

The New England Journal of Medicine

© Copyright, 2001, by the Massachusetts Medical Society

VOLUME 344

JANUARY 18, 2001

NUMBER 3



A RANDOMIZED TRIAL OF THE DISCONTINUATION OF PRIMARY AND SECONDARY PROPHYLAXIS AGAINST *PNEUMOCYSTIS CARINII* PNEUMONIA AFTER HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN PATIENTS WITH HIV INFECTION

JUAN C. LOPEZ BERNALDO DE QUIROS, M.D., JOSE M. MIRO, M.D., JOSE M. PEÑA, M.D., DANIEL PODZAMCZER, M.D.,
JUAN C. ALBERDI, M.D., ESTEBAN MARTÍNEZ, M.D., JAIME COSIN, M.D., XAVIER CLARAMONTE, M.D.,
JUAN GONZALEZ, M.D., PERE DOMINGO, M.D., JOSE L. CASADO, M.D., ESTEBAN RIBERA, M.D.,
AND THE GRUPO DE ESTUDIO DEL SIDA 04/98*

ABSTRACT

Background Prophylaxis against *Pneumocystis carinii* pneumonia is indicated in patients with human immunodeficiency virus (HIV) infection who have less than 200 CD4 cells per cubic millimeter and in those with a history of *P. carinii* pneumonia. However, it is not clear whether prophylaxis can be safely discontinued after CD4 cell counts increase in response to highly active antiretroviral therapy.

Methods We conducted a randomized trial of the discontinuation of primary or secondary prophylaxis against *P. carinii* pneumonia in HIV-infected patients with a sustained response to antiretroviral therapy, defined by a CD4 cell count of 200 or more per cubic millimeter and a plasma HIV type 1 (HIV-1) RNA level of less than 5000 copies per milliliter for at least three months. Prophylactic treatment was restarted if the CD4 cell count declined to less than 200 per cubic millimeter.

Results The 474 patients receiving primary prophylaxis had a median CD4 cell count at entry of 342 per cubic millimeter, and 38 percent had detectable HIV-1 RNA. After a median follow-up period of 20 months (388 person-years), there had been no episodes of *P. carinii* pneumonia in the 240 patients who discontinued prophylaxis (95 percent confidence interval, 0 to 0.85 episode per 100 person-years). For the 113 patients receiving secondary prophylaxis, the median CD4 cell count at entry was 355 per cubic millimeter, and 24 percent had detectable HIV-1 RNA. After a median follow-up period of 12 months (65 person-years), there had been no episodes of *P. carinii* pneumonia in the 60 patients who discontinued prophylaxis (95 percent confidence interval, 0 to 4.57 episodes per 100 person-years).

Conclusions In HIV-infected patients receiving highly active antiretroviral therapy, primary and secondary prophylaxis against *P. carinii* pneumonia can be safely discontinued after the CD4 cell count has increased to 200 or more per cubic millimeter for more than three months. (N Engl J Med 2001;344:159-67.)

Copyright © 2001 Massachusetts Medical Society.

PNEUMOCYSTIS *carinii* pneumonia was a common and often fatal infection in patients infected with the human immunodeficiency virus (HIV) in the early 1980s.¹ Before the use of primary prophylaxis became standard, the proportion of patients with *P. carinii* pneumonia as the initial event defining the presence of the acquired immunodeficiency syndrome (AIDS) was 62 percent, and about 80 percent of patients with CD4 cell counts below 200 per cubic millimeter had this complication.^{2,3} It was calculated that without secondary prophylaxis, 50 percent of patients would relapse within 24 weeks after an episode of *P. carinii* pneumonia.⁴ Chemoprophylaxis has been dramatically effective, and it is currently recommended for all patients with less than 200 CD4 cells per cubic millimeter.^{4,5} Trimethoprim-sulfamethoxazole is the first choice for prophylaxis, and it can be taken in double-strength form three times a week.⁶⁻⁸ However, adverse effects of trimethoprim-sulfamethoxazole may occur in as many as 50 percent of patients so treated, and 30 percent will need to change their regimen for this reason.^{9,10} The alternatives include aerosolized pentamidine, dapsone with or without pyrimethamine, and atovaquone.^{11,12}

The use of highly active antiretroviral therapy has changed the course of HIV infection, resulting in a striking reduction in morbidity and mortality.^{13,14} The

From the Hospital Universitario Gregorio Marañón, Madrid (J.C.L.B.Q., J.C.); the Institut d'Investigacions Biomèdiques August Pi I Sunyer and Hospital Clinic Universitari, Barcelona (J.M.M., E.M., X.C.); the Ciudad Sanitaria La Paz, Madrid (J.M.P., J.G.); the Hospital de Bellvitge, Barcelona (D.P.); the Consejería de Sanidad Comunidad Autónoma de Madrid, Madrid (J.C.A.); the Hospital de Sant Pau, Barcelona (P.D.); the Hospital Ramón y Cajal, Madrid (J.L.C.); and the Hospital Universitari de la Vall d'Hebron, Barcelona (E.R.) — all in Spain. Address reprint requests to Dr. Lopez at the Division of Infectious Diseases, Hospital Gregorio Marañón, Dr. Esquerdo 46, 28007 Madrid, Spain, or at juanlopez@retemail.es.

