Discontinuation of Primary Prophylaxis for *Pneumocystis carinii* Pneumonia and Toxoplasmic Encephalitis in Human Immunodeficiency Virus Type I–Infected Patients: The Changes in Opportunistic Prophylaxis Study

Cristina Mussini,[1] Patrizio Pezzotti,[4] Alessandra Govoni,[5] Vanni Borghi,[1] Andrea Antinori,[5] Antonella d'Arminio Monforte,[7] Andrea De Luca,[6] Nicola Mongiardo,[1] Maria Chiara Cerri,[1] Francesco Chiodo,[8] Ercole Concia,[9] Lucio Bonazzi,[3] Mauro Moroni,[7] Luigi Ortona,[6] Roberto Esposito,[1] Andrea Cossarizza,[2] and Bruno De Rienzo,[1] for the Changes in Opportunistic Prophylaxis (CIOP) Study[a]

[1]Clinica Malattie Infettive, Azienda Policlinico, [2]Dipartimento di Scienze Biomediche, University of Modena and Reggio Emilia Hospital, and [3]Divisione di Malattie Infettive, Reggio Emilia Hospital, Modena; [4]Istituto Superiore di Sanità, [5]Istituto di Ricovero e Cura a Carattere Scientifico "L. Spallanzani," and [6]Clinica Malattie Infettive, Catholic University, Rome; [7]Clinica Malattie Infettive, University of Milan; [8]Clinica Malattie Infettive, University of Bologna; and [9]Clinica Malattie Infettive, University of Verona, Italy

A multicenter open, randomized, controlled trial was conducted to determine whether primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis can be discontinued in patients infected with human immunodeficiency virus type 1 (HIV-1) whose $CD4^+$ T cell counts have increased to >200 cells/mm^3 (and who have remained at this level for at least 3 months) as a result of highly active antiretroviral therapy (HAART). Patients were randomized to either the discontinuation arm (i.e., those who discontinued prophylaxis; $n = 355$) or to the continuation arm ($n = 353$); the 2 arms of the study were similar in terms of demographic, clinical, and immunovirologic characteristics. During the median follow-ups of 6.4 months (discontinuation arm) and 6.1 months (continuation arm) and with a total of 419 patient-years, no patient developed *P. carinii* pneumonia or toxoplasmic encephalitis. The results of this study strongly indicate that primary prophylaxis for *P. carinii* pneumonia and toxoplasmic encephalitis can be safely discontinued in patients whose $CD4^+$ T cell counts increase to >200 cells/mm^3 during HAART.

The use of highly active antiretroviral therapy (HAART) in persons infected with human immunodeficiency virus type–1 (HIV-1) has resulted in improved survival and in an increase in the length of time that patients remain free from opportunistic infections [1, 2]. These effects seem to be the result of an increase in the number of $CD4^+$ T lymphocytes, which can be considered the marker of a complex immunological improvement, after the suppression of HIV-1 replication [3, 4]. However, although many studies have described the kinetics of the reconstitution of the peripheral $CD4^+$ T cell pool [5, 6], it is not clear whether the newly circulating $CD4^+$ T cells are able to protect against all opportunistic agents and thus reacquire a complete repertoire [7–9].

Nonetheless, a sharp decline in the incidence of several serious opportunistic infections, including *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis, has been reported, even in patients with advanced HIV disease [10]. Thus, the question has arisen as to whether primary prophylaxis for these opportunistic infections can be discontinued in patients who are undergoing HAART and whose $CD4^+$ T cell counts increase to >200 cells/mm^3.

The several observational studies and the 1 randomized trial conducted included patients who discontinued primary prophylaxis against *P. carinii* pneumonia and toxoplasmic encephalitis, since they showed a very low risk of developing these 2 infections [11–14]. Although the results are encouraging, observational studies could have a selection bias that is represented by the fact that the patients who decided to discontinue prophylaxis were those who considered themselves to be at lower risk for *P. carinii* pneumonia and toxoplasmic encephalitis on the basis not only of their immunologic conditions but also of their general conditions and clinical history. To determine whether prophylaxis can be discontinued in clinical prac-

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The study was approved by the local ethics committees.

Written informed consent was obtained from all patients. Enrolled patients were insured for adverse events for the entire duration of the study.

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[a] Institutions and investigators participating in the CIOP Study are listed at the end of the text.

Reprints or correspondence: Dr. Cristina Mussini, Dept. of Infectious Diseases, Policlinico, University of Modena and Reggio Emilio Hospital, Via del Pozzo, 71, 41100 Modena, Italy (crimuss@unimo.it).

