

**DISCONTINUATION OF SECONDARY PROPHYLAXIS
AGAINST *PNEUMOCYSTIS CARINII* PNEUMONIA IN PATIENTS
WITH HIV INFECTION WHO HAVE A RESPONSE TO ANTIRETROVIRAL THERAPY**

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ABSTRACT

Background Patients with human immunodeficiency virus (HIV) infection and a history of *Pneumocystis carinii* pneumonia are at high risk for relapse if they are not given secondary prophylaxis. Whether secondary prophylaxis against *P. carinii* pneumonia can be safely discontinued in patients who have a response to highly active antiretroviral therapy is not known.

Methods We analyzed episodes of recurrent *P. carinii* pneumonia in 325 HIV-infected patients (275 men and 50 women) in eight prospective European cohorts. Between October 1996 and January 2000, these patients discontinued secondary prophylaxis during treatment with at least three anti-HIV drugs after they had at least one peripheral-blood CD4 cell count of more than 200 cells per cubic millimeter.

Results Secondary prophylaxis was discontinued at a median CD4 cell count of 350 per cubic millimeter; the median nadir CD4 cell count had been 50 per cubic millimeter. The median duration of the increase in the CD4 cell count to more than 200 per cubic millimeter after discontinuation of secondary prophylaxis was 11 months. The median follow-up period after discontinuation of secondary prophylaxis was 13 months, yielding a total of 374 person-years of follow-up; for 355 of these person-years, CD4 cell counts remained at or above 200 per cubic millimeter. No cases of recurrent *P. carinii* pneumonia were diagnosed during this period; the incidence was thus 0 per 100 patient-years (99 percent confidence interval, 0 to 1.2 per 100 patient-years, on the basis of the entire follow-up period, and 0 to 1.3 per 100 patient-years, on the basis of the follow-up period during which CD4 cell counts remained at or above 200 per cubic millimeter).

Conclusions It is safe to discontinue secondary prophylaxis against *P. carinii* pneumonia in patients with HIV infection who have an immunologic response to highly active antiretroviral therapy. (N Engl J Med 2001; 344:168-74.)

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THE life expectancy of patients with human immunodeficiency virus (HIV) infection has dramatically improved,¹⁻⁴ and the risk of opportunistic infections, including *Pneumocystis carinii* pneumonia, has markedly declined in industrialized countries since 1996^{1,5} because of the widespread use of highly active antiretroviral therapy. This decline has suggested that highly active antiretroviral therapy results in clinically important immune

reconstitution. The absolute risk of the progression of HIV disease was markedly lower in patients who had an increase in CD4 cell counts in peripheral blood to more than 200 per cubic millimeter than in patients who had no such increase.⁶ The degree of protection conferred could have been overestimated in these studies, because the majority of patients continued to use standard prophylactic medication against various opportunistic infections, including *P. carinii* pneumonia. However, several studies have subsequently indicated that the reduction in the risk of primary *P. carinii* pneumonia is maintained after the discontinuation of specific chemoprophylaxis.⁷⁻¹⁰ These findings resulted in recommendations for the discontinuation of primary prophylaxis against *P. carinii* pneumonia in patients who have a response to antiretroviral therapy.¹¹

The risk of recurrence of *P. carinii* pneumonia is substantially higher than the risk of primary *P. carinii* pneumonia.¹² This increase in risk is almost certainly due to the fact that the immune system is more profoundly compromised in patients in whom pneumonia has already developed, and to the presence of residual *P. carinii* organisms in the lungs despite a clinical response to therapy.¹³ Thus, recommendations regarding the safety of discontinuing primary prophylaxis cannot simply be extrapolated to the discontinuation of secondary prophylaxis.

We therefore analyzed data on eight European cohorts of HIV-infected patients who had been successfully treated for an episode of *P. carinii* pneumonia, whose CD4 cell count had risen to more than 200 per cubic millimeter, and who subsequently discontinued chemoprophylaxis against recurrent *P. carinii* pneumonia.

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*Members of the study groups are listed in the Appendix.

METHODS

Participating Cohort Studies

Our analysis included data from eight large prospective European cohort studies (Table 1), all of which have been approved by local ethics committees, use standardized methods of data collection, and schedule follow-up visits at least once every six months. Additional measurements of peripheral-blood CD4 cell counts and plasma levels of HIV type 1 (HIV-1) RNA, determined at the time of routine evaluations at the 162 participating clinics, are also recorded. One of the eight studies, the EuroSIDA study, is a multicenter study and may include patients who are also members of the other cohorts. Therefore, each of the other cohort studies verified that none of its patients were also enrolled in the EuroSIDA study.