*Other members of the Grupo de Estudio del SIDA (GESIDA) are listed in the Appendix.

persistent suppression of HIV replication leads to a sustained increase in CD4 cells, even in patients with severe immunosuppression. There have been several reports of dramatic declines in the incidence of opportunistic infections, such as *P. carinii* pneumonia, cytomegalovirus (CMV) retinitis, and *Mycobacterium avium* infections.¹⁵⁻¹⁷ Recently, observational and retrospective studies have suggested that *P. carinii* prophylaxis may be safely discontinued in patients receiving highly active antiretroviral therapy who have improved immunologic function.¹⁸⁻²³ A task force of the U.S. Public Health Service and the Infectious Diseases Society of America has recommended the discontinuation of primary prophylaxis against *P. carinii* pneumonia but recognizes that "the optimal criteria for discontinuation remain to be defined."²⁴

In a randomized multicenter trial, we tested the hypothesis that primary and secondary prophylaxis against *P. carinii* pneumonia can be safely discontinued in patients in whom highly active antiretroviral treatment results in immune reconstitution, as long as their CD4 cell counts remain at 200 or more per cubic millimeter.

METHODS

Patients

Patients were eligible for the study if they had had previous CD4 cell counts of less than 200 per cubic millimeter or had had a previous episode of *P. carinii* pneumonia; if they were receiving treatment with any of the regimens accepted for prophylaxis against *P. carinii* pneumonia; if they had a sustained response to highly active antiretroviral therapy, defined by a CD4 cell count of 200 or more per cubic millimeter and a plasma HIV type 1 (HIV-1) RNA level of less than 5000 copies per milliliter for more than three months; and if they had a Karnofsky score higher than 80. Patients were excluded if they were under 18 years of age, if they were pregnant, or if they had poor adherence to antiretroviral treatment.

Study Design

The study was a randomized, nonblinded, multicenter trial that evaluated whether primary and secondary prophylaxis against *P. carinii* pneumonia can be safely discontinued in HIV-infected patients. Patients were recruited from 19 Spanish public hospitals; the staff at each had broad experience in the treatment and care of HIV-infected patients. The randomization, based on permuted blocks, was stratified according to center. The trial was approved by the institutional review boards of the participating hospitals, and all the patients gave written informed consent.

Patients were randomly assigned to continue or to discontinue prophylaxis against *P. carinii* pneumonia. Accepted regimens of prophylaxis were those recommended in the 1997 guidelines of the Public Health Service and the Infectious Diseases Society of America.¹¹ Accepted highly active antiretroviral therapy involved at least three antiretroviral drugs, one of which was a protease inhibitor or a non-nucleoside reverse-transcriptase inhibitor. *P. carinii* pneumonia was diagnosed either after microbiologic confirmation in respiratory samples or when the clinical and radiographic presentation was strongly suggestive of *P. carinii* pneumonia and there was a response to treatment only with agents active against *P. carinii*. When the CD4 cell counts of patients assigned to discontinue prophylaxis fell below 200 per cubic millimeter, prophylaxis was immediately reinstated, although the patients were kept in the study. An increase in the HIV-1 RNA level was not a criterion for re-starting prophylaxis.

Patients were evaluated at three-month intervals with a clinical assessment and laboratory monitoring that included measurements of CD4 cell counts and HIV-1 RNA levels, which were performed at each site. Lymphocyte subpopulations were measured at all centers by three-color flow cytometry. HIV-1 RNA levels were determined by either a polymerase-chain-reaction assay (Amplicor HIV-1 Monitor Assay, Roche Molecular Systems, Somerville, N.J.) or a branched-chain DNA assay (Chiron, Emeryville, Calif.). When the study was designed, most of the hospitals used techniques with a limit of detection of 400 copies per milliliter for the polymerase-chain-reaction assay or 500 copies per milliliter for the branched-chain DNA assay. Although by the end of the study all of the hospitals were able to detect levels as low as 200 copies per milliliter with the polymerase-chain-reaction assay or less than 50 copies per milliliter with the branched-chain DNA assay, we kept 500 copies per milliliter as the limit of detection for the HIV-1 RNA level throughout the study.

End Points and Follow-up

The primary end point in the assessment of safety was the occurrence of *P. carinii* pneumonia. The secondary end points were the development of an AIDS-defining event other than *P. carinii* pneumonia (a "C" event as defined by the Centers for Disease Control and Prevention [CDC]), the occurrence of drug-related adverse effects, the development of non-AIDS-defining bacterial infections, changes in CD4 cell counts and HIV-1 RNA levels, and death. Patients were removed from the study during follow-up if one of the following occurred: an AIDS-defining event (including *P. carinii* pneumonia), hypersensitivity to the prophylactic agents, discontinuation of highly active antiretroviral therapy, or voluntary withdrawal from the study. A fall in CD4 cell counts to under 200 per cubic millimeter was not a criterion for removal from the study.

Statistical Analysis

We assumed that *P. carinii* pneumonia would develop in 5 percent of patients receiving primary prophylaxis during the 12 months of follow-up and in at least 15 percent of patients who discontinued prophylaxis.²⁵ We estimated that at least 200 patients at risk would be needed in each group for the study to be able to detect a 10 percent difference with 90 percent certainty and a 5 percent significance level. Ten percent of patients were expected to be lost to follow-up.

We assumed that *P. carinii* pneumonia would develop in 15 percent of patients receiving secondary prophylaxis during the first 12 months of follow-up, and in at least 60 percent of patients who discontinued prophylaxis.⁴ We estimated that at least 30 patients at risk would be needed in each group to permit us to detect a 45 percent difference with 90 percent certainty and a 5 percent significance level. Ten percent of patients were expected to be lost to follow-up.

An intention-to-treat analysis was performed. Medians and interquartile ranges (25th to 75th percentile) were used as measures of central tendency and dispersion. Confidence intervals for both groups were calculated with the use of Poisson distribution tables. For the base-line variables, comparisons between groups were made with the chi-square test for categorical variables and the Mann-Whitney nonparametric test for quantitative variables. Multivariate analysis of variance with repeated measures was used to compare CD4 cell counts at enrollment and at the first, second, third, and fourth follow-up visits. A polynomial contrast was used to model the within-group sum of squares, and a difference contrast was used to model the between-group sum of squares. All reported P values were two-sided.