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tice, we conducted a study on the effects of discontinuing primary prophylaxis against *P. carinii* pneumonia and toxoplasmic encephalitis among HIV-1–infected patients whose $CD4^+$ T cell counts increased to >200 cells/mm^3 as a result of HAART.

Patients and Methods

The Changes in Opportunistic Prophylaxis (CIOP) Study was designed as an open, randomized, controlled trial and was begun in January 1998. Trial patients were enrolled in 41 clinical centers that are located throughout Italy and in 1 clinical center in Paris; all analyses were performed at the trial's coordinating center (Infectious Disease Clinic, University of Modena and Reggio Emilia, Modena, Italy).

Inclusion and exclusion criteria. To be included in the study, patients were required to be aged >18 years, to have a $CD4^+$ T cell count <200 cells/mm^3 on initiation of HAART, and to be undergoing 1 of the following regimens of primary prophylaxis against *P. carinii* pneumonia and toxoplasmic encephalitis: trimethoprim-sulfamethoxazole (TMP-SMZ; 160/800 mg or 80/400 mg every day or 160/800 every other day); aerosolized pentamidine (300 mg once a month, for *P. carinii* pneumonia only); or dapsone (50 or 100 mg every day) plus pyrimethamine (50 mg weekly) or dapsone (200 mg weekly) plus pyrimethamine (75 mg weekly). Patients also had to be on a potent antiretroviral regimen, which was defined as a combination of at least 3 antiretroviral agents, including nucleoside reverse-transcriptase inhibitors (NRTIs) plus protease inhibitors (PIs) and/or 1 non-NRTI. Furthermore, $CD4^+$ T cell counts had to have increased to >200 cells/mm^3 on 2 consecutive measurements (at least 1 month apart) in the 3 months prior to enrollment. The only criterion for exclusion from the study was a previous episode of *P. carinii* pneumonia (laboratory confirmed or presumptive) or toxoplasmic encephalitis.

Randomization. At study enrollment, the clinical centers recorded demographic data, HIV-1 stage (according to the classification of the US Centers for Disease Control and Prevention [CDC] [15]), history of prophylaxis against *P. carinii* pneumonia and toxoplasmic encephalitis, and history of antiretroviral therapy. This information was sent to the coordinating center, which confirmed that patients fulfilled the inclusion criteria. Within 24 h of receiving this information, the coordinating center randomized patients to 1 of the following 2 arms of the study: patients who would discontinue primary prophylaxis against *P. carinii* pneumonia and toxoplasmic encephalitis (i.e., the discontinuation arm) and those who would continue prophylaxis (i.e., the continuation arm). The ratio of patients between the 2 arms of the study was 1 : 1; to reduce potential imbalance among clinical centers, randomization was blocked for every 8 enrolled patients per center. Clinical and biohumoral controls and $CD4^+$ T cell count measurements were performed every 2 months; plasma HIV viral load was measured at least every 4 months. Patients randomized to the discontinuation arm whose $CD4^+$ T cell counts decreased to <200 cells/mm^3 (measured twice, 1 month apart) during the study period were newly offered prophylaxis, which they continued with for the entire duration of the study.

End points. The primary end points of the study were a definitive diagnosis of *P. carinii* pneumonia, a definitive or presumptive diagnosis of toxoplasmic encephalitis, and death related to these opportunistic infections. The criteria used for diagnosing *P. carinii* pneumonia were the detection of *P. carinii* cysts (by immunofluorescence) in induced sputum and/or bronchoalveolar lavage fluid or histologic demonstration of microorganisms in transbronchial or open-lung biopsy samples. The diagnosis of extrapulmonary pneumocystosis was based on the identification of *P. carinii* in histological or cytological material obtained from extrapulmonary sites during life or at death. A definitive diagnosis of toxoplasmic encephalitis was based on the histological examination of brain-biopsy specimens. A presumptive diagnosis of toxoplasmic encephalitis was made on the basis of all of the following criteria: presence of serum IgG antibodies to *Toxoplasma gondii;* recent onset of clinical neurological alterations consistent with intracranial disease, with a reduced level of consciousness or headache or fever; a neuroradiological picture characterized by at least 1 cerebral lesion that involved the cortex or deep brain nuclei, with a mass effect or positive enhancement with contrast medium; and a response to standard treatment for toxoplasmic encephalitis.

