

# Discontinuation of primary prophylaxis in HIV-infected patients at high risk of *Pneumocystis carinii* pneumonia: prospective multicentre study

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**Objectives:** To assess the safety of discontinuation of primary prophylaxis in HIV-infected patients on antiretroviral combination therapy at high risk of developing *Pneumocystis carinii* pneumonia.

**Design:** Prospective multicentre study.

**Patients and methods:** The incidence of *P. carinii* pneumonia after discontinuation of primary prophylaxis was studied in 396 HIV-infected patients on antiretroviral combination therapy who experienced an increase in their CD4 cell count to at least  $200 \times 10^6/l$  and 14% of total lymphocytes; the study population included 191 patients with a history of CD4 cell counts below  $100 \times 10^6/l$  (245 person-years) and 144 patients with plasma HIV RNA above 200 copies/ml (215 person-years).

**Results:** There was one case of *Pneumocystis* pneumonia, an incidence of 0.18 per 100 person-years [95% confidence interval (CI), 0.005–1.0 per 100 person-years]. No case was diagnosed in groups with low nadir CD4 cell counts (95% CI, 0–1.2 per 100 person-years) or detectable plasma HIV RNA (95% CI, 0–1.4 per 100 person-years).

**Conclusions:** Discontinuation of primary prophylaxis against *Pneumocystis* pneumonia is safe in patients who have responded with a sustained increase in their CD4 cell count to antiretroviral combination therapy, irrespective of the CD4 cell count nadir and the viral load at the time of stopping prophylaxis. © 2001 Lippincott Williams & Wilkins

AIDS 2001, 15:501–507

**Keywords:** HIV, CD4 cell count, nadir CD4 cell count, plasma HIV RNA, antiretroviral combination therapy, *Pneumocystis carinii* pneumonia, primary prophylaxis, discontinuation of prophylaxis, immune reconstitution, cohort study

## Introduction

The introduction of potent antiretroviral therapy in HIV-infection has lead to an increase in CD4-positive T lymphocytes, to the suppression of plasma virus

concentration, often to undetectable levels, and to a substantial decline in HIV-associated morbidity and mortality [1–3]. The question as to whether or not treatment-associated restoration of the immune response allows prophylaxis against *Pneumocystis carinii*

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Received: 23 June 2000; revised: 21 December 2000; accepted: 09 January 2001.

pneumonia (PCP) to be discontinued has been examined in several cohort studies. Findings from the Swiss HIV Cohort Study [4], the EuroSIDA Study [5] and other prospective studies [6] showed that discontinuation of primary prophylaxis against PCP may be safe in patients who respond to potent antiretroviral therapy with a sustained increase in CD4 cell count. The preliminary results from an ongoing randomized trial confirm these findings [7,8]. However, follow-up in these studies was short (typically 1 year or shorter) and concern about the long-term safety of stopping prophylaxis therefore remains. There is also concern about discontinuation in patients who experienced very low CD4 cell counts before initiating antiretroviral combination therapy, and in patients in whom suppression of plasma virus concentration was incomplete when stopping prophylaxis [9–11]. For example, the 1999 USPHS/IDSA guidelines [12] state that 'additional criteria (for discontinuation) might include sustained reduction in viral load for at least 3–6 months.'

The present study extends a previous analysis of the Swiss HIV Cohort Study [4] to a larger patient group with longer follow-up and focuses on groups where concern remains about the safety of discontinuing prophylaxis [9–11]: patients who experienced very low CD4 cell counts before initiating antiretroviral combination therapy, and patients in whom suppression of plasma virus concentration was incomplete when stopping prophylaxis.

## Patients and methods

Described in detail elsewhere, the Swiss HIV Cohort Study (SHCS) is a prospective cohort study of adult HIV-infected patients [1,13]. Patients are followed in one of seven study centres (Basle, Berne, Geneva, Lausanne, Lugano, St Gall, and Zurich). Enrolment is independent of stage of disease or degree of immunosuppression, and information is collected according to standardized criteria on structured forms at enrolment and at follow-up visits at 6 monthly intervals. Clinical stage is defined according to the 1993 classification system for HIV infection of the Centers for Disease Control and Prevention (CDC) [14]. CD4 cell counts are measured using flow-cytometric assays and plasma HIV-RNA levels are measured using the Roche Amplicor assay with a lower detection limit of about 200 copies/ml. An ultrasensitive modification of the assay with a limit of detection of 2–40 copies/ml was introduced during 1998 [15].

