Low Incidence of Community-Acquired Pneumonia among Human Immunodeficiency Virus–Infected Patients after Interruption of *Pneumocystis carinii* Pneumonia Prophylaxis

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We compared the incidence of bacterial pneumonia among 336 patients who discontinued trimethoprim-sulfamethoxazole (TMP-SMX) as prophylaxis against *Pneumocystis carinii* pneumonia (PCP) with that among 75 patients who fulfilled the criteria for discontinuation but continued receiving prophylaxis. The difference in the overall incidence rates for the 2 groups (1.2 events per 100 person-years) was not statistically significant. Discontinuation of TMP-SMX prophylaxis against PCP is not associated with a significant increase in the incidence of bacterial pneumonia among patients with a sustained CD4 cell count increase to >200 cells/μL.

The risk for bacterial pneumonia is substantially increased among patients with HIV infection [1, 2], and bacterial pulmonary infections are a major cause of morbidity among HIV-positive individuals, especially patients who are injection drug users [3, 4]. The mortality associated with bacterial pneumonia is substantial, especially among patients with advanced stages of HIV infection [1, 5].

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The incidence of bacterial pneumonia depends on the case mix within cohorts and increases significantly with advancing immunodeficiency [6]. In 1995, Hirschtick et al. [1] reported an overall incidence of 5.5 cases of bacterial pneumonia per 100 person-years among HIV-positive individuals, compared with 0.9 cases per 100 person-years among HIV-negative individuals. The risk factors for bacterial pneumonia in HIV-positive individuals include a low CD4 count, injection drug use, cigarette smoking, and a history of bacterial pneumonia [1].

In 1990, use of trimethoprim-sulfamethoxazole (TMP-SMX) as chemoprophylaxis was recommended for patients who had experienced recurrent pulmonary bacterial infection [4]. In 1995, Hirschtick et al. [1] were the first to report a considerable reduction (67%) in the incidence of bacterial pneumonia among HIV-infected individuals receiving prophylaxis with TMP-SMX [1].

The influence of antiretroviral combination therapy on the incidence of bacterial pneumonia is not well defined. However, there seems to be significant decrease in the incidence of bacterial pneumonia after the introduction of potent antiretroviral combination therapy [7, 8]. In a multivariate model in one study, prophylaxis with TMP-SMX did not further reduce the risk of bacterial pneumonia [8]. Nevertheless, bacterial pneumonia remained an important cause of morbidity in these studies [7, 8]. For patients who have a sustained increase in the CD4 cell count while receiving successful antiretroviral combination therapy, discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia (PCP) is safe with regard to the associated risk for PCP [9–13].

The incidence of suspected or confirmed bacterial pneumonia was 3.1 cases per 100 person-years among patients in Switzerland who discontinued PCP prophylaxis [14]; a similar rate was noted in an American study [10]. In recently published randomized trials of discontinuation of primary PCP prophylaxis, there was no evidence of an increased risk of bacterial pneumonia among patients who discontinued prophylaxis [11, 12]. However, because of the low incidence of bacterial pneumonia, the power of these studies was limited. The aim of the present study was to assess the influence of withdrawal of TMP-SMX–based primary PCP prophylaxis on the incidence of community-acquired pneumonia (CAP) among patients receiving antiretroviral combination therapy.

Patients and methods. The Swiss HIV Cohort Study (SHCS) is a prospective cohort study with continuing enrollment of HIV-1–infected patients [15]. Follow-up of patients

≥16 years of age is done at 1 of 7 outpatient clinics. Enrollment is independent of the stage of disease or the degree of immunosuppression, and information is collected, according to standardized criteria, at registration and at follow-up visits every 6 months. Clinical status is defined according to the 1993 classification system for HIV infection established by the Centers for Disease Control and Prevention (CDC; Atlanta, GA). The CD4 cell count is measured using flow cytometry. Plasma HIV RNA levels are measured using the Roche Amplicor assay, which has a lower limit of detection of ~200 copies/mL. An ultrasensitive modification of the assay, which had a limit of detection of 2–40 copies/mL, was introduced in 1998 [16].

Two groups of patients enrolled in the SHCS were selected for the present study. Group I included patients who discontinued receiving primary prophylaxis against PCP. All 396 participants in a study of the discontinuation of primary prophylaxis against PCP (i.e., the StopCox1 study [14]) were potentially eligible for analysis. This study enrolled patients from June 1997 through October 1999, and data from follow-up that lasted until the end of 1999 were included in the analysis. All patients had to have a sustained increase in the CD4 cell count (to ≥200 cells/μL; 14% of the total lymphocyte count) that lasted for ≥12 weeks before discontinuation of PCP prophylaxis. For 60 patients (15%), the type of prophylaxis that was discontinued was not TMP-SMX prophylaxis; these 60 patients were excluded from the analysis. Therefore, group I consisted of 336 patients.

