining event was 0.251×10^9 cells/L (range, 0.033 to 0.648×10^9 cells/L). Of note, the time to development of a new or recurrent AIDS-defining illness was significantly longer for patients assigned to azithromycin therapy (hazard ratio, 3.60 [CI, 1.19 to 10.95]; *P* = 0.016) (Figure), but the number of patients with events was relatively small. In a Cox proportional hazards model, baseline plasma HIV-1 RNA level and CD4⁺ cell count were significant predictors in addition to azithromycin treatment; the treat-

ment effect (hazard ratio, 3.66 [CI, 1.18 to 11.34]) remained significant even after controlling for these baseline predictors (Table 4). Results of the Cox model are shown in Table 4.

Changes in Plasma HIV-1 RNA Level and CD4⁺ Cell Counts

At baseline, 66% of patients with available baseline measurements in each treatment group had plasma HIV-1 RNA levels less than 500 copies/mL (baseline values were missing for 30 patients). After the baseline visit, the proportion of patients with plasma HIV-1 RNA levels less than 500 copies/mL was slightly lower in the placebo group; this difference was marginally significant over all study visits (*P* = 0.051).

At baseline, the median CD4⁺ cell count was 0.02×10^9 cells/L lower among patients assigned to placebo than among those assigned to azithromycin; this difference between the study groups persisted over time, leading to a marginally significant difference (*P* = 0.097). Overall, the CD4⁺ cell count increased by about 0.006×10^9 cells/L for every 8 weeks of study, and this increase over time was statistically significant (*P* < 0.001).

Adverse Events

The proportion of patients who discontinued treatment because of toxicity was significantly higher among azithromycin recipients than placebo recipients (Table 2). The proportion of patients with signs or symptoms that were severe (grade 3) or life-threatening (grade 4) was 16% in the azithromycin group and 20% in the placebo group (hazard ratio, 1.28 [CI, 0.89 to 1.83]; *P* = 0.188). The most common symptoms were aches and pains (49 patients), diarrhea (16 patients), fever (13 patients), and headache (12 patients). The proportion of study patients who developed a severe (grade 3) or life-threatening (grade 4) laboratory toxicity (18% of those receiving azithromycin and 21% of those receiving placebo) did not differ significantly (hazard ratio, 1.19 [CI, 0.84 to 1.69]; *P* > 0.2). Patients assigned to placebo had a marginally significantly higher rate of grade 4 laboratory toxicities than did those assigned to azithromycin therapy (11% vs. 7%; hazard ratio, 1.60 [CI, 0.95 to 2.71]; *P* = 0.074) and a marginally significantly higher rate of any grade 4 adverse event (13% vs. 8%; hazard ratio, 1.62 [CI, 0.99 to 2.65]; *P* = 0.051).

