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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

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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.)

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

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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 reinstituted, although the patients were kept in the study. An increase in the HIV-1 RNA level was not a criterion for restarting 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,

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)
At base line		
Age — yr		
Median	36	36
Interquartile range	33–41	33–40
Male sex — no. (%)	175 (73)	169 (72)
Mode of acquisition — no. (%)		
Intravenous drug use	125 (52)	131 (56)
Homosexual activity	48 (20)	42 (18)
Heterosexual activity	57 (24)	59 (25)
Other	10 (4)	2 (1)
Time from diagnosis of HIV — yr		
Median	7	8
Interquartile range	4–9	5–11
CDC group — no. (%)†		
A-3	110 (46)	98 (42)
B-3	46 (19)	40 (17)
C-3	84 (35)	96 (41)
CD4 count — cells/mm³		
Nadir		
Median	113	98
Interquartile range	56–156	44–147
At base line		
Median	342	329
Interquartile range	277–440	268–407
HIV-1 RNA		
<500 copies/ml — no. (%)	197 (82)	199 (85)
Level if >500 copies/ml		
Median	1100	2256
Interquartile range	791–2455	1448–2587
Time with CD4 ≥200/mm³ and HIV-1 RNA <5000/ml — mo		
Median	9	8
Interquartile range	5–14	5–11
Time receiving prophylaxis — mo		
Median	34	35
Interquartile range	19–49	22–51
Time receiving HAART — mo		
Median	15	16
Interquartile range	10–59	10–20
At base line (cont.)		
Treatment received — no. of patients		
Lamivudine	189	186
Stavudine	165	157
Indinavir	147	157
Zidovudine	66	75
Saquinavir	50	43
Ritonavir	26	29
Nelfinavir	29	22
Didanosine	23	37
Nevirapine	14	14
Zalcitabine	6	2
At follow-up		
Episodes of *P. carinii* pneumonia — no.	0	0
Duration of follow-up after randomization		
Months		
Median	20	19
Interquartile range	17–25	15–24
Person-years	387.9	370.5
95% CI for no. of episodes/100 person-yr	0–0.85	0–0.89
99% CI for no. of episodes/100 person-yr	0–1.23	0–1.28
Duration of follow-up while CD4 ≥200/mm³		
Months		
Median	19	19
Interquartile range	16–24	15–24
Person-years	377.7	360.1
95% CI for no. of episodes/100 person-yr	0–0.98	0–1.02
Duration of follow-up while CD4 <200/mm³		
Months		
Median	13	10
Interquartile range	11–18	8–14
Person-years	10.2	10.4
95% CI for no. of episodes/100 person-yr		
"C" events	1	1

*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.[26]

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.

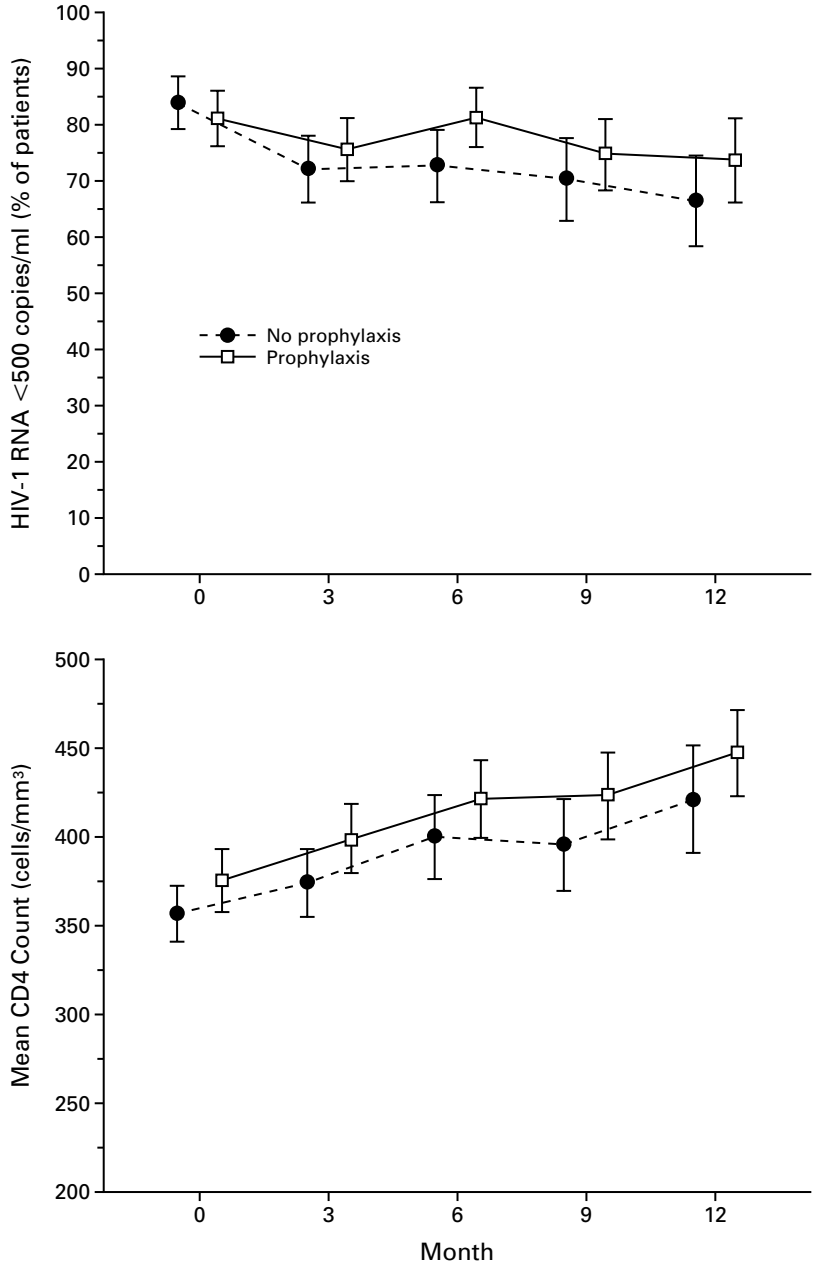
Secondary Prophylaxis

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 available 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 nonnucleoside 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/mm³		
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 *P. carinii* pneumonia to enrollment — mo		
Median	26	27
Interquartile range	18–41	10–37
Time with CD4+ ≥200/mm³ 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
Saquinavir	9	5
Nevirapine	6	4
At follow-up		
CD4 cell count during follow-up — cells/mm³		
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 *P. carinii* 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.

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APPENDIX

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