RESULTS

Primary Prophylaxis

A total of 474 patients with no history of *P. carinii* pneumonia were enrolled in the study between January 1, 1998, and January 31, 1999. Of these,

DISCONTINUATION OF *PNEUMOCYSTIS CARINII* PROPHYLAXIS IN HIV-INFECTED PATIENTS

TABLE 1. MAIN CHARACTERISTICS OF PATIENTS DISCONTINUING PRIMARY PROPHYLAXIS OR CONTINUING PRIMARY PROPHYLAXIS.*

| CHARACTERISTIC | GROUP DISCONTINUING PRIMARY PROPHYLAXIS (N=240) | GROUP CONTINUING PRIMARY PROPHYLAXIS (N=234) | CHARACTERISTIC | GROUP DISCONTINUING PRIMARY PROPHYLAXIS (N=240) | GROUP CONTINUING PRIMARY PROPHYLAXIS (N=234) |
|--|---|--|--|---|--|
| At base line | | | At base line (cont.) | | |
| Age — yr | | | Treatment received — no. of patients | | |
| Median | 36 | 36 | Lamivudine | 189 | 186 |
| Interquartile range | 33–41 | 33–40 | Stavudine | 165 | 157 |
| Male sex — no. (%) | 175 (73) | 169 (72) | Indinavir | 147 | 157 |
| Mode of acquisition — no. (%) | | | Zidovudine | 66 | 75 |
| Intravenous drug use | 125 (52) | 131 (56) | Saquinavir | 50 | 43 |
| Homosexual activity | 48 (20) | 42 (18) | Ritonavir | 26 | 29 |
| Heterosexual activity | 57 (24) | 59 (25) | Nelfinavir | 29 | 22 |
| Other | 10 (4) | 2 (1) | Didanosine | 23 | 37 |
| Time from diagnosis of HIV — yr | | | Nevirapine | 14 | 14 |
| Median | 7 | 8 | Zalcitabine | 6 | 2 |
| Interquartile range | 4–9 | 5–11 | | | |
| CDC group — no. (%)† | | | At follow-up | | |
| A-3 | 110 (46) | 98 (42) | Episodes of <i>P. carinii</i> pneumonia — no. | 0 | 0 |
| B-3 | 46 (19) | 40 (17) | Duration of follow-up after randomization | | |
| C-3 | 84 (35) | 96 (41) | Months | | |
| CD4 count — cells/mm ³ | | | Median | 20 | 19 |
| Nadir | | | Interquartile range | 17–25 | 15–24 |
| Median | 113 | 98 | Person-years | 387.9 | 370.5 |
| Interquartile range | 56–156 | 44–147 | 95% CI for no. of episodes/100 person-yr | 0–0.85 | 0–0.89 |
| At base line | | | 99% CI for no. of episodes/100 person-yr | 0–1.23 | 0–1.28 |
| Median | 342 | 329 | Duration of follow-up while CD4 ≥200/mm ³ | | |
| Interquartile range | 277–440 | 268–407 | Months | | |
| HIV-1 RNA | | | Median | 19 | 19 |
| <500 copies/ml — no. (%) | 197 (82) | 199 (85) | Interquartile range | 16–24 | 15–24 |
| Level if >500 copies/ml | | | Person-years | 377.7 | 360.1 |
| Median | 1100 | 2256 | 95% CI for no. of episodes/100 person-yr | 0–0.98 | 0–1.02 |
| Interquartile range | 791–2455 | 1448–2587 | Duration of follow-up while CD4 <200/mm ³ | | |
| Time with CD4 ≥200/mm ³ and HIV-1 RNA <5000/ml — mo | | | Months | | |
| Median | 9 | 8 | Median | 13 | 10 |
| Interquartile range | 5–14 | 5–11 | Interquartile range | 11–18 | 8–14 |
| Time receiving prophylaxis — mo | | | Person-years | 10.2 | 10.4 |
| Median | 34 | 35 | 95% CI for no. of episodes/100 person-yr | | |
| Interquartile range | 19–49 | 22–51 | “C” events | 1 | 1 |
| Time receiving HAART — mo | | | | | |
| Median | 15 | 16 | | | |
| Interquartile range | 10–59 | 10–20 | | | |

*CDC denotes Centers for Disease Control and Prevention, HAART highly active antiretroviral therapy, and CI confidence interval.

†Category A includes patients who have had no HIV-related diseases; category B includes patients who have had HIV-related diseases that are not in category C; category C includes patients who have had HIV-related diseases that are considered to be AIDS defining.^{2b}

240 were randomly assigned to discontinue prophylaxis and 234 to continue it. The groups were well balanced with regard to demographic characteristics (Table 1). Most of the patients were men and had at least a five-year history of HIV infection that included a long period with a CD4 cell count of less than 200 per cubic millimeter. One hundred twenty-one patients (54 in the group discontinuing prophylaxis and 67 in the group continuing prophylaxis) had a nadir CD4 cell count of no more than 50 per cubic millimeter. Ninety-one percent were receiving prophylaxis with trimethoprim-sulfamethoxazole. A total of 472 patients were receiving highly active antiretroviral therapy with a protease inhibitor and only

2 with a non-nucleoside reverse-transcriptase inhibitor. At enrollment, patients had had more than 200 CD4 cells per cubic millimeter and less than 5000 copies of HIV-1 RNA per milliliter for a median of 8 months (range, 3 to 72). A total of 172 patients had 200 to 299 CD4 cells per cubic millimeter at enrollment, and 169 were enrolled during the first 12 months of highly active antiretroviral therapy.