Table 3. Clinical Events by Treatment Group

| Type of Event | All Patients (n = 643) | Azithromycin Recipients (n = 322) | Placebo Recipients (n = 321) | Hazard Ratio (95% CI)* | Log-Rank P Value |
|--|---------------------------|---|------------------------------------|---------------------------|---------------------|
| | ←————— n (%) —————→ | | | | |
| Conditions potentially preventable by azithromycin prophylaxis† | | | | | |
| <i>Mycobacterium avium</i> complex infection | 2 (0.3) | 0 (0.0) | 2 (0.6) | | |
| <i>Pneumocystis carinii</i> pneumonia, histologically proven | 1 (0.2) | 1 (0.3) | 0 (0) | | |
| <i>P. carinii</i> pneumonia, clinical diagnosis | 3 (0.5) | 1 (0.3) | 2 (0.6) | | |
| Bacterial pneumonia | 9 (1.4) | 2 (0.6) | 7 (2.2) | | |
| Bacterial sinusitis | 7 (1.1) | 3 (0.9) | 4 (1.3) | | |
| Bacterial gastrointestinal disease‡ | 2 (0.3) | 2 (0.6) | 0 (0.0) | | |
| Bacterial sepsis | 3 (0.5) | 1 (0.3) | 2 (0.6) | | |
| Bacterial deep-tissue infection | 6 (0.9) | 3 (0.9) | 3 (0.9) | | |
| Cryptosporidiosis | 1 (0.2) | 0 (0.0) | 1 (0.3) | | |
| Total | 34 | 13 | 21 | | |
| Patients with one or more conditions potentially preventable by azithromycin prophylaxis | 32 (5.0) | 13 (4.0) | 19 (5.9) | 1.5 (0.75–3.07) | >0.2 |
| AIDS-defining illnesses‡ | | | | | |
| <i>M. avium</i> complex infection | 2 (0.3) | 0 (0.0) | 2 (0.6) | | |
| <i>P. carinii</i> pneumonia, histologically proven | 1 (0.2) | 1 (0.3) | 0 (0.0) | | |
| <i>P. carinii</i> pneumonia, clinical diagnosis | 3 (0.5) | 1 (0.3) | 2 (0.6) | | |
| Cytomegalovirus retinitis | 2 (0.3) | 0 (0.0) | 2 (0.6) | | |
| Viral esophagitis | 1 (0.2) | 0 (0.0) | 1 (0.3) | | |
| Cryptosporidiosis | 1 (0.2) | 0 (0.0) | 1 (0.3) | | |
| Esophageal candidiasis | 6 (0.9) | 2 (0.6) | 4 (1.3) | | |
| Kaposi sarcoma | 2 (0.3) | 0 (0.0) | 2 (0.6) | | |
| HIV wasting syndrome | 1 (0.2) | 1 (0.3) | 0 (0.0) | | |
| Total | 19 | 5 | 14 | | |
| Patients with one or more AIDS-defining illness | 18 (2.8) | 4 (1.2) | 14 (4.4) | 3.60 (1.19–10.95) | 0.016 |

* Hazard ratio calculated from Cox proportional hazards model comparing placebo with azithromycin.

† "n" refers to the number of cases of the condition; the percentage of patients is given in parentheses.

‡ Infection with *Clostridium difficile*.

DISCUSSION

Our results support the growing consensus that potent antiretroviral therapy can reverse susceptibility to multiple opportunistic infections. Among patients with AIDS who experienced increases in CD4⁺ cell counts from less than 0.05×10^9 cells/L to greater than 0.10×10^9 cells/L while receiving potent antiretroviral therapy, the rate of *M. avium* complex infection over a median follow-up of 16 months was very low. The incidence of *M. avium* complex infection in the placebo group was 2 of 321 patients, or 0.5 event per 100 person-years, a rate substantially lower than that achieved by prophylaxis before the use of potent antiretroviral therapy (2, 3). For example, in the California Collaborative Treatment Group study of *M. avium* complex prophylaxis, the incidence of disseminated infection in patients with CD4⁺ cell counts less than 0.10×10^9 cells/L was 15.3 per 100 patient-years with rifabutin, 7.6 per 100 patient-years with azithromycin, and 2.8 per 100 patient-years with both drugs.

The two cases of *M. avium* complex infection observed in patients assigned to placebo were localized to the vertebral spine and paraspinal soft tissues, with neither systemic symptoms nor bacteremia. Several case reports and clinical series have identified localized and atypical cases of *M. avium* complex infection among responders to antiretroviral therapy (17–22). In general, these reports have described localized inflammatory disease in the lymph nodes with fever in patients who recently started receiving protease inhibitor-containing regimens. Because many of the reported cases occurred shortly after initiation of potent antiretroviral therapy in patients with a history of very low CD4⁺ cell counts, these cases may represent unmasking of subclinical mycobacterial disease by increased inflammation from an improved immune response to *M. avium* complex (14). The two cases in our study did not appear to fit this pattern because the duration of time since the first CD4⁺ cell count greater than 0.10×10^9 cells/L occurred 43 and 65 weeks before the diagnosis of *M. avium* complex

