

## Discontinuation of Chemoprophylaxis against *Pneumocystis carinii* Pneumonia in Patients with HIV Infection

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**Background:** HIV-infected patients with sustained immunologic improvement from antiretroviral therapy may be able to discontinue chemoprophylaxis against *Pneumocystis carinii* pneumonia (PCP).

**Objective:** To compare PCP incidence in HIV-infected patients who had sustained CD4<sup>+</sup> lymphocyte counts greater than 200 cells/mm<sup>3</sup> and who either discontinued or continued PCP prophylaxis.

**Design:** Nonrandomized prospective cohort study.

**Setting:** 10 HIV clinics in eight U.S. cities.

**Patients:** 146 patients had follow-up visits for a mean of 18.2 months after discontinuation of PCP prophylaxis, and 345 patients who continued PCP prophylaxis had follow-up visits for a mean of 14.0 months.

**Measurements:** Incidence of PCP.

**Results:** Patients who discontinued PCP prophylaxis had higher maximum and minimum CD4<sup>+</sup> cell counts and lower viral loads than patients who continued PCP prophylaxis. *Pneumocystis carinii* pneumonia did not develop in either group (upper 95% exact binomial confidence limit of incidence for those who discontinued PCP prophylaxis, 2.3/100 person-years).

**Conclusions:** Discontinuation of PCP chemoprophylaxis may be appropriate for some HIV-infected ambulatory patients.

Highly active antiretroviral therapy (HAART) has substantially affected the care and the disease course of HIV-infected patients. In the HIV Outpatient Study (HOPS), a study of ambulatory HIV-infected patients in HIV clinics across the United States, we have observed several phenomena related to the use of HAART. Mortality and morbidity rates have declined remarkably and substantially in this population with the advent of more effective antiretroviral therapies (1), but the typical patient must take an average of 13 pills per day to maintain a good virologic and immunologic result (2). Meanwhile, as CD4<sup>+</sup> lymphocyte counts have increased in treated patients, the incidence of *Pneumocystis carinii* pneumonia (PCP) has declined dramatically (1, 3).

Given the low incidence of PCP, the occasional toxicity of PCP chemoprophylaxis, and the numerous pills that ambulatory HIV patients receive, many HIV clinicians have begun cautiously discontinuing PCP prophylaxis—normally trimethoprim-sulfamethoxazole given three or more times per week—among patients who have sustained immunologic and virologic responses to HAART. In this study, we sought to determine whether discontinuing PCP prophylaxis in HOPS patients who had sustained CD4<sup>+</sup> cell counts greater than 200 cells/mm<sup>3</sup> changed the rates of development of PCP compared with patients who continued PCP prophylaxis.

### Methods

The methods used in HOPS, a dynamic cohort study, have been described elsewhere (1, 4). This continuously recruiting study now includes prospective, electronically collected summaries of physician-patient interactions and the course of disease for more than 4800 HIV-infected ambulatory patients seen in more than 82 000 outpatient visits since 1992. Our analysis included persons who visited a HOPS site from June 1995 through December 1998. Our study sites were 10 HIV clinics, of which 8 were private and 2 were public, in 8 U.S. cities: Tampa, Florida; Washington, D.C.; Denver, Colorado; Portland, Oregon; Oakland, California; Chicago, Illinois; Stony Brook, New York; and Philadelphia, Pennsylvania. Of the 12 HOPS physicians, 11 are board-certified in internal medicine and in-

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\*For members of the HIV Outpatient Study Investigators, see Appendix.