Of the 22 patients who dropped out of the study, 12 were lost to follow-up (7 assigned to discontinue prophylaxis and 5 assigned to continue it), 3 discontinued highly active antiretroviral therapy, 5 assigned to continue prophylaxis discontinued it after enrollment, and 2 in the group discontinuing prophylaxis

decided to resume it because they were concerned about the risk of *P. carinii* pneumonia. There were no significant differences in base-line characteristics between the patients who dropped out of the study and those who remained in it. To our knowledge, only a single patient (in the group continuing prophylaxis) had *P. carinii* pneumonia after dropping out of the study.

The median duration of follow-up was 20 months (range, 16 to 24). The CD4 cell counts and the proportion of patients with less than 500 copies of HIV-1 RNA per milliliter during follow-up were similar in the two groups ($P=0.67$ and $P=0.41$, respectively) (Fig. 1). In 21 patients (9 in the group discontinuing prophylaxis), CD4 cell counts fell below 200 per cubic millimeter, and prophylaxis had to be reintroduced for those in whom it had been discontinued. Ninety-two patients in the group discontinuing prophylaxis and 89 in the group continuing prophylaxis had more than 500 copies of HIV-1 RNA per milliliter during 136 person-years of follow-up (group discontinuing prophylaxis: median, 3250 copies per milliliter; range, 510 to 57,599; group continuing prophylaxis: median, 3458 copies per milliliter; range, 515 to 61,057). During follow-up, the protease inhibitor was replaced with a non-nucleoside reverse-transcriptase inhibitor in 36 patients (17 in the group discontinuing prophylaxis and 19 in the group continuing prophylaxis).

There were no episodes of *P. carinii* pneumonia in either group during follow-up — neither among those with a nadir CD4 cell count of less than 50 per cubic millimeter before enrollment (95 percent confidence interval, 0 to 4.6 episodes per 100 person-years for the group discontinuing prophylaxis vs. 0 to 4.3 for the group continuing prophylaxis; $P=0.48$) nor among those with more than 500 copies of HIV-1 RNA per milliliter during follow-up (95 percent confidence interval, 0 to 4.0 episodes per 100 person-years for the group discontinuing prophylaxis vs. 0 to 4.0 for the group continuing prophylaxis; $P=0.63$). Two patients (one in each group) had a “C” event, both with diagnoses of extrapulmonary tuberculosis. Two patients (one in each group) died of cancer (hepatic carcinoma and laryngeal carcinoma). *P. carinii* pneumonia did not develop during follow-up in any of the 21 patients whose CD4 cell counts fell below 200 per cubic millimeter.

Fourteen patients (seven in each group) had an infection during follow-up, including six with community-acquired pneumonia. In all of these patients, *P. carinii* was ruled out as the cause of the infection by microbiologic methods. No patient received empirical anti-*P. carinii* treatment in therapeutic doses. Drug-related adverse effects occurred in 49 patients (23 in the group discontinuing prophylaxis and 26 in the group continuing prophylaxis); they were related in most patients to the use of protease inhibitors and in 4 patients to the use of prophylactic agents

(3 of them discontinued prophylaxis). Finally, the antiretroviral treatment had to be modified in 78 patients (41 in the group discontinuing prophylaxis and 37 in the group continuing prophylaxis), either because of adverse effects of the antiretroviral drugs or because of virologic evidence of treatment failure.