Inclusion and Exclusion Criteria

We included patients with HIV-1 infection who had previously been given a definitive or presumptive diagnosis of *P. carinii* pneumonia and had received secondary prophylaxis against recurrent pneumonia, which was discontinued between October 1996 and January 2000, during highly active antiretroviral treatment after their CD4 cell counts had risen to more than 200 per cubic millimeter. The decision to discontinue prophylaxis was the result of consultation between individual patients and their physicians and reflected the assumption that the increased CD4 cell counts induced by highly active antiretroviral therapy were indeed clinically protective. In some countries, discontinuation of secondary prophylaxis against *P. carinii* pneumonia was even formulated in official treatment guidelines.

Secondary prophylaxis was defined as treatment with any drug with known activity against *P. carinii* or *Toxoplasma gondii* and included trimethoprim-sulfamethoxazole, inhaled pentamidine, dapsone, pyrimethamine, and atovaquone. Highly active antiretroviral therapy was defined as therapy with at least one protease inhibitor or non-nucleoside-analogue reverse-transcriptase inhibitor in combination with at least two nucleoside-analogue reverse-transcriptase inhibitors. Patients whose CD4 cell counts for the six months pre-

ceding the discontinuation of secondary prophylaxis were unavailable and patients who were unavailable for follow-up were excluded from the analysis.

End Points

Recurrence of *P. carinii* pneumonia, diagnosed definitively or presumptively, after the discontinuation of secondary prophylaxis was the primary end point of the study. A diagnosis was considered definitive if *P. carinii* was found on microscopical analysis of induced sputum or bronchoalveolar-lavage fluid or on histologic examination of a specimen of lung tissue. The diagnosis of *P. carinii* pneumonia was considered presumptive if results from invasive pulmonary diagnostic procedures were not available. At a minimum, a presumptive diagnosis required a recent history of dyspnea on exertion or nonproductive cough, an appropriate response to any of the standard recommended treatments for *P. carinii* pneumonia, and the absence of evidence of bacterial pneumonia.

The secondary end points of the study were bacterial pneumonia, death or any new illness classified as defining the acquired immunodeficiency syndrome (AIDS), CD4 cell counts of less than 200 per cubic millimeter, and reinstitution of secondary prophylaxis — all occurring after the discontinuation of secondary prophylaxis. A diagnosis of bacterial pneumonia required documentation of a compatible clinical history, including an acute onset of pulmonary symptoms, and typical pulmonary infiltrates on a chest radiograph, together with a response to antibacterial drugs with no known activity against *P. carinii*. Furthermore, most study groups performed a careful retrospective chart review of all patients to identify single episodes of bacterial pneumonia and to confirm the other study end points.

Statistical Analysis

Patient selection and data extraction were performed at the data centers of the participating cohort studies. Data on a predefined set of anonymous demographic, laboratory, and clinical variables from the selected patients were then pooled and analyzed centrally. Follow-up was measured from the date of discontinuation of secondary

TABLE 1. COHORTS INCLUDED IN THE STUDY.*

VARIABLE	EUROSIDA	ATHENA†	SWISS HIV COHORT STUDY	DANISH COHORT OF PATIENTS STOPPING PROPHYLAXIS	FRANKFURT HIV COHORT	HSR COHORT	NICE DMI-2 COHORT	ICONA
Initial report	Lundgren et al. ¹⁴	—	Ledergerber et al. ¹⁵	Kirk et al. ¹⁰	Brodth et al. ¹⁶	Rizzardi et al. ¹⁷	Pradiri et al. ¹⁸	d'Arminio Monforte et al. ¹⁹
Country	20 in Europe	Netherlands	Switzerland	Denmark	Germany	Italy	France	Italy
No. of centers	60	22	7	5	1	1	1	65
Year of initiation of study	1994	1998‡	1988	1997	1988	1991	1988	1997
Interval between follow-up visits — mo	6	3–4	6	3	1–2	3	6	6
Cumulative no. of patients	8457	2553	10,763	346	4789	3600	5175	4166
No. of patients receiving highly active antiretroviral therapy as of April 2000	4845	2553	3,212	—§	2100	2150	1856	2040
No. of patients included in analysis	81	85	62	29	26	17	15	10
No. of person-years of follow-up after discontinuation of secondary prophylaxis	104	99	60	34	33	21	15	8

*ATHENA denotes AIDS Therapy Evaluation Project Netherlands; HSR Hospedale San Raffaele; DMI-2 Dossier Médico-économique de l'Immuno-déficience Humaine, version 2; and ICONA Italian Cohort of Patients Naive to Antiretrovirals.