Table 4. Multivariate Cox Proportional Hazards Models

| Baseline Predictor | Patients, n | Estimated Hazard Ratio (95% CI) | P Value |
|--|-------------|---------------------------------|---------|
| First AIDS-defining illness* | 612† | | |
| Treatment | | 3.66 (1.18–11.34) | 0.025 |
| CD4 ⁺ cell count | | 1.14 (0.99–1.32) | 0.066 |
| Log ₁₀ RNA copies | | 1.59 (1.09–2.31) | 0.015 |
| First diagnosis potentially preventable by azithromycin prophylaxis‡ | 643 | | |
| Weeks receiving highly active antiretroviral therapy | | 0.99 (0.97–0.99) | 0.037 |
| Female sex | | 2.13 (0.95–4.77) | 0.066 |

* Nonsignificant baseline predictors ($P < 0.1$ based on a forward or backward selection model) were age, intravenous drug use, previous AIDS-defining illness, previous *Mycobacterium avium* complex prophylaxis, previous *Pneumocystis carinii* pneumonia prophylaxis, sex, previous weeks receiving combination therapy, ethnicity, Karnofsky score, lowest preentry CD4⁺ cell count, and weeks since lowest CD4⁺ cell count.

† Thirty-one patients for whom data on log₁₀ RNA copies at baseline were excluded from analysis.

‡ Nonsignificant baseline predictors ($P < 0.1$ based on a forward or backward selection model) were treatment, age, intravenous drug use, previous AIDS-defining illness, previous *M. avium* complex prophylaxis, previous *P. carinii* pneumonia prophylaxis, ethnicity, Karnofsky score, lowest preentry CD4⁺ cell count, and weeks since lowest CD4⁺ cell count.

infection. Although these unusual presentations are rare, clinicians should be aware that they can occur many months after sustained increases in CD4⁺ cell count occur (20).

In addition to these unusual cases of *M. avium* complex, opportunistic infections occurred in several patients despite sustained increases in CD4⁺ cell count and suppressed viral load (median CD4⁺ cell count before a new opportunistic infection, 0.251×10^9 cells/L). These results suggest that more sensitive markers of ongoing risk for opportunistic infection may be needed to identify the rare patient who remains at risk despite an increased CD4⁺ cell count.

The rate of other infections potentially prevented by azithromycin, such as bacterial infections and *P. pneumoniae*, were reduced in both the azithromycin and placebo groups. Of note, women had twice the risk for an azithromycin-preventable infection compared with men; although this difference was only marginally significant, it is notable that a sex difference in the rate of bacterial infections has been reported but remains unexplained (23, 24). The protective effect of a longer duration of combination antiretroviral therapy on the rate of azithromycin-preventable diagnoses is consistent with the theory that immune reconstitution continues to improve over time.

The low incidence of *M. avium* complex and other opportunistic infections in our study severely limited its

power to detect prophylactic effects of azithromycin. Despite this limitation, we were surprised to find that the rate of new or recurrent AIDS-defining illnesses was significantly decreased in the azithromycin group compared with the placebo group. This difference did not result from lower rates of recurrent bacterial pneumonia or *P. carinii* pneumonia. Thus, azithromycin seemed to have benefited the patients by a mechanism independent of prophylaxis against opportunistic infections, such as *M. avium* complex or bacterial and *P. carinii* pneumonia. One potential mechanism is prevention of mucosal colonization and local invasion of respiratory or gastrointestinal flora by azithromycin. Such suppression of mucosal colonization might reduce immune activation. However, the lower rate of AIDS-defining illnesses in the azithromycin group must be interpreted with caution. The number of AIDS-defining events was low ($n = 19$), and although losses to follow-up were similar in the treatment groups, undetected clinical events may have occurred in patient who were lost to follow-up. Because this protection was unanticipated and not found in a similar study (25), it is not an adequate basis for recommending azithromycin prophylaxis.