**Table 1. Demographic and Clinical Characteristics of Patients Who Discontinued and Those Who Continued *Pneumocystis carinii* Pneumonia Chemoprophylaxis\***

Characteristic	Patients Who Discontinued Prophylaxis (n = 146)	Patients Who Continued Prophylaxis (n = 345)	Odds Ratio (95% CI)	P Value
	n (%)			
Demographic				
Sex				
Male	118 (81)	296 (86)	Referent	0.16
Female	28 (19)	49 (14)	1.43 (0.86–2.38)	
Ethnicity				
White	119 (81)	231 (67)	Referent	0.001
Other	27 (19)	114 (33)	0.46 (0.29–0.74)	
HIV risk group				
Homosexual/bisexual man	94 (64)	238 (69)	Referent	>0.2
Injection drug user	15 (10)	29 (8)	0.76 (0.39–1.49)	
Heterosexual person	36 (21)	71 (22)	0.78 (0.49–1.23)	
Education (high school)				
Less than graduate	8 (6)	24 (7)	Referent	>0.2
Graduate	25 (17)	42 (12)	0.56 (0.22–1.43)	
More than graduate	87 (60)	212 (76)	0.81 (0.35–1.89)	
Clinical				
Previous AIDS diagnosis				
Yes	31 (21)	96 (28)	Referent	0.13
No	115 (79)	249 (72)	1.42 (0.91–2.27)	
Previous PCP diagnosis				
Yes	15 (10)	58 (17)	Referent	0.06
No	131 (90)	315 (83)	1.75 (0.97–3.23)	

\* Study data were collected from June 1995 through December 1998. PCP = *Pneumocystis carinii* pneumonia.

fectious diseases; these physicians routinely care for hundreds of HIV-infected patients every year and thus are experienced HIV caregivers.

Information in five general categories is abstracted from each patient visit by trained study staff and is electronically entered in a common data collection system that spans the time of observation. Data are collected centrally, and they are reviewed and corrected before being added to the database. The five categories of information are demographic characteristics and risk behaviors for HIV infection; symptoms; diagnosed diseases (definitive and presumptive); prescribed medications, including dosage and duration; and laboratory values, including CD4<sup>+</sup> lymphocyte counts and viral loads (HIV RNA copies/mL of plasma).

In this analysis, we assessed patients whose CD4<sup>+</sup> cell counts increased from 200 cells/mm<sup>3</sup> or less to greater than 200 cells/mm<sup>3</sup> after antiretroviral therapy (HAART was being given in more than 80% of patients by 1998 [1]) and who were nonrandomly chosen by their clinicians to discontinue or continue PCP prophylaxis. The observation periods for all patients who had two consecutive cell counts greater than (that is, sustained higher than) 200 CD4<sup>+</sup> cells/mm<sup>3</sup> started when they first had a CD4<sup>+</sup> cell count greater than 200 cells/mm<sup>3</sup>.

We compared the demographic (age, sex, race or ethnicity, geographic site, HIV risk group, education level, and insurance or payment source), clinical (previous PCP, other opportunistic infections, and AIDS diagnosis), immunologic (CD4<sup>+</sup> cell count, including lowest and highest), and most recent viro-

logic (copies of HIV RNA [viral load]) characteristics of patients who either discontinued or continued PCP prophylaxis.

Data collected in the HOPS were analyzed by using SAS software, version 6.0 (SAS Institute, Inc., Cary, North Carolina), and EpiInfo, version 6.04 (Centers for Disease Control and Prevention, Atlanta, Georgia). We calculated, by using an exact binomial test, the upper confidence limits for (zero) PCP incidence in patients who discontinued and those who continued prophylaxis. The characteristics of those who discontinued PCP prophylaxis were compared with the characteristics of those who continued it by using the chi-square test or Wilcoxon rank-sum test, as appropriate.

The HOPS as a whole and this substudy are funded entirely by the Centers for Disease Control and Prevention.

## Results

Of patients who maintained CD4<sup>+</sup> lymphocyte counts greater than 200 cells/mm<sup>3</sup>, 146 who discontinued PCP prophylaxis were followed for a mean of 18.2 months (221.4 total person-years) and 345 who continued PCP prophylaxis were followed for a mean of 14.0 months (402.5 total person-years) (**Table 1**). Patients and their physicians were more likely to discontinue PCP prophylaxis in succeeding calendar years of the study (data not shown). Neither patients who discontinued nor those who continued PCP prophylaxis acquired definitive or presumptive

PCP (upper 95% exact binomial confidence limits, 2.3/100 person-years for patients who discontinued prophylaxis and 1.3/100 person-years for patients who continued prophylaxis).