†A retrospective chart review to identify single episodes of bacterial pneumonia was not feasible for this cohort.

‡Retrospective information was available for all patients who were receiving highly active antiretroviral therapy as of July 1996.

§This cohort included only patients who discontinued prophylaxis against opportunistic infections.

prophylaxis against *P. carinii* pneumonia until the date of the last clinical follow-up, the date of reinitiation of secondary prophylaxis, or the date of diagnosis of recurrent *P. carinii* pneumonia. In a separate analysis, follow-up was restricted to the periods when CD4 cell counts remained at or above 200 per cubic millimeter. The closing date for the analysis was April 19, 2000. Recurrent cases of *P. carinii* pneumonia and bacterial pneumonia were assumed to have a Poisson distribution, and exact confidence intervals were calculated for the incidence. The length of time to the documentation of a CD4 cell count of less than 200 per cubic millimeter and the length of time to the reinitiation of secondary prophylaxis were analyzed by the Kaplan–Meier method. All reported P values are two-sided. We used Stata software (version 6.0, Stata, College Station, Tex.) for statistical analyses.

RESULTS

A total of 325 patients fulfilled the inclusion criteria. Their characteristics at the time of the discontinuation of secondary prophylaxis against *P. carinii* pneumonia are shown in Table 2. The median age was 38 years, and 85 percent of the patients were men. The median CD4 cell count at the time secondary prophylaxis was discontinued was 350 per cubic millimeter; the median nadir CD4 cell count had been 50 per cubic millimeter. Highly active antiretroviral therapy included a single protease inhibitor and two nucleoside-analogue reverse-transcriptase inhibitors in 74 percent of the patients. Two protease inhibitors or a non-nucleoside-analogue reverse-transcriptase inhibitor, together with at least two nucleoside-analogue reverse-transcriptase inhibitors, were used in 17 percent and 9 percent of patients, respectively.

CD4 Cell Dynamics

The evolution of CD4 cell counts from the diagnosis of *P. carinii* pneumonia to the start of highly active antiretroviral therapy, the discontinuation of secondary prophylaxis, and the last available CD4 cell count are shown in Figure 1. The median increase in CD4 cell counts from the nadir to the value at the time secondary prophylaxis was discontinued was 283 per cubic millimeter. After secondary prophylaxis was discontinued, the CD4 cell counts increased further by a median of 50 per cubic millimeter, but in 27 patients (8 percent) they dropped to less than 200 per cubic millimeter (Table 3). The probability that a patient would have a CD4 cell count of less than 200 per cubic millimeter 12 and 24 months after secondary prophylaxis was discontinued was 8 percent (95 percent confidence interval, 5 to 12 percent) and 14 percent (95 percent confidence interval, 9 to 23 percent), respectively. In 20 (74 percent) of the 27 patients whose CD4 cell counts fell to less than 200 per cubic millimeter after discontinuation of secondary prophylaxis, the last available CD4 count (after a median of eight months) was again well above 200 cells per cubic millimeter, with a median of 316 cells per cubic millimeter.

Incidence of Events during Follow-up

No diagnoses of recurrent *P. carinii* pneumonia were recorded during 374 person-years of follow-up

TABLE 2. CHARACTERISTICS OF THE 325 STUDY PATIENTS AT THE DISCONTINUATION OF SECONDARY PROPHYLAXIS AND CD4 CELL COUNTS AT THE END OF THE STUDY.