### Inclusion criteria

SHCS participants on primary prophylaxis against PCP were eligible if they responded to antiretroviral combination therapy with an increase in their CD4 cell

counts to at least  $200 \times 10^6/l$  and 14% of peripheral lymphocyte count and if the CD4 cell count remained above these levels for at least 12 weeks. The ethics committees of all seven centres approved the study and written informed consent was obtained from all patients. According to the protocol primary PCP prophylaxis would be resumed if the CD4 cell count fell below one of the threshold values on two consecutive measurements. Recruitment started in June 1997, and ended in October 1999.

### Definitions of high risk groups and endpoints

Two groups of patients at potentially high risk of developing PCP were defined. The first group included all patients whose lowest ever measured CD4 cell count was below  $100 \times 10^6/l$ . The second group included patients whose plasma HIV-1 RNA at study entry was above 200 copies/ml. The two groups were not mutually exclusive.

A diagnosis of PCP was the primary endpoint of this study: A diagnosis of PCP was made: if *P. carinii* was found microscopically in induced sputum or bronchoalveolar fluid or in a histological lung specimen; or if there was a history of dyspnoea on exertion or non-productive cough in the absence of evidence of bacterial pneumonia and the patient responded to standard PCP treatment. CDC clinical stage B and C events and treatments with antibiotics were secondary endpoints.

It was decided *a priori* that discontinuation of primary prophylaxis would be considered to be safe if the upper 95% confidence limit of the incidence was below the upper 95% confidence limit recorded in a historical cohort of 1277 patients who were followed up in the SHCS with CD4 cell counts of  $200\text{--}500 \times 10^6/l$  in the period 1990–1994, before potent therapies became available. In this patient group primary prophylaxis against PCP is not indicated according to current guidelines [12]. The incidence of PCP in this group was 1.1 per 100 person-years [95% confidence interval (CI), 0.6–1.8] [4].

### Statistical analysis

The closing date for the present analysis was December 31 1999. In January 2000 all charts were reviewed and patients were contacted by telephone if the treating physician had not seen them within the previous month. The length of follow-up was measured from the date that primary prophylaxis was discontinued to the date of last contact, the date of reaching an endpoint or the date of withdrawal. Events were assumed to have a Poisson distribution, and exact 95% CI were calculated for the incidence of endpoints. One-sided upper 95% confidence limits were calculated if no event was recorded. Stata software (version 6.0;

College Station, Texas, USA) was used for statistical analysis.

## Results

A total of 491 patients followed up within the SHCS fulfilled the entry criteria. As of October 1999, 396 (80.1%) of them had been enrolled. There were no statistically significant differences ( $P > 0.05$ ) between the patients enrolled and not enrolled with respect to age, sex, transmission mode, clinical stage, or nadir CD4 cell count.

In 336 patients (84.8%) the discontinued prophylactic regimen consisted of cotrimoxazole. The median duration of prophylaxis was 26 months. Characteristics at baseline and at study end are shown in Table 1. The subgroup of patients whose lowest ever measured CD4 cell count was below  $100 \times 10^6/l$  consisted of 191 participants, and the subgroup of patients whose plasma HIV-1 RNA at study entry was above 200 copies/ml consisted of 144 patients. Sixty-one participants were included in both subgroup analyses and 122 participants were not included in any subgroup analysis.

The distribution across sex, age and transmission categories was similar in the different patient groups. Between one-quarter and one-third of patients had a

history of an AIDS-defining illness. About half of the patients (187, 47.2%) had a history of a condition known to be associated with PCP (oral thrush, *Candida* esophagitis, unexplained weight loss, unexplained fever, wasting syndrome or recurrent bacterial pneumonia) [16,17]. In 30 patients (7.6%) follow-up was censored before the closing date: 16 resumed prophylaxis because their CD4 cell count fell below threshold values, two resumed prophylaxis for recurrent lower and upper respiratory tract infections, six patients could not be located and two patients withdrew consent. Four patients died: one of hepatocellular carcinoma, one of non-Hodgkin's Lymphoma, one of heroin overdose and one of sudden death, probably cardiac arrest.