Another recently published study that compared weekly azithromycin prophylaxis with use of placebo in patients similar to ours observed no *M. avium* complex infections in 520 patients after a median of 12 months of follow-up (25). Blood cultures for mycobacteria were collected only at baseline in that study compared with every 8 weeks in our study. This difference was not likely to influence the conclusions, however, because even though we routinely performed blood cultures, no patient in our study had bacteremia. As in our study, rates of bacterial and *P. carinii* pneumonia were low and did not differ between treatment groups in the previous study. In contrast to our finding of decreased rates of new or recurrent opportunistic infections, that study found no differences between treatment groups in rates of progression of HIV disease. The longer follow-up in our study (65% more person-years) may have contributed to the differences in the effect of azithromycin on AIDS-defining events (if in fact it has clinical significance). The overall rate of *M. avium* complex infection in the two studies combined is estimated to be 0.16 event per 100 person-years of follow up, strengthening the assertion of low risk.

Our results support the recently revised recommendations that it is safe to withdraw or withhold primary prophylaxis against *M. avium* complex disease in adults with

HIV infection who experience increases in CD4⁺ count cell from less than 0.5×10^9 cells/L to greater than 0.10×10^9 cells/L (1, 26). The consensus that prophylaxis of *M. avium* complex is unnecessary for patients whose CD4⁺ cell counts increase to above a previous threshold for vulnerability to *M. avium* complex is paralleled by similar findings for *P. carinii* pneumonia prophylaxis. Several studies have demonstrated that both primary and secondary prophylaxis against *P. carinii* pneumonia can be discontinued in patients with sustained CD4⁺ cell count counts greater than 0.20 to 0.25×10^9 cells/L (27–35). Likewise, several small studies have suggested that secondary prophylaxis against cytomegalovirus may be safely discontinued in patients in whom increases in CD4⁺ cell count are maintained (36–41).

The ability to discontinue prophylaxis of *M. avium* complex infection has several advantages for patients with a history of severe immunosuppression and for the health care system. Benefits include a lower pill burden, which could improve adherence to therapy; lower risk for drug interactions; reduced risk for bacterial resistance; reduced risk for direct toxicity of the prophylactic agent; and reduction in the costs of prophylaxis.

Several factors must be considered for applying our results to clinical practice. Study patients were required to have a CD4⁺ cell count greater than 0.10×10^9 cells/L at entry; however, the median CD4⁺ cell count for the study sample was higher (0.23×10^9 cells/L) and remained on an upward trend throughout follow-up. Patients with more modest increases in CD4⁺ cell count or with declining counts may not be as immunologically reconstituted as the bulk of our patients. The optimal time to restart prophylaxis in patients with declining CD4⁺ cell counts was not addressed because very few patients experienced a decline in CD4⁺ cell count to less than 0.5×10^9 cells/L and we routinely restarted azithromycin in those who did. Finally, two thirds of the study patients had plasma HIV-1 RNA levels less than 500 copies/mL at entry, and these levels remained suppressed throughout follow-up. Although we observed protection against *M. avium* complex and other opportunistic infections even in patients without complete viral suppression, patients who have sustained increases in plasma HIV-1 RNA levels may be at risk and should be followed closely. Long-term follow-up of this cohort is ongoing to further characterize the clinical outcomes among patients with a history of severe immunodeficiency treated with potent combination antiretroviral therapy.

From University of California Los Angeles, Los Angeles, California; Harvard School of Public Health, Boston, Massachusetts; Ohio State University, Columbus, Ohio; University of Rochester Medical Center, Rochester, New York; Northwestern University Medical School; Duke University Medical Center, Durham, North Carolina; National Institutes of Health, Bethesda, Maryland; Johns Hopkins University, Baltimore, Maryland; Pfizer, Inc., New York, New York; University of Colorado Health Sciences Center, Denver, Colorado; Case Western Reserve University, Cleveland, Ohio; University of California, San Francisco, San Francisco, California; and University of California, San Diego, San Diego, California.

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Requests for Single Reprints: Judith S. Currier, MD, MSc, University of California, Los Angeles, 10833 LeConte Avenue, Room BH-412, Los Angeles, CA 90095; e-mail, jscurrier@mednet.ucla.edu.