Group II included patients who continued receiving prophylaxis despite having elevated CD4 cell counts. A total of 82 patients fulfilled the criteria for discontinuation of PCP prophylaxis at the end of enrollment in the StopCox1 study but continued receiving PCP prophylaxis. Of those 82 patients, 75 (92%) were receiving TMP-SMX and constituted group II in the analysis. The earliest start date for follow-up of group II was 1 July 1997, and the latest end date for follow-up was 15 March 2001.

The primary end point of the present study was diagnosis of CAP. "CAP" was defined as the occurrence of symptoms of acute lower respiratory infection in association with the presence of an infiltrate on a chest radiograph. The presence of symptoms of acute lower respiratory infection with clinical findings consistent with pneumonia (but without radiological signs of pneumonia) was not accepted as a definition of pneumonia. We studied the incidence of CAP in the 2 groups.

Patients in group I were followed from the date that primary prophylaxis was discontinued to the date of death, the date of loss to follow-up, or the date of the end of the StopCox1 study. The data for group II had to be collected retrospectively because single episodes of pneumonia are not recorded in the SHCS database. The patients' medical charts were reviewed by members of the SHCS during February and March 2001. Complete follow-up was calculated from the date when patients would have fulfilled the entry criteria for StopCox1 until the date of death, the date of discontinuation of TMP-SMX prophylaxis, or the date of last contact with the patient. The earliest follow-up start date for patients in group II was 1 July 1997, and the last censor date was 15 March 2001.

Incidence rates were assessed assuming a Poisson distribution of events. The difference in the incidence rates between the 2 groups and the corresponding 95% CI were calculated. A 2-sided P value of <.05 was considered statistically significant. We used Stata software, version 6.0 (Stata), for analyses.

Results. Characteristics of the patients studied are shown in table 1. There were no statistically significant differences between patients who were enrolled in the study and patients who were not enrolled, with respect to age, sex, the type of regimen that included a protease inhibitor, and plasma HIV RNA level. Patients in group II had a history of more advanced immunodeficiency (with more patients in group II with clinical stage C, according to the CDC classification) and lower nadir CD4 cell counts, compared with patients in group 1. The absolute CD4 cell count at the beginning of the study was significantly lower in group II than in group I, although there was no difference between the 2 groups with regard to the percentage of CD4 cells.

For group I, the median duration of follow-up was 1.5 years, which was significantly longer than that for group II (0.84 years); total length of follow-up was 471 person-years for group I and 77 person-years for group II. Four patients in group I died during follow-up; 1 died of hepatocellular carcinoma; 1, of non-Hodgkin lymphoma; 1, of a heroin overdose; and 1, of sudden death (probably cardiac arrest). Two patients in group II died during the study: 1 patient committed suicide, and 1 died of a heroin overdose. Follow-up of 60 persons in group II (80%) had to be censored before the date of chart review because these patients had discontinued receiving TMP-SMX after the results of the StopCox1 study became available.

Twelve patients in group I had CAP. Four of these 12 patients had a history of injection drug use; 4 patients had stage C clinical status and 7 had stage B clinical status, according to CDC classification. The nadir CD4 cell count was <100 cells/μL for 8 of these patients. One patient in group II who had stage B clinical status (according to CDC classification), a history of injection drug use, and a nadir CD4 cell count of 68 cells/μL developed CAP during the study. An etiological diagnosis was possible for only 2 episodes of CAP: *Streptococcus pneumoniae* was found in the blood culture of 1 patient, and 1 case of pneumonia was thought to have been caused by *Haemophilus influenzae* that was found abundantly in a sputum sample. All episodes of CAP responded well to antibacterial

Table 1. Characteristics, at baseline, of participants in a study comparing the incidence of community-acquired pneumonia among patients who discontinued trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis against *Pneumocystis carinii* pneumonia (group I) with that among patients who continued receiving such prophylaxis (group II).

Characteristic	Group I (n = 336)	Group II (n = 75)	P value[a]
Age, median years (IQR)	37 (34–45)	37 (33–41)	.3381
Male sex	236 (70.2)	45 (60.0)	.085
Transmission group			.192
Men who have sex with men	127 (38.0)	20 (26.7)	
Heterosexual contact	94 (28.0)	21 (28.0)	
Injection drug use	104 (31.0)	32 (42.7)	
Other or unknown	11 (3.3)	2 (2.7)	
CDC clinical stage[b]			<.001
A	92 (27.4)	8 (10.7)	
B	166 (49.4)	35 (46.7)	
C	78 (23.2)	32 (42.3)	
Antiretroviral regimen containing a PI	290 (86.3)	62 (82.7)	
CD4 cell count, median cells/μL (IQR)	326 (273–403)	294 (248–371)	.002
CD4 cell percentage[c] (IQR)	22 (18–26)	21 (17–25)	.930
Nadir CD4 cell count, median cells/μL (IQR)	104 (57–144)	75 (31–129)	.008
Virus load, median $\log_{10}$ copies/mL (IQR)	1.70 (1.70–2.90)	2.00 (1.70–3.00)	.884
Duration of TMP-SMX prophylaxis,[d] median days (IQR)	757 (464–1151)	1038 (556–1718)	.024
Follow-up, median years (IQR)	1.53 (0.83–1.93)	0.84 (0.33–1.57)	<.0001

NOTE. Data are no. (%) of study participants, unless otherwise indicated. CDC, Centers for Disease Control and Prevention (Atlanta, GA); IQR, interquartile range; PI, protease inhibitor.