## Incidence of PCP

One patient was diagnosed with PCP. He presented with chronic cough for several weeks without dyspnoea, fever or decrease in general performance. On clinical examination he had prolonged expiration and wheezing. His chest X-ray was considered normal. *P. carinii* was detected by immunofluorescence in a smear of spontaneous sputum. He was treated with cotrimoxazole for 3 weeks and the cough resolved. The CD4 cell count at diagnosis was  $530 \times 10^6/l$  and plasma HIV RNA was 38 copies/ml. He had started primary prophylaxis with cotrimoxazole 18 months earlier with a nadir cell CD4 count of  $250 \times 10^6/l$  because of *Candida* oesophagitis and recurrent oral thrush and discontinued prophylaxis 5 months before the diagnosis

**Table 1.** Characteristics of study participants. Number of patients (%) or median (interquartile range) are shown. Groups are not mutually exclusive. For definition of subgroups see text.

	All patients (n = 396)	Patients with CD4 cell count nadir < $100 \text{ cells} \times 10^6/l$ (n = 191)	Patients with plasma HIV RNA above 200 copies/ml at study entry (n = 144)
Mean age [years (range)]	37 (34–44)	37 (33–42)	37 (34–46)
Male sex [n (%)]	271 (68.4)	121 (63.4)	100 (69.4)
Transmission group [n (%)]			
Men who had sex with men	146 (36.9)	67 (35.1)	53 (36.8)
Heterosexual contact	109 (27.5)	54 (28.3)	41 (28.5)
Intravenous drug use	127 (32.1)	66 (35.6)	43 (30.0)
Other	14 (3.5)	10 (5.2)	7 (4.9)
Clinical stage [n (%)]			
CDC stage A	109 (27.5)	24 (12.6)	39 (27.1)
CDC stage B	192 (48.5)	105 (55.0)	68 (47.2)
CDC stage C	95 (24.0)	62 (32.5)	37 (25.7)
Mean duration of antiretroviral therapy at study entry [months (range)]			
At least two drugs	24 (16–34)	26 (18–37)	24 (16–33)
At least three drugs <sup>a</sup>	18 (12–25)	21 (16–27)	17 (11–25)
Mean CD4 cell count [ $\times 10^6/l$ (range)]			
Lowest count ever	102 (51–140)	49 (20–77)	110 (60–142)
At study entry	326 (274–405)	308 (269–381)	336 (273–408)
At study end	412 (320–546)	399 (320–535)	388 (300–527)
Viral load (log <sub>10</sub> copies/ml)			
At study entry	2.0 (2.0–2.8)	2.0 (2.0–2.7)	3.3 (2.7–4.0)
At study end	1.4 (1.3–2.7)	1.3 (1.0–2.3)	2.9 (1.5–4.0)

<sup>a</sup>Based on a total of 370 patients, including 187 patients with CD4 cell count nadir <  $100 \text{ cells} \times 10^6/l$  and 128 patients with plasma HIV RNA above 200 copies/ml at study entry.

was made when his cell CD4 count was  $302 \times 10^6/l$  and plasma HIV RNA was undetectable.

The overall incidence of PCP was thus 0.18 (95% CI, 0–1.0 per 100 person-years). The patient with a PCP diagnosis was in neither of the two subgroups at potentially increased risk, so that the incidence in these subgroups was 0 per 100 person-years (Table 2). In all instances the upper 95% confidence limits were below the predefined threshold incidence of 1.8 per 100 patient years.

### Other AIDS events and bacterial infections

Five patients experienced a CDC C event other than PCP (two *Candida* oesophagitis, two non-Hodgkin's lymphoma, one cryptosporidiosis) and 10 patients presented with a CDC B event (three multidermatomal herpes zoster, two cervical dysplasia, two thrombocytopenia, two oral hairy leukoplakia and one unexplained weight loss). Sixty-eight patients (17%) had a total of 81 courses of systemic antibiotic treatment for the following conditions: 38 respiratory infections such as sinusitis, pharyngitis, otitis media and bronchitis, 17 typical or atypical pneumonia, 10 skin or soft tissue infections, eight urinary tract infections, five diarrhoea, two sexually transmitted diseases, and one sepsis with *Staphylococcus aureus*. The incidence of pneumonia was 3.1 episodes per 100 person-years (95% CI, 1.8–4.9 per 100 person-years). The incidence of pneumonia in intravenous drug users was similar: 4.2 per 100 person-years (95% CI, 1.6–8.6 per 100 person-years).