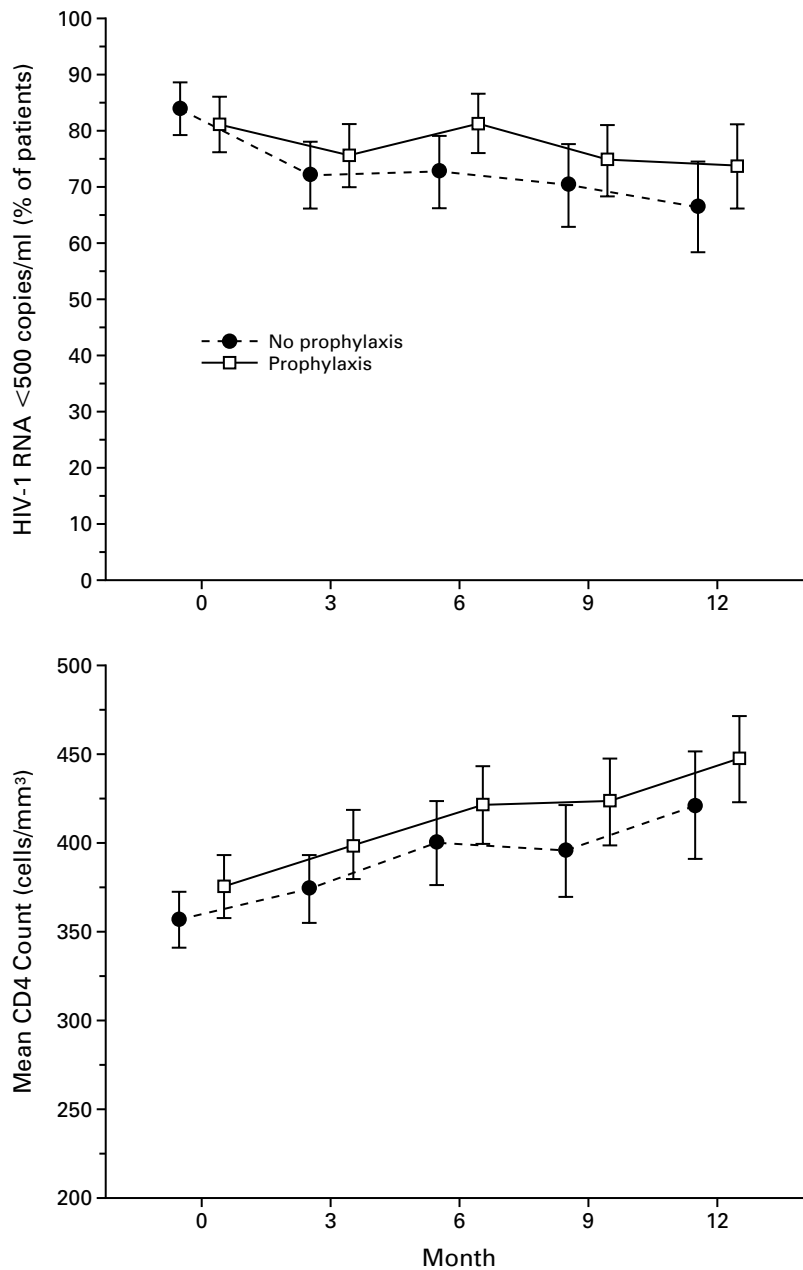
Secondary Prophylaxis

Between January 1, 1998, and June 30, 1999, 113 patients who had had a previous episode of *P. carinii* pneumonia were enrolled in the study. In 93 patients (82 percent), the infection had been diagnosed by microbiologic methods (48 in the group discontinuing prophylaxis and 45 in the group continuing prophylaxis). Sixty patients were randomly assigned to discontinue prophylaxis. The characteristics of the patients who were receiving secondary prophylaxis at study entry are shown in Table 2. Seventy-seven patients (68 percent) had a nadir CD4 cell count of less than 50 per cubic millimeter, and 61 (54 percent) were enrolled more than two years after the initial episode of *P. carinii* pneumonia. Ninety-five patients were receiving prophylaxis with trimethoprim-sulfamethoxazole. In all patients, the initial highly active antiretroviral therapy included a protease inhibitor, which resulted in steady increases in the CD4 cell counts. Twenty-seven patients (24 percent) had more than 500 copies of HIV-1 RNA per milliliter during follow-up (median, 1730; range, 506 to 26,494). The changes in CD4 cell counts, the number of patients with undetectable HIV-1 RNA levels, and the number of patients withdrawn from the study were similar in the group assigned to discontinue secondary prophylaxis and that assigned to continue prophylaxis (Table 2).

Two patients withdrew from the group discontinuing prophylaxis (one stopped highly active antiretroviral therapy, and the other decided to resume prophylaxis after *Haemophilus influenzae* pneumonia was diagnosed). Neither has had *P. carinii* pneumonia since they withdrew. After 65 person-years of follow-up, there were no episodes of *P. carinii* pneumonia or other “C” events in these patients (95 percent confidence interval for the incidence of *P. carinii* pneumonia or other “C” events in the group discontinuing prophylaxis, 0 to 4.57 episodes per 100 person-years of follow-up; and in the group continuing prophylaxis, 0 to 5.19 episodes per 100 person-years). The highly active antiretroviral regimen was modified in five patients in each group because of virologic evidence of treatment failure or because of adverse effects. One patient in each group had an episode of bacterial pneumonia.

DISCUSSION

This multicenter, randomized, nonblinded trial tested the safety of discontinuing primary and secondary prophylaxis against *P. carinii* pneumonia. We enrolled



NO. OF PATIENTS

| | | | | | |
|----------------|-----|-----|-----|-----|-----|
| No prophylaxis | 240 | 224 | 203 | 178 | 137 |
| Prophylaxis | 234 | 215 | 189 | 152 | 130 |

Figure 1. Mean CD4 Cell Counts and Proportions of Patients Who Had Undetectable HIV-1 RNA Levels at Base Line (Month 0) and during Follow-up, According to Whether They Were Assigned to Discontinue or Continue Primary Prophylaxis against *P. carinii* Pneumonia.

The bars represent 95 percent confidence intervals. Only data for the first 12 months of follow-up are included because of the small number of patients followed for more than 1 year. The curves have been offset for ease of viewing; all measurements were made at three-month intervals.

more than 500 patients at 19 Spanish hospitals. The patients were representative of the HIV-infected population in our country; that is, most of them were former intravenous drug users who had low CD4 cell counts and had been infected with HIV for a long period. Under these circumstances, *P. carinii* pneumonia can be expected to develop in a proportion of patients not receiving prophylaxis. However, none of them had an episode of *P. carinii* pneumonia after the discontinuation of prophylaxis; this was the case even among those receiving secondary prophylaxis, those with low nadir CD4 cell counts, and those with detectable HIV-1 RNA levels during follow-up. These data suggest that both primary and secondary prophylaxis against *P. carinii* pneumonia can be safely discontinued in HIV-infected patients who have improved immunologic function while receiving highly active antiretroviral therapy, as long as the CD4 cell count has remained at 200 or more per cubic millimeter for more than three months.