[a] By the Wilcoxon rank sum test, for numerical data; by χ^2 test, for categorical data.
[b] As defined by the 1993 CDC classification system for HIV infection.
[c] Percentage of the total lymphocyte count.
[d] Before the start of the study.

drugs given for no longer than 14 days (β-lactam antibiotics were given to 9 patients, and macrolides were given to 4 patients). For 5 of the patients, previous vaccination against *S. pneumoniae* had been recorded on the medical chart.

Follow-up and incidence data for the 2 groups are shown in table 2. For both groups, the incidence of CAP was <3 cases per 100 person-years of follow-up. Although the point estimate of the CAP incidence rate was 49% lower in the group that continued receiving prophylaxis, compared with the group that discontinued prophylaxis, the difference was far from statistically significant because of the very low absolute risk.

Discussion. The present study demonstrates a low incidence of CAP among HIV-infected persons who are receiving successful antiretroviral combination therapy and who have a sustained increase in the CD4 cell count to ⩾200 cells/μL. This effect was observed regardless of whether TMP-SMX prophylaxis was continued or interrupted. In fact, CAP incidence rates for the studied populations with CD4 cell counts of mainly 200–500 cells/μL were in the range of the CAP incidence rates noted for patients in a large cohort who had CD4 cell counts of >500 cells/μL before potent antiretroviral combination therapy became available [1].

The main limitation of the present study is the comparison of nonrandomized groups. For example, patients in group II had a slightly lower nadir CD4 cell count than did patients in group I. Therefore, we cannot exclude a bias toward discontinuation of prophylaxis for patients with a lower risk of pneumonia. In addition, the total follow-up in the group that continued receiving prophylaxis was limited, mainly because of the interruption of TMP-SMX prophylaxis, once data from the StopCox1 study were available. Another limitation of the present study is the different nature of data collection for the 2 study groups; collection was done prospectively for group I and retrospectively for group II. This could have led to underestimation of the incidence of CAP in group II.

However, the results of the present study are in concordance with the observations of Sullivan et al. [8], who reported a significantly reduced risk of bacterial pneumonia among HIV-infected patients who were receiving protease inhibitor–based antiretroviral therapy independently of PCP prophylaxis. In 2

Table 2. Follow-up for and incidence of community-acquired pneumonia (CAP) among patients who discontinued trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis carinii* pneumonia (group I) and those who continued receiving such prophylaxis (group II).

Finding	Group I (n = 336)	Group II (n = 75)
Total follow-up, person-years	472	77
CAP episodes, no.	12	1
Incidence rate[a] (95% CI)	2.5 (1.3–4.4)	1.3 (0.03–7.2)

[a] No. of CAP cases per 100 person-years. The difference in the incidence rates between groups I and II was 1.2 CAP cases per 100 person-years (95% CI, −1.6 to 4.1) (P = .6).

recently published randomized trials of discontinuation of primary prophylaxis, the incidence of bacterial pneumonia was low in both arms of the study, and there was no statistically significant difference in the incidence of CAP between the 2 patient groups [11, 12].

Injection drug use has been a risk factor for bacterial pneumonia in most cohorts of HIV-infected patients studied to date [1, 6, 8, 17]. A history of injection drug use was not associated with a higher risk of CAP in our study. However, drug substitution programs are widely used in Switzerland, which leads to better social situations for injection drug users, which might diminish the risk of CAP.

Discontinuation of PCP prophylaxis has been proven safe with regard to risk of PCP if there is a sustained increase in the CD4 cell count during antiretroviral combination therapy [9, 13, 18]. There remain concerns about safety with regard to the risk of bacterial pneumonia.

The present study adds to the evidence that an increase in the risk of CAP after discontinuation of TMP-SMX is, at most, minimal. A quite hypothetical advantage of continuing use of a prophylactic antibiotic is outweighed by the disadvantages of side effects, pill burden, and development of bacterial resistance in a population [19].

STUDY GROUP MEMBERS

The members of the Swiss HIV Cohort Study are M. Battegay, E. Bernasconi, H. Bucher, Ph. Bürgisser, M. Egger, P. Erb, W. Fierz, M. Fischer, and M. Flepp (Chairman of the Clinical and Laboratory Committee); P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, CH-1011- Lausanne); H. J. Furrer, M. Gorgievski, H. Günthard, P. Grob, B. Hirschel, L. Kaiser, C. Kind, Th. Klimkait, B. Ledergerber, U. Lauper, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.-C. Piffaretti, and M. Rickenbach (Head of Data Center); C. Rudin (Chairman of the Mother & Child Substudy); J. Schupbach, R. Speck, A. Telenti, A. Trkola, and P. Vernazza (Chairman of the Scientific Board); and Th. Wagels, R. Weber, and S. Yerly (Chairman of the Mother & Child Substudy).

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