CHARACTERISTIC	VALUE
Age — yr	
Median	38
Interquartile range	34–45
Sex — no. (%)	
Male	275 (85)
Female	50 (15)
Risk factor for transmission — no. (%)	
Male homosexual contact	184 (57)
Heterosexual contact	74 (23)
Injection-drug use	40 (12)
Other or unknown	27 (8)
Nadir CD4 count — cells/mm ³	
Median	50
Interquartile range	18–106
Type of diagnosis of <i>P. carinii</i> pneumonia — no. (%)	
Definitive	270 (83)
Presumptive	55 (17)
CD4 count during <i>P. carinii</i> pneumonia — cells/mm ³ *	
Median	60
Interquartile range	20–134
Type of prophylaxis against <i>P. carinii</i> pneumonia — no. (%)	
Trimethoprim–sulfamethoxazole	216 (66)
Pentamidine	65 (20)
Dapsone and pyrimethamine	29 (9)
Other	15 (5)
Duration of prophylaxis — mo	
Median	26
Interquartile range	15–38
Highly active antiretroviral therapy — no. (%)	
3 Drugs	264 (81)
>3 Drugs	61 (19)
Regimen including a protease inhibitor	313 (96)
Duration of highly active antiretroviral therapy at discontinuation of secondary prophylaxis — mo	
Median	19
Interquartile range	12–26
Duration of increase in CD4 count to ≥200 cells/mm ³ at discontinuation of secondary prophylaxis — mo	
Median	11
Interquartile range	6–18
CD4 count at discontinuation of secondary prophylaxis — cells/mm ³	
Median	350
Interquartile range	277–477
Plasma HIV-1 RNA level at discontinuation of secondary prophylaxis — no. (%)†	
<500 copies/ml	246 (76)
500–10,000 copies/ml	55 (17)
>10,000 copies/ml	23 (7)
CD4 count at end of study — cells/mm ³	
Median	425
Interquartile range	337–555

*Values were available within six months before diagnosis for 231 patients.

†Values were available for 324 patients.

in the absence of secondary prophylaxis (Table 3). The incidence was therefore 0, with an upper 99 percent confidence limit of 1.2 per 100 person-years of follow-up. For 355 person-years of follow-up, CD4 cell counts were at or above 200 per cubic millimeter, resulting in an upper 99 percent confidence limit of 1.3 per 100 person-years.

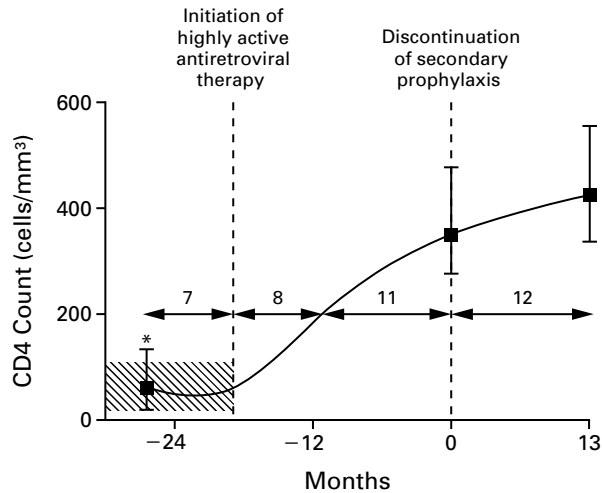


Figure 1. Evolution of CD4 Cell Counts in 325 Patients with HIV Infection and a History of *P. carinii* Pneumonia in Whom Highly Active Antiretroviral Therapy Was Initiated and Secondary Prophylaxis Was Subsequently Discontinued after CD4 Cell Counts Had Risen to More Than 200 per Cubic Millimeter.

Median CD4 cell counts are shown, with interquartile ranges. CD4 cell counts measured within six months before the diagnosis of *P. carinii* pneumonia (asterisk) were available for 231 patients. The numbers above the arrows indicate the median times (in months) between the various periods. The hatched area denotes the nadir CD4 cell counts (with the interquartile range).

One patient decided to stop highly active antiretroviral therapy but resumed secondary prophylaxis; in this patient, a presumptive diagnosis of *P. carinii* pneumonia with a CD4 cell count of 12 per cubic millimeter was made six months later. Five patients had a new AIDS-defining illness, and four patients died during follow-up. A diagnosis of bacterial pneumonia was made in 7 of the 222 patients from the seven cohorts that had collected this information.

Reinstitution of Secondary Prophylaxis

Fifteen of 325 patients (5 percent) began secondary prophylaxis again during follow-up, including 11 patients whose CD4 cell counts remained above 200 per cubic millimeter (Fig. 2). For most of these 11 patients, the reason for the reinstitution of secondary prophylaxis was a decline in CD4 cell counts, which frequently occurred in conjunction with incomplete control of HIV replication.

DISCUSSION

This study supports the hypothesis that the CD4 cell recovery associated with highly active antiretroviral therapy leads to profoundly improved protection against opportunistic infections that are common in patients with HIV infection who have low CD4 cell

TABLE 3. CHARACTERISTICS OF THE 325 STUDY PATIENTS DURING FOLLOW-UP.