After the institution of highly active antiretroviral therapy, there is improvement in various immunologic variables,^{27,28} and after several years immune reconstitution may be achieved.^{29,30} The effect of therapy is reflected in a decrease in the incidence of opportunistic infections and death in HIV-infected patients.¹⁵⁻¹⁷ There are few studies of the discontinuation of primary prophylaxis against *P. carinii* pneumonia in patients with improved immunologic function during highly active antiretroviral therapy. Most of the studies have been observational, and *P. carinii* pneumonia developed in only one patient during follow-up.¹⁸⁻²² In a recent randomized trial in Italy in which primary prophylaxis against *P. carinii* was discontinued, no episodes of *P. carinii* pneumonia were reported after a median follow-up of six months.³¹

All these data, as well as the results of our own study, support the recommendation of the CDC that primary prophylaxis be discontinued in patients who have a sustained increase in the CD4 cell count to 200 or more per cubic millimeter for at least three to six months. Although there are no guidelines for the reintroduction of prophylaxis against *P. carinii* pneumonia, it is reasonable to resume it according to the criteria used for primary prophylaxis — i.e., when the CD4 cell count drops to less than 200 per cubic millimeter.

Among the patients in our study, 113 had had a previous episode of *P. carinii* pneumonia and were receiving secondary prophylaxis. It is well known that the risk of relapse after an initial episode is high without secondary prophylaxis; in these cases, the incidence of recurrent *P. carinii* pneumonia is 65 percent in patients who survive for more than 18 months.^{4,32} Indeed, the 1999 CDC guidelines do not recommend the discontinuation of secondary prophylaxis. There are few data regarding the discontinuation of prophylaxis in such patients, and most of the avail-

able data are from observational studies. An analysis of several European observational studies identified no cases of *P. carinii* pneumonia after 236 person-years of follow-up in 246 patients who discontinued prophylaxis.³³ Taken together, these results and those of our study — in which patients receiving secondary prophylaxis were randomly assigned to continue or discontinue it — suggest that prophylaxis can be discontinued even in patients who have had a previous episode of *P. carinii* pneumonia. However, this group is at higher risk for *P. carinii* pneumonia than those receiving primary prophylaxis, and patients who discontinue secondary prophylaxis should remain under close medical supervision.

Only two of our patients were receiving a non-nucleoside reverse-transcriptase inhibitor at the time of enrollment. Most previous studies of immune reconstitution in HIV-infected patients have been performed with the use of a protease inhibitor, and a recent study suggests that these drugs may also have activity against *P. carinii*.³⁴ For all these reasons, discontinuation of prophylaxis should be undertaken cautiously when patients are receiving protease-inhibitor-sparing regimens.

It is difficult to establish clear criteria for discontinuing prophylaxis against *P. carinii* pneumonia after highly active antiretroviral treatment has begun. We know the importance of the CD4 cell count and the HIV-1 RNA level in the development of opportunistic infections.^{1,35-37} After the initiation of highly active antiretroviral therapy, there have been reports of opportunistic infections developing during the first two or three months, especially in patients with less than 50 CD4 cells per cubic millimeter.^{38,39} For these reasons, our inclusion criteria for the discontinuation of prophylaxis against *P. carinii* pneumonia required that patients receive triple therapy resulting in an increase in the CD4 cell count to 200 or more per cubic millimeter and total or partial suppression of viral replication for at least three months. New studies should be undertaken to determine whether it is safe to discontinue prophylaxis when only one or two of these criteria are met.

It has been suggested that patients receiving highly active antiretroviral therapy that results in an increase in CD4 cell counts to 200 or more per cubic millimeter, but only partial suppression of viral replication, may not be as well protected as patients with full viral suppression.⁴⁰ Thirty-eight percent of our patients who discontinued either primary or secondary prophylaxis had more than 500 copies of HIV-1 RNA per milliliter at some point during follow-up, and neither *P. carinii* pneumonia nor any other opportunistic infections developed in any of these patients. Our data, as well as data from other studies,^{41,42} suggest that the HIV-1 RNA level is less predictive of the evolution of AIDS in patients receiving highly active antiretroviral therapy who have CD4 cell counts of

TABLE 2. MAIN CHARACTERISTICS OF PATIENTS DISCONTINUING SECONDARY PROPHYLAXIS OR CONTINUING SECONDARY PROPHYLAXIS.*

| CHARACTERISTIC | GROUP DISCONTINUING SECONDARY PROPHYLAXIS (N=60) | GROUP CONTINUING SECONDARY PROPHYLAXIS (N=53) |
|---|--|---|
| At base line | | |
| Age — yr | | |
| Median | 37 | 36 |
| Interquartile range | 33–39 | 32–40 |
| Male sex — no. (%) | 45 (75) | 41 (77) |
| Mode of acquisition — no. (%) | | |
| Intravenous drug use | 25 (42) | 24 (45) |
| Homosexual activity | 13 (22) | 10 (19) |
| Heterosexual activity | 20 (33) | 15 (28) |
| Other | 2 (3) | 4 (8) |
| CD4 count — cells/mm ³ | | |
| Nadir | | |
| Median | 32 | 26 |
| Interquartile range | 14–82 | 10–57 |
| At base line | | |
| Median | 355 | 350 |
| Interquartile range | 280–447 | 266–426 |
| HIV-1 RNA | | |
| <500 copies/ml — no. (%) | 52 (86) | 46 (87) |
| Level if >500 copies/ml | | |
| Median | 3161 | 2170 |
| Interquartile range | 2273–3942 | 1000–2828 |
| Time from <i>P. carinii</i> pneumonia to enrollment — mo | | |
| Median | 26 | 27 |
| Interquartile range | 18–41 | 10–37 |
| Time with CD4+ ≥200/mm ³ and HIV-1 RNA <5000/ml — mo | | |
| Median | 9 | 7 |
| Interquartile range | 6–14 | 4–16 |
| Time receiving HAART — mo | | |
| Median | 19 | 18 |
| Interquartile range | 13–24 | 13–25 |
| Treatment received — no. of patients | | |
| Lamivudine | 47 | 47 |
| Stavudine | 42 | 31 |
| Indinavir | 31 | 39 |
| Zidovudine | 16 | 22 |
| Ritonavir | 15 | 3 |
| Nelfinavir | 10 | 8 |
| Didanosine | 6 | 5 |
| Saqinavir | 9 | 5 |
| Nevirapine | 6 | 4 |
| At follow-up | | |
| CD4 cell count during follow-up — cells/mm ³ | | |
| Month 3 | | |
| Median | 408 | 370 |
| Interquartile range | 320–520 | 273–473 |
| Month 6 | | |
| Median | 430 | 380 |
| Interquartile range | 364–533 | 292–471 |
| Month 9 | | |
| Median | 476 | 400 |
| Interquartile range | 368–628 | 280–506 |
| Month 12 | | |
| Median | 491 | 513 |
| Interquartile range | 404–632 | 416–578 |
| Episodes of <i>P. carinii</i> pneumonia — no. | 0 | 0 |
| Duration of follow-up after randomization | | |
| Months | | |
| Median | 12 | 11 |
| Interquartile range | 10–16 | 10–15 |
| Person-years | 65.4 | 57.6 |
| 95% CI for no. of episodes/100 person-yr | 0–4.57 | 0–5.19 |
| 99% CI for no. of episodes/100 person-yr | 0–7.29 | 0–8.28 |
| “C” events — no. | 0 | 0 |