## Discussion

The discontinuation of primary prophylaxis against PCP in HIV-infected patients responding to potent antiretroviral therapy could improve the quality of life of patients, reduce the risks associated with adverse effects and drug interactions, and decrease costs to health services. But when can primary prophylaxis be discontinued safely? The present study extends a previous analysis of the SHCS [4] to a larger patient group with longer follow-up and gives special consideration to the experience of patients perceived to be at increased risk. To our knowledge this study represents the largest database of patients followed prospectively after discontinuing primary prophylaxis against PCP. Our results indicate that it is safe to discontinue prophylaxis in patients who responded with a sustained increase in CD4 cell count to at least  $200 \times 10^6/l$  and 14% of the total lymphocyte count, irrespective of the CD4 cell count nadir and the viral load at the time of stopping prophylaxis. We showed recently that this is true also for patients on primary prophylaxis who are seropositive for IgG against *Toxoplasma gondii* [18].

**Table 2.** Incidence of *Pneumocystis carinii* pneumonia (PCP).

	No at risk	Median follow-up time [years (range)]	Total follow-up time (years)	Number of events	Incidence of PCP per 100 patient-years (95% CI)
All patients	396	1.5 (0.1–2.5)	550.7	1	0.18 (0.005–1.0)
Patients with CD4 count nadir $< 100 \text{ cells} \times 10^6/l$	191	1.3 (0.1–2.5)	244.7	0	0.0 (0–1.2)
Patients with plasma HIV RNA above 200 copies/ml at study entry	144	1.6 (0.1–2.5)	215.3	0	0.0 (0–1.4)

CI, Confidence interval.

High viral load has been shown to be an independent predictor of progression to AIDS [19], including PCP [20], in the era before potent antiretroviral drugs became available. The restoration of some immune functions *in vivo* depends on the rate of viral load decline during the initial phase of antiretroviral combination therapy [21]. However, our findings suggest that a detectable viral load does not impair *Pneumocystis*-specific immune response if the CD4 cell count has increased above the threshold levels described. This finding is in agreement with the sustained immunological and clinical benefit observed in patients treated with antiretroviral combination therapy whose viraemia is suppressed suboptimally [22–25].

In patients who achieved CD4 cell count level of more than  $200 \times 10^6/l$  while on antiretroviral combination therapy the incidence of new opportunistic infections was dependent on the nadir CD4 cell count before therapy was started, as shown in a recently published analysis of the EuroSIDA cohort [26]. The hazard of new AIDS-defining infections was more than three times higher in patients with CD4 cell count nadirs below  $100 \times 10^6/l$  as compared to those with nadirs above  $150 \times 10^6/l$ . However the median follow-up was only 4 months in this study, indicating that most opportunistic infections occurred during the first months after reaching the CD4 threshold mentioned above. Our results indicate that the CD4 cell count nadir that was reached before starting potent combination therapy is irrelevant for the decision to discontinue prophylaxis once a CD4 cell count of at least  $200 \times 10^6/l$  and 14% of total lymphocytes is maintained for at least 12 weeks.

PCP was diagnosed in one patient who was treated successfully with antiretroviral combination therapy. His CD4 cell count was above  $500 \times 10^6/l$  and his plasma HIV RNA was below 50 copies/ml at the time the diagnosis was made. Although the clinical picture was atypical, *P. carinii* was found in the sputum and the chronic cough subsided after treatment. This raises a question about the spectrum of clinical signs and symptoms, and whether subclinical infections or reactivations occur in patients treated successfully with antiretroviral combination therapy. *P. carinii* may be found in body fluids of immunocompromised patients who do not progress to clinically overt PCP [27]. This possibility should be taken into account in future studies of PCP in HIV-infected patients treated with potent antiretroviral therapy.

Our study has a number of limitations. Firstly, it was an uncontrolled, observational study. Selection bias could have been introduced, for example if patients at low risk were included preferentially. Such bias is unlikely for several reasons. The SHCS is a study with national coverage and includes approximately 70% of

patients with advanced HIV disease in the country [28]. A large proportion of the eligible patients was included, and those who were not included had characteristics similar to those who were not. The results from a randomized trial from Spain, presented at recent conferences, have shown zero events in the discontinuation arm [7]. Second, although the median follow-up was 18 months and 75 patients were followed-up for longer than 2 years our study cannot exclude with certainty an increased risk of *P. carinii* pneumonia several years after stopping prophylaxis. This seems unlikely, however, as immune function increases with time after initiation of combination therapy [29]. An earlier analysis of the Swiss cohort showed that the incidence of opportunistic infections declines rapidly 3 months after starting therapy [25]. Third, our results cannot be extended to patients who do not respond to potent therapy with a sustained increase of the CD4 cell count. Finally, we did not study secondary prophylaxis, but a recent retrospective analysis of eight European cohorts indicated that discontinuation of secondary PCP prophylaxis may also be safe [30].