The secondary end points consisted of death that was not related to the primary end points, other HIV-related events (i.e., those reported in stage B and C of the CDC HIV classification), bacterial infections (on the basis of clinical criteria of response to antibiotic treatment and/or microbiological isolation), a $CD4^+$ T cell count <200 cells/mm^3, and non–HIV-related events. Side effects and eventual changes in prophylactic regimens and antiretroviral therapy were recorded every 2 months.

Every 3 months the coordinating center sent clinical monitors to the participating clinical centers, to ensure that patients were being selected properly and that accurate data were being provided. The clinical centers were required to report suspected diagnoses of a primary end point to the coordinating center within 24 h.

Sample size. The initial calculations of the sample size were based on the assumption that patients whose $CD4^+$ T cell counts had decreased to <200 cells/mm^3 prior to antiretroviral therapy and that subsequently increased to >200 cells/mm^3 had a higher risk of developing *P. carinii* pneumonia and toxoplasmic encephalitis than did patients with similar $CD4^+$ T cell counts who had never had a $CD4^+$ T cell count <200 cells/mm^3 [16]. We were interested in testing the hypothesis that the risk of *P. carinii* pneumonia was at least 3 times higher in patients who were discontinuing prophylaxis. Assuming that the incidence rate of *P. carinii* in these patients was equal to 3 cases per 100 patient-years, to obtain a statistical power of 80% (i.e., the probability of detecting this difference given that the hypothesis is true), we calculated a sample size of 1700 patients (850 per arm) to be enrolled for a 2-year period and to be followed up for a median of 1 year.

Interim analyses were conducted every 6 months to evaluate the monthly enrollment rate and the incidence of end points. Eighteen months after the trial began (708 patients and 419 patient-years of follow-up), we decided to stop the trial, because no events of *P. carinii* pneumonia or toxoplasmic encephalitis had been observed and because the confidence intervals of the incidence of the primary end points in both arms of the study were lower than the minimum incidence rate expected among patients who discontinued primary prophylaxis. Thus, enrollment lasted from January 1998 to June 1999.

Statistical analysis. The analysis was performed by use of the

Table 1. Characteristics of the 708 patients in the Changes in Opportunistic Prophylaxis Study, by randomized arm of the study, 1998–1999.

Characteristic	Patients discontinuing prophylaxis	Patients continuing prophylaxis	*P*
n	355 (50.1)	353 (49.9)	
Sex			.37
Male	259 (73.0)	268 (75.9)	
Female	96 (27.0)	85 (24.1)	
HIV-1 exposure category			.47
Injection drug use	155 (43.7)	160 (45.3)	
Male homosexual intercourse	71 (20.0)	70 (19.8)	
Heterosexual intercourse	112 (31.5)	98 (27.8)	
Other or unknown	17 (4.8)	42 (7.1)	
Median age in years (range)	37.1 (23.7–68.8)	37.1 (25.8–73.7)	.84
CDC HIV stage[a]			.35
A	123 (34.6)	108 (30.6)	
B	111 (31.3)	127 (36.0)	
C	121 (34.1)	118 (33.4)	
Patients naive when starting HAART	78 (22.0)	96 (27.2)	.11
HAART			.24
2NRTI+IDV	190 (53.5)	218 (61.8)	
2NRTI+RTV	69 (19.4)	54 (15.3)	
2NRTI+HG-SQV	46 (13.0)	37 (10.5)	
2NRTI+NFV	15 (0.3)	16 (4.5)	
Other	35 (9.8)	28 (7.9)	
Values at initiation of HAART median (IQR)			
$CD4^+$ T cell count, cells/mm^3	89 (34–154)	90 (37–140)	.47
CD4, %	8.2 (4.0–12.4)	8.5 (4.0–12.7)	1.00
HIV-RNA , $\log_{10}$ copies/mL	4.72 (3.97–5.39)	4.99 (4.18–5.43)	.07
Values at enrollment median (IQR)			
$CD4^+$ T cell count, cells/mm^3	324 (268–411)	336 (270–418)	.14
CD4, %	16.8 (12.7–21.5)	17.3 (13.6–22.0)	.08
HIV-RNA, $\log_{10}$ copies/mL	<2.70 (<2.70–5.20)	<2.70 (<2.70–5.06)	.23
Patients with HIV-RNA <500 copies/mL	203	206	.75
Prophylactic regimens			.67
Trimethoprim-sulfamethoxazole	273 (77.3)	281 (80.1)	
Aerosolized pentamidine	68 (19.3)	59 (16.8)	
Dapsone-pyrimethamine	12 (3.4)	11 (3.1)	

NOTE. Data are no. (%) unless otherwise indicated. CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; HG-SQV, hard gel saquinavir; HIV-1, human immunodeficiency virus type 1; IDV indinavir; IQR, interquartile range; NFV, nelfinavir; NRTI, nucleoside reverse-transcriptase inhibitor; RTV, ritonavir.