*HAART denotes highly active antiretroviral treatment, and CI confidence interval.

200 or more per cubic millimeter than in patients not receiving highly active antiretroviral therapy.

In conclusion, the results of this randomized study suggest that primary and secondary prophylaxis against *P. carinii* pneumonia may be safely discontinued during highly active antiretroviral therapy when the CD4 cell count has remained above 200 cells per cubic millimeter for more than three months — even in patients with incomplete suppression of viral replication. In the absence of further data, it seems prudent to reinstitute prophylaxis when the CD4 cell count drops below 200 per cubic millimeter.

Supported by the Grupo de Estudio del SIDA de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (GESIDA/SEIMC), by the National AIDS Plan Secretariat of the Spanish Ministry of Health, and by DuPont Pharma Laboratories.

Presented in part at the 6th Conference on Retrovirus and Opportunistic Infections, Chicago, January 31–February 4, 1999, and at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, San Francisco, September 26–29, 1999.

We are indebted to Thomas O'Boyle for his assistance with the English version of the manuscript.

APPENDIX

The members of the GESIDA 04/98 Study Group were as follows: J. Berenguer, P. Miralles, and B. Padilla, Hospital Gregorio Marañón, Madrid; B. Gómez and J.M. Gatell, Institut d'Investigacions Biomèdiques August Pi I Sunyer and Hospital Clinic Universitari, Barcelona; J.R. Arribas and J.J. Vazquez, Hospital La Paz, Madrid; M. Santín, E. Ferrer, and F. Guardiola, Ciutat Sanitaria de Bellvitge, L'Hospitalet; A. Pahissa, Hospital General Vall d'Hebron, Barcelona; J. Arrizabalaga, J.A. Iribarren, and M.A. von Wichmann, Hospital Nuestra Señora de Aránzazu, Donostia; P. Viciana, Hospital Virgen del Rocío, Seville; F. Laguna and E. Valencia, Hospital Carlos III, Instituto de Salud Carlos III, Madrid; R. Rubio and F. Pulido, Hospital 12 de Octubre, Madrid; F. Dronza, A. Antela, and S. Moreno, Hospital Ramón y Cajal, Madrid; G. Siera and B. Clotet, Hospital Germans Trias i Pujol, Badalona; C. Barros, Hospital General de Móstoles, Madrid; D. Dalmau and X. Martínez-Lacasa, Mutua de Terrassa, Terrassa; H. Knobel, Hospital de Nuestra Señora del Mar, Barcelona; K. Aguirrebengoa and M. Montejo, Hospital de Cruces, Vizcaya; J. Sola, Hospital de Navarra, Pamplona; J. Gómez, Hospital Severo Ochoa, Madrid; J. Sanz, Hospital Principe de Asturias, Madrid; and V. de Miguel, Agencia de Ensayos Clínicos de GESIDA/SEIMC, Madrid — all in Spain. The members of the GESIDA 04/98 steering committee were J.C. Lopez, J.M. Miro, J.M. Peña, D. Podzamczar, X. Claramonte, J.C. Alberdi, and V. de Miguel.