Our findings are in agreement with other observational studies examining the risk of discontinuing primary prophylaxis against *P. carinii*, as summarized in Table 3. There are two studies with a prospective design similar to this, one from the Netherlands [6] and one from Denmark [31]. Combining the data from the present study with the two previous studies gives a total of 651 patients, 777 person-years of follow-up and two cases of PCP, an incidence of 0.26 per 100 person-years (95% CI, 0.03–0.94 per 100 person-years). In addition there are two analyses of cohort studies, one from Europe [5] and one from the USA [32]. No case of PCP was identified in these studies (Table 3). As more and more data become available about discontinuation of primary and secondary prophylaxis against opportunistic infections a collaboration by the different research groups to combine the results should be attempted.

Chronic treatment with cotrimoxazole may prevent other bacterial infections in HIV-infected patients, especially bacterial pneumonia. The incidence of pneumonia observed in our study (3.1 episodes per 100 person-years) was lower than that observed in an American study [33] before antiretroviral combination therapy became available. In the latter study the incidence of pneumonia was 6.8 per 100 person-years among patients with CD4 cell counts between 200 and  $500 \times 10^6/l$ . Given the increased risk of development of bacterial resistance against cotrimoxazole [34] during prophylaxis and the low fatality rate of bacterial pneumonia, prophylaxis of bacterial pneumonia cannot be justified in this population.

We conclude that it is safe to stop primary PCP

**Table 3.** Overview of published studies addressing the safety of stopping primary prophylaxis against *Pneumocystis carinii* pneumonia.

Study (location, year of publication)	Inclusion criteria	No of patients	Person-years of follow-up	No of cases of <i>P. carinii</i>	Incidence per 100 person-years (95% CI)
<b>Prospective observational studies</b>					
Schneider <i>et al.</i> [6] (The Netherlands, 1999)	CD4 cells > 200 × 10 <sup>6</sup> /l for at least 1 month	62	72.0	0	0 (0–4.2)
Kirk <i>et al.</i> [31] (Denmark, 1999)	CD4 cells > 200 × 10 <sup>6</sup> /l for at least 6 months	193	154.4	1	0.65 (0.02–3.6)
Current Study (Switzerland)	CD4 cells ≥ 200 × 10 <sup>6</sup> /l and ≥ 14% of total lymphocyte count for at least 3 months	396	550.7	1	0.18 (0.005–1.0)
Combined		651	777.1	2	0.26 (0.03–0.94)
<b>Analysis of cohort data</b>					
Weverling <i>et al.</i> [5] (17 European countries, 1999)	Start of highly active antiretroviral therapy	319	197.0	0	0 (0–1.5)
Yangco <i>et al.</i> [32] (USA, 2000) <sup>a</sup>	CD4 cells > 200 × 10 <sup>6</sup> /l	146	221.4	0	0 (0–1.4)
Combined		465	418.4	0	0 (0–0.72)

<sup>a</sup>The study by Yangco *et al.* [32] included 15 patients on secondary prophylaxis. CI, Confidence interval.

prophylaxis in patients who have responded to combination antiretroviral therapy with a sustained increase in the CD4 cell count to at least 200 × 10<sup>6</sup>/l and 14% of their total peripheral lymphocyte count, irrespective of CD4 cell count nadir and viral load at the time of stopping prophylaxis.

## Acknowledgements

We are indebted to our patients who gave their consent for enrolment into this study knowing that there might be a risk of acquiring opportunistic infections. We thank the physicians and study nurses of the SHCS centres and the general practitioners who cared for the patients in the study. We thank especially A. Christen, study nurse in Berne, who co-ordinated data collection, and N. Low and P. Vernazza who made useful comments on earlier drafts of the manuscript.

*Sponsorship: Supported by the Swiss Federal Office of Public Health (Grant no 3600.010.1).*

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## Appendix

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