Toxoplasmosis did not occur in either group. Bacterial infections, such as pneumonia, sinusitis, bronchitis, and urinary tract infections, occurred somewhat less often in patients who discontinued PCP prophylaxis (18.6%) than in those who continued PCP prophylaxis (28.3%), but the difference was not significant (Yates-corrected chi-square test,  $P = 0.14$ ).

Compared with patients who continued PCP prophylaxis, more of those who discontinued prophylaxis were white than belonged to any other racial or ethnic groups, and fewer of these patients had had a previous episode of PCP (Table 1). The median patient age did not significantly differ between the group that discontinued PCP prophylaxis and the group that continued PCP prophylaxis (median, 39.2 years compared with 39.9 years; Wilcoxon test,  $P = 0.2$ ). We also analyzed the insurance (payer) status of patients; no significant differences were seen in care between the two groups, whether their care was compensated by the patient, private insurance, public insurance, or assistance such as Medicare and Medicaid (data not shown).

Of patients discontinuing PCP prophylaxis, 75% were receiving protease inhibitor-based antiretroviral therapy at the time of discontinuation, but this percentage did not differ from rates of protease inhibitor use in the HOPS cohort in the same years (1).

According to laboratory data, patients who discontinued PCP prophylaxis had a significantly higher CD4<sup>+</sup> cell nadir (lowest recorded CD4<sup>+</sup> cell count), a higher acme (highest recorded CD4<sup>+</sup> cell count), a longer period during which CD4<sup>+</sup> cell counts were greater than 200 cells/mm<sup>3</sup>, and a lower (most recent) viral load. In addition, more (51.9%) patients who discontinued PCP prophylaxis had 400 or fewer copies of HIV-1 RNA per mL ("undetectable") than patients who continued PCP prophylaxis (Table 2).

We also analyzed patterns of discontinuing PCP prophylaxis at the 10 study sites and found that the percentage of patients who discontinued such prophylaxis ranged from 8.3% to 46.9% of all potentially eligible patients (those with CD4<sup>+</sup> counts > 200 cells/mm<sup>3</sup>). Of the 146 patients who discontinued PCP prophylaxis, only 6 (4%) patients did so because of chemoprophylactic agent toxicity (trimethoprim-sulfamethoxazole) or potential drug interactions.

## Discussion

Our study suggests that discontinuing PCP prophylaxis may be appropriate for selected HIV-infected ambulatory patients who have sustained clinical, immunologic, and virologic improvement with antiretroviral therapy. In more than 2655 person-months of observation, PCP did not develop in any of the 146 U.S. patients who discontinued prophylaxis; this result corresponds with results of European studies of 78 HIV-infected patients in the Netherlands (5), 235 patients in three separate studies in Spain (6–8), 40 patients in France (9), and 262 patients in Switzerland (10). In those observational studies (5, 7–10) and the single randomized trial (6), a total of 615 patients discontinued PCP prophylaxis after their CD4<sup>+</sup> cell counts increased to more than 200 cells/mm<sup>3</sup>; after follow-up of more than 5888 person-months, PCP had not developed in any patient. On the basis of these results, recent guidelines for opportunistic infection prevention suggest that providers consider discontinuation of PCP prophylaxis in HIV-infected patients with sustained CD4<sup>+</sup> cell counts greater than 200 cells/mm<sup>3</sup> (11).

It is evident that HOPS physicians were careful in selecting patients for discontinuation of PCP prophylaxis. In general, patients who discontinued PCP prophylaxis had higher CD4<sup>+</sup> cell counts before and after antiretroviral therapy, had maintained CD4<sup>+</sup> cell counts greater than 200 cells/mm<sup>3</sup> for a longer

**Table 2. Virologic and Immunologic Characteristics of Patients Who Discontinued and Those Who Continued *Pneumocystis carinii* Pneumonia Chemoprophylaxis\***