Current Author Addresses: Dr. Currier: University of California, Los Angeles, CARE Center, 10833 LeConte Avenue, Room BH-412 CHS, Los Angeles, CA 90095.

Dr. Williams: Statistical and Data Analysis Center, Department of Biostatistics, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115.

Dr. Koletar: Ohio State University Hospitals, Doan Hall, N-115, 410 West 10th Avenue, Columbus, OH 43210.

Dr. Cohn: Infectious Diseases Unit, University of Rochester Medical Center, 601 Elmwood Avenue, Box 689, Rochester, NY 14642.

Dr. Murphy: Northwestern University Medical School, Passavant Pavilion, Room 828, 303 East Superior Street, Chicago, IL 60611.

Dr. Heald: Duke University Medical Center, Box 3284, Durham, NC 27710.

Dr. Hafner: Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Room 5107, 6700-B Rockledge Drive, MSC 7620, Bethesda, MD 20892-7620.

Dr. Bassily: Statistical and Data Analysis Center, Harvard School of Public Health, COMP RAC Section, FXB Building, Room 614, 651 Huntington Avenue, Boston, MA 02115.

Dr. Lederman: Johns Hopkins Hospital, CMSC 1102, 600 North Wolfe Street, Baltimore, MD 21287.

Dr. Knirsch: Pfizer, Inc., 235 East 42nd Street, Mailstop 235/14/5, New York, NY 10017.

Dr. Benson: University of Colorado Health Sciences Center, Division of Infectious Diseases, 4200 East Ninth Avenue, Box B-196, Denver, CO 80262.

Dr. Valdez: Division of Infectious Diseases, Case Western Reserve University, 2061 Cornell Road, Room 301B, Cleveland, OH 44106.

Dr. Aberg: AIDS Clinical Trials Unit, Washington University School of Medicine, 4511 Forest Park Boulevard, Suite 304, St. Louis, MO 63108.

Dr. McCutchan: Treatment Center, University of California San Diego, 2760 Fifth Avenue, Suite 300, San Diego, CA 92103.

Author Contributions: Conception and design: J.S. Currier, P.L. Williams, S.L. Koletar, S.E. Cohn, R.L. Murphy, A.E. Heald, R. Hafner, H.M. Lederman, J.A. McCutchan.

Analysis and interpretation of the data: J.S. Currier, P.L. Williams, S.L. Koletar, S.E. Cohn, R.L. Murphy, A.E. Heald, E.L. Bassily, H.M. Lederman, C. Knirsch, C.A. Benson, H. Valdez, J.A. McCutchan.

Drafting of the article: J.S. Currier, P.L. Williams, S.E. Cohn, H.M. Lederman, C.A. Benson, J.A. Aberg, J.A. McCutchan.

Critical revision of the article for important intellectual content: J.S. Currier, P.L. Williams, S.L. Koletar, R.L. Murphy, A.E. Heald, R. Hafner, E.L. Bassily, C. Knirsch, C.A. Benson, H. Valdez, J.A. Aberg, J.A. McCutchan.

Final approval of the article: J.S. Currier, P.L. Williams, S.L. Koletar, S.E. Cohn, R.L. Murphy, A.E. Heald, R. Hafner, H.M. Lederman, C. Knirsch, C.A. Benson, H. Valdez, J.A. Aberg, J.A. McCutchan.

Provision of study materials or patients: J.S. Currier, S.L. Koletar, S.E. Cohn, R.L. Murphy, A.E. Heald, C. Knirsch, C.A. Benson, H. Valdez, J.A. Aberg.

Statistical expertise: P.L. Williams, E.L. Bassily.

Obtaining of funding: C.A. Benson, J.A. McCutchan.

Administrative, technical, or logistic support: J.S. Currier, C. Knirsch, C.A. Benson.

Collection and assembly of data: J.S. Currier, E.L. Bassily, H. Valdez.

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