REFERENCES

- Phair J, Muñoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. *N Engl J Med* 1990;322:161-5.
- Selik RM, Starcher ET, Curran JW. Opportunistic diseases reported in AIDS patients: frequencies, associations, and trends. *AIDS* 1987;1:175-82.
- Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. *JAMA* 1989;262:335-9.
- Montaner JS, Lawson LM, Gervais A, et al. Aerosol pentamidine for secondary prophylaxis of AIDS-related *Pneumocystis carinii* pneumonia: a randomized, placebo-controlled study. *Ann Intern Med* 1991;114:948-53.
- Fischl MA, Dickinson GM, La Voie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. *JAMA* 1988;259:1185-9.
- Raviglione MC, Nsah EN, Cortes H, Mariuz P, Sanjana V. Intermittent co-trimoxazole prophylaxis against *Pneumocystis carinii* pneumonia. *Lancet* 1990;336:180.
- Podzamczar D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of *Pneumocystis pneumonia* and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995;122:755-61.
- Schneider MME, Hoepelman AIM, Eeftink Schattenkerk JKM, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. *N Engl J Med* 1992;327:1836-41.
- Bozzette SA, Fothall D, Sattler FR, et al. The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease. *Am J Med* 1995;98:177-82.
- Martin MA, Cox PH, Beck K, Styer CM, Beall GN. A comparison of the effectiveness of three regimens in the prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients. *Arch Intern Med* 1992;152:523-8.
- 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep* 1997;46(RR-12):1-46.
- El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998;339:1889-95.
- Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997;337:734-9.
- Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of zidovudine in advanced HIV-1 disease. *Lancet* 1998;351:543-9.
- Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* 1998;352:1725-30.
- Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;338:853-60.
- Forrest DM, Seminari E, Hogg RS, et al. The incidence and spectrum of AIDS-defining illnesses in persons treated with antiretroviral drugs. *Clin Infect Dis* 1998;27:1379-85.
- Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. *N Engl J Med* 1999;340:1301-6.
- Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS* 1999;13:1647-51.
- Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet* 1999;353:201-3.
- Weverling GJ, Mocroft A, Ledergerber B, et al. Discontinuation of *Pneumocystis carinii* pneumonia after start of highly active antiretroviral therapy in HIV-1 infection. *Lancet* 1999;353:1293-8.
- Soriano V, Dona C, Rodríguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS* 2000;14:383-6.
- Lopez JC, Peña JM, Miro JM, Podzamczar D, GESIDA 04/98 Study Group. Discontinuation of PCP prophylaxis is safe in HIV-infected patients with immunological recovery with HAART: preliminary results of an open, randomized and multicentric clinical trial (GESIDA 04/98). In: Program and abstracts of the Sixth Conference on Retrovirus and Opportunistic Infections, Chicago, January 31–February 4, 1999. Alexandria, Va.: Foundation for Human Retrovirology, 1999:206. abstract.
- 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). *MMWR Morb Mortal Wkly Rep* 1999;48(RR-10):1-59, 61-6.
- Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome: AIDS Clinical Trials Group protocol 021. *N Engl J Med* 1992;327:1842-8.
- 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep* 1992;41(RR-17):1-13.
- Gorochoff G, Neumann AU, Kereveur A, et al. Perturbation of CD4+ and CD8+ T-cell repertoires during progression to AIDS and regulation of the CD4+ repertoire during antiviral therapy. *Nat Med* 1998;4:215-21.
- Valdez H, Smith K, Lederman M, et al. Response to immunization with recall antigens and neoantigens after 48 weeks of HAART. In: Program and abstracts of the Sixth Conference on Retrovirus and Opportunistic

- istic Infections, Chicago, January 31–February 4, 1999. Alexandria, Va.: Foundation for Human Retrovirology, 1999:130. abstract.
29. Gea-Banacloche JC, Lane HC. Immune reconstitution in HIV infection. *AIDS* 1999;13:Suppl A:S25-S38.
30. Carcelain G, Li T, Autran B. Immune reconstitution under highly active antiretroviral therapy. *AIDS Rev* 1999;1:51-6.
31. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis* 2000;181:1635-42.
32. Huang L, Stansell JD. *Pneumocystis carinii* pneumonia. In: Sande MA, Volberding PA, eds. *The medical management of AIDS*. 6th ed. Philadelphia: W.B. Saunders, 1999:305-30.
33. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. *N Engl J Med* 2001;344:168-74.
34. Atzori C, Angeli E, Mainini A, Agostoni F, Micheli V, Cargnel A. In vitro activity of human immunodeficiency virus protease inhibitors against *Pneumocystis carinii*. *J Infect Dis* 2000;181:1629-34.
35. Stansell JD, Osmond DH, Charlebois E, et al. Predictors of *Pneumocystis carinii* pneumonia in HIV-infected persons. *Am J Respir Crit Care Med* 1997;155:60-6.
36. Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996;272:1167-70. [Erratum, *Science* 1997;275:14.]
37. Romeu J, Balague M, Ruiz L, et al. Short-term risk for AIDS-indicator diseases predicted by plasma HIV-1 RNA and CD4+ lymphocytes. *Scand J Infect Dis* 1999;31:37-42.
38. Jacobson MA, Zegans M, Pavan PR, et al. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. *Lancet* 1997;349:1443-5.
39. Michelet C, Arvieux C, Francois C, et al. Opportunistic infections occurring during highly active antiretroviral treatment. *AIDS* 1998;12:1815-22.
40. Masur H, Kaplan J. Does *Pneumocystis carinii* prophylaxis still need to be lifelong? *N Engl J Med* 1999;340:1356-8.
41. Moore RD, Keruly JC, Chaisson RE. Decline in CMV and other opportunistic diseases with combination antiretroviral therapy. In: Program and abstracts of the Fifth Conference on Retrovirus and Opportunistic Infections, Chicago, February 1–5, 1998. Alexandria, Va.: Foundation for Retrovirus and Human Health, 1999:113. abstract.
42. Kaplan JE, Hanson DL, Dworkin MS, Jones JL. HIV plasma RNA, an independent predictor of opportunistic infections in HIV-infected persons. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 26–29, 1999. Washington, D.C.: American Society for Microbiology, 1999: 124. abstract.

Copyright © 2001 Massachusetts Medical Society.

FULL TEXT OF ALL *JOURNAL* ARTICLES ON THE WORLD WIDE WEB

Access to the complete text of the *Journal* on the Internet is free to all subscribers. To use this Web site, subscribers should go to the *Journal's* home page (www.nejm.org) and register by entering their names and subscriber numbers as they appear on their mailing labels. After this one-time registration, subscribers can use their passwords to log on for electronic access to the entire *Journal* from any computer that is connected to the Internet. Features include a library of all issues since January 1993, a full-text search capacity, a personal archive for saving articles and search results of interest, and free software for downloading articles so they can be printed in a format that is virtually identical to that of the typeset pages.