Characteristic	Patients Who Discontinued Prophylaxis (n = 146)			Patients Who Continued Prophylaxis (n = 345)			P Value†
	Mean	Median	Range	Mean	Median	Range	
Observed time with CD4 <sup>+</sup> cell count > 200 cells/mm <sup>3</sup> , mo	18.2	16.8	0.5–37.9	14.0	12.6	0.7–39.9	<0.001
Lowest CD4 <sup>+</sup> cell count (nadir), cells/mm <sup>3</sup>	105	113	0–196	90	89	0–199	0.016
Highest CD4 <sup>+</sup> cell count (acme), cells/mm <sup>3</sup>	472	423	226–1690	380	344	200–979	<0.001
Most recent plasma viral load, HIV RNA copies/mL	9632	499	1–133 027	39 303	1900	1–617 912	0.014

\* Study data collected from June 1995 through December 1998.

† P values determined by Wilcoxon rank-sum test.

period, had significantly lower recent viral loads, and had fewer previous episodes of PCP compared with patients who continued PCP prophylaxis. These clinical, immunologic, and virologic factors may be important in deciding to discontinue PCP prophylaxis in an HIV-infected patient.

Although we did not examine whether adherence to antiretroviral therapy might be improved by discontinuation of PCP prophylaxis, an approximately contemporaneous, anonymous survey of 504 HOPS patients showed statistically significant greater adherence to all medicines in patients who did not receive prophylaxis against opportunistic infections (80%) than in those who did (75%) ( $P = 0.027$ ) (2). Aside from the possible benefit of adherence to therapy in those patients taking fewer pills, we were concerned about potential adverse effects on bacterial infection and toxoplasmosis rates in patients who discontinued trimethoprim-sulfamethoxazole therapy. However, we did not observe any increased rates of bacterial infection or toxoplasmosis in patients who discontinued PCP prophylaxis compared with patients who continued prophylaxis.

Finally, the special characteristics of this population should be considered because they reflect the demographics of patients with AIDS rather than HIV-infected patients (3): more patients in this population are white, are men who have sex with men, and generally adhere to their regimens (2); also, follow-up time has been comparatively short. Thus, it is not clear how applicable the results of this study are to populations with less access or adherence to antiretroviral therapy over a longer period. However, this analysis suggests that selected patients who have sustained  $CD4^+$  cell counts greater than 200 cells/mm<sup>3</sup> may discontinue PCP prophylaxis without untoward effect and that discontinuation of such prophylaxis would be appropriate to examine in a randomized, controlled clinical trial.

## Appendix: Institutions and Investigators in the HIV Outpatient Study

Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia: Anne C. Moorman, Jennifer C. Von Bargen, Paul J. Weidle, and Scott D. Holmberg; Health Research Network of APACHE Medical Systems, Inc., McLean, Virginia: Kathleen C. Wood and Rose K. Baker; Northwestern University Medical School, Chicago, Illinois: Frank J. Palella, Joan S. Chmiel, Cheeling Chan, and Jason Arnold; Columbia Rose Medical Center, Denver, Colorado: Kenneth A. Lichtenstein, Kenneth S. Greenberg, Benjamin Young, Barb Widick, Cheryl Stewart, and Peggy Zellner; Infectious Disease Research Institute, Tampa, Florida: Bienvenido G. Yangco, Kalliope Halkias, and Cheryl Lapiere;

Washington, D.C.: Douglas J. Ward and Chuck Owen; State University of New York, Stony Brook, New York: Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, and Mary Nekola; Temple University Hospital, Philadelphia, Pennsylvania: Ellen M. Tedaldi, Linda Walker-Kornegay, and Suzanne Smith; Adult Immunology Clinic, Oakland, California: Joseph B. Marzouk, Roger T. Phelps, and Mark Rachel; Fairmont Hospital, Oakland, California: Robert E. McCabe and Mark Rachel.

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Final approval of the article: S.D. Holmberg.

Provision of study materials or patients: B.G. Yangco.

Statistical expertise: J.C. Von Bargen.

Obtaining of funding: S.D. Holmberg.

Administrative, technical, or logistic support: A.C. Moorman, S.D. Holmberg.

Collection and assembly of data: B.G. Yangco, A.C. Moorman.

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