CHARACTERISTIC	VALUE
Duration of follow-up — mo	
Median	13
Interquartile range	7–19
Total follow-up — person-yr*	374
Incidence of recurrent <i>P. carinii</i> pneumonia — per 100 person-yr†	0
Upper 95% confidence limit	0.8
Upper 99% confidence limit	1.2
Incidence of bacterial pneumonia — per 100 person-yr‡	2.7
95% confidence interval	1.1–5.6
99% confidence interval	0.8–6.6
New AIDS-defining events — no. of patients§	5
Death — no. of patients¶	4
Patients lost to follow-up — no. (%)	23 (7)
Patients in whom CD4 counts dropped below 200 cells/mm ³ — no. (%)	27 (8)
Patients with reinstitution of secondary prophylaxis — no. (%)	15 (5)
Patients with reinstitution of secondary prophylaxis after CD4 counts dropped below 200 cells/mm ³ — no. (%)	4 (1)

*For 355 years of follow-up, CD4 cell counts were at or above 200 per cubic millimeter, resulting in a 99 percent confidence interval for the incidence of recurrent *P. carinii* pneumonia of 0 to 1.3 per 100 person-years.

†The exact Poisson confidence limits are one-sided.

‡Seven patients had bacterial pneumonia 0.4, 1, 6, 7, 9, 10, and 29 months after the discontinuation of secondary prophylaxis. One patient had a clinical diagnosis only; bacterial pneumonia was confirmed in all other patients by evidence of infiltrates on chest radiographs and good responses to antibacterial-drug treatment. This analysis is based on 222 patients, who accounted for 258 person-years of follow-up, since not all cohorts were able to provide data on single episodes of bacterial pneumonia.

§One patient each had candida esophagitis two weeks after the discontinuation of secondary prophylaxis, wasting syndrome at four months, atypical mycobacteriosis at six months, Kaposi's sarcoma at eight months, and indeterminate intracerebral lesions at nine months.

¶Deaths occurred 11, 13, 14, and 18 months after the discontinuation of secondary prophylaxis and were due to laryngeal carcinoma, bacterial pneumonia (3 months after the reinstitution of secondary prophylaxis), liver cirrhosis, and an unknown cause, respectively.

counts.^{20,21} If CD4 cell recovery were not associated with protection against recurrent *P. carinii* pneumonia, we would have expected — on the basis of historical data — that more than 50 percent of the patients would have a relapse of *P. carinii* pneumonia during follow-up.¹² However, *P. carinii* pneumonia did not develop in any of the patients after secondary prophylaxis was discontinued.

Several studies have previously addressed this issue, with similar results,^{7,8,10,22} but none of these studies were conclusive, given their small samples and hence their wide confidence intervals. The upper 99 percent confidence limit of the incidence of *P. carinii* pneumonia in the present study was only 1.2 cases per 100 person-years of follow-up. Thus, although we cannot exclude the possibility that *P. carinii* pneumonia may develop in patients who discontinue secondary prophylaxis, the risk is very low. Similarly, although a relatively low risk of a primary episode of *P. carinii*

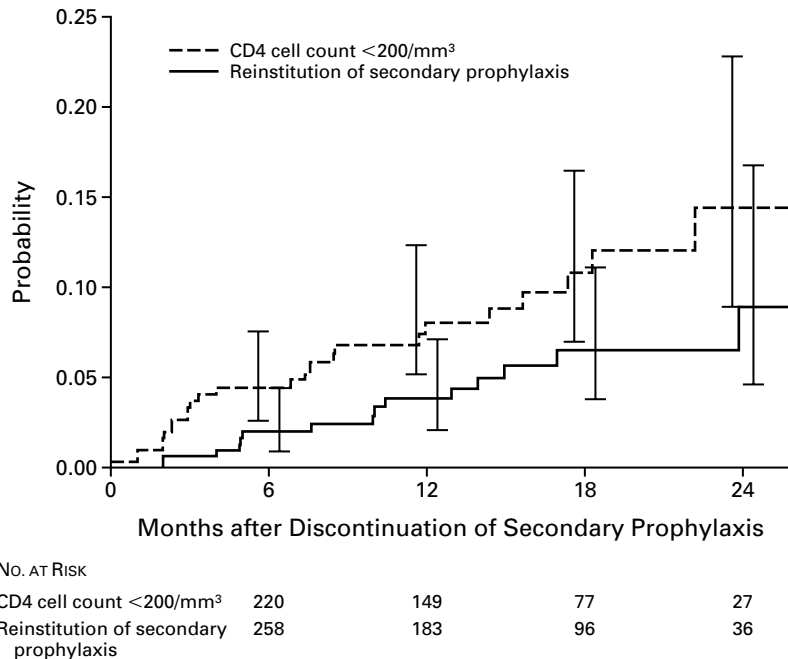


Figure 2. Kaplan–Meier Curves Showing the Probability of a Decline in the CD4 Cell Count to Less Than 200 per Cubic Millimeter and the Probability of Reinstatement of Secondary Prophylaxis against *P. carinii*.

The bars indicate the 95 percent confidence intervals.

pneumonia was found in patients with CD4 cell counts above 200 per cubic millimeter,^{9,23–25} the threshold CD4 cell count for instituting primary prophylaxis was set at 200 per cubic millimeter.²⁶ Guidelines for the initiation or discontinuation of prophylaxis (which define the group of patients in whom it is not needed) will always be based on the evaluation not only of the relative benefits but also of the risks of the prophylactic treatment. Potential problems associated with prophylaxis are diverse and drug-specific and include hypersensitivity to sulfonamides,^{27,28} the development of drug-resistant *P. carinii*^{29,30} and bacteria,³¹ the high cost (especially of inhaled pentamidine³² and atovaquone³³), and the number of additional pills that must be taken.

A particular concern regarding the discontinuation of trimethoprim–sulfamethoxazole is the loss of protection against common bacterial infections.³⁴ In this study, the incidence of bacterial pneumonia after the discontinuation of secondary prophylaxis against *P. carinii* pneumonia was only 2.7 episodes per 100 person-years of follow-up. This rate is considerably lower than was reported in a study undertaken before highly active antiretroviral therapy became available,³⁵ despite the fact that we used quite liberal criteria to identify possible cases of bacterial pneumonia. However, we cannot rule out the possibility that patients who

are at higher risk for bacterial pneumonia might benefit from antibacterial chemoprophylaxis, such as may be provided by continued use of trimethoprim–sulfamethoxazole. We also did not observe any cases of cerebral toxoplasmosis, an infection that may also be prevented by prophylaxis against *P. carinii* pneumonia.³⁶

Most patients in this study had been taking combination antiretroviral-drug therapy for more than one year before prophylaxis was discontinued. Thus, their physicians apparently were concerned about discontinuing secondary prophylaxis prematurely, since *P. carinii* pneumonia is a severe infection associated with a 10 to 15 percent case fatality rate.^{25,37} Therefore, caution should be exercised in extrapolating our findings to persons who have smaller increases in CD4 cell counts or have been treated for shorter periods with highly active antiretroviral therapy.

Our study does not directly address the question of when secondary prophylaxis should be restarted, but it does provide some clues. Almost 10 percent of all patients had a decrease in the CD4 cell counts to less than 200 per cubic millimeter, a threshold below which prophylaxis against *P. carinii* pneumonia is generally recommended.¹¹ As compared with the remaining patients, those in whom secondary prophylaxis against *P. carinii* pneumonia was reinstated or whose CD4 cell counts decreased to less than 200 per cu-

bic millimeter already had lower CD4 cell counts when secondary prophylaxis was discontinued (data not shown). Thus, patients who discontinue secondary prophylaxis against *P. carinii* pneumonia when their CD4 cell counts are marginally above 200 per cubic millimeter, particularly if they have subsequent negative trends in their CD4 cell counts or evidence of increased HIV replication, should be carefully monitored for decreases in CD4 cell counts to less than 200 per cubic millimeter and hence the need for reinstatement of secondary prophylaxis.

Several limitations of our study should be noted. First, it was not a controlled clinical trial but a compilation of data from several observational cohorts; there may have been undetected differences between the cohorts. However, clinical suspicion and diagnosis of *P. carinii* pneumonia are an integral part of routine care at the sites participating in this study, and it is unlikely that any cases of *P. carinii* pneumonia remained undiagnosed. Most of the cases of *P. carinii* pneumonia in this study (83 percent) were definitively diagnosed on the basis of microscopy rather than clinical suspicion. All the studies have well-implemented quality-control procedures to ensure the correct transfer of data from patients' records to the cohort data base. Although our study was not randomized, such a design would not have improved the interpretability of the findings, since no case of recurrent *P. carinii* pneumonia was diagnosed.

In conclusion, as has been demonstrated for primary prophylaxis, secondary prophylaxis against *P. carinii* pneumonia can be safely discontinued in patients with HIV infection who have had a response to highly active antiretroviral therapy (indicated by a CD4 cell count above 200 per cubic millimeter) with a minimal risk of recurrent *P. carinii* pneumonia.

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APPENDIX

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