[a] CDC HIV stage according to the CDC 1993 classification system.

intention-to-treat principle. To compare demographic, clinical, virologic, and immunologic characteristics between the 2 arms of the study at the time of enrollment, we used the χ^2 test or the Wilcoxon rank sum test, depending on whether the variable was categorical or continuous. The length of follow-up was calculated as the time that elapsed between the date of randomization and the first date of the following: diagnosis of *P. carinii* pneumonia, diagnosis of toxoplasmic encephalitis, death, first measurement of a $CD4^+$ T cell count that was <200 cells/mm^3, or June 1999. We calculated exact confidence intervals and *P* values to compare the 2 groups for the incidence of the end points, after having assumed that the events followed a Poisson distribution. For toxoplasmic encephalitis, we restricted the calculation to patients who were serologically positive for IgG antibodies to *T. gondii* and who were receiving either TMP-SMZ or dapsone-pyrimethamine at enrollment.

The Kaplan-Meier method was used to estimate the cumulative probability of having $CD4^+$ T cell counts <200 cells/mm^3 at different points in time after enrollment. To calculate the crude and adjusted relative hazards of progression to each specific end point for those who were discontinuing primary prophylaxis compared with those who were continuing prophylaxis, we also applied univariate and multivariate proportional hazards regression models.

Results

Characteristics of the study patients at enrollment. From January 1998 to June 1999, 708 patients were enrolled in the study: 355 were randomized to the discontinuation arm and 353 to the continuation arm. No statistically significant differences were found between the 2 arms of the study with regard to patients' demographic, immunologic, virologic, or clinical characteristics (table 1). Most patients were males (74.4%), and the median age at enrollment was 37.1 years in both arms of the study. Injection drug use was the most frequently reported risk factor for HIV-1 infection. With regard to CDC clinical stage, 34.1% of the patients in the discontinuation arm and 33.4% in the continuation arm were in clinical stage C. Data

Table 2. Incidence of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in the Changes in Opportunistic Prophylaxis Study, 1998–1999.

Event, variable	Patients discontinuing prophylaxis	Patients continuing prophylaxis	Total	*P*
Pneumocystis carinii pneumonia				
No. of patients	355	353	708	
Median follow-up in months (IQR)	6.36 (3.0–10.8)	6.12 (4.32–10.7)		
Patient-years	210	209	419	
Incidence, for 100 patient-years	0	0		NE
Upper 99% confidence limit	2.5	2.5		
Toxoplasmic encephalitis				
No. of *Toxoplasma gondii*–positive patients (% of total)	115/247 (46.6)	128/246 (52.0)	243/493	
Median follow-up in months (IQR)	7.44 (4.0–10.8)	6.48 (4.3–10.7)		
Patient-years	72	72	144	
Incidence, for 100 patient-years	0	0		NE
Upper 99% confidence limit	7.3	7.3		
Other, no. of patients				
Withdrawals	9	11	20	.66
HIV-related events	5	5	10	.99
Deaths	3	2	5	.69
Bacterial infections	28	18	46	.15

NOTE. HIV, human immunodeficiency virus; IQR, interquartile range; NE, not estimable.

concerning IgG antibodies to *T. gondii* were available for 493 patients; antibodies were positive in 115 (46.6%) of 247 patients in the discontinuation arm and in 128 (52%) of 246 patients in the continuation arm. A total of 174 patients had been naive for any type of antiretroviral therapy before starting HAART: 78 (22.0%) were in the discontinuation arm and 96 (27.2%) in the continuation arm. The median duration of prophylaxis was 28.3 months in the discontinuation arm and 28.0 months in the continuation arm. The median time between beginning HAART and enrollment was 17.7 months. At the time of starting HAART, the median $CD4^+$ T cell count was 89 cells/mm^3 in the discontinuation arm and 90 cells/mm^3 in the continuation arm, with a median percentage of 8.2% and 8.5%, respectively. The median HIV plasma viral load was 4.72 $\log_{10}$ copies/mL in the discontinuation arm and 4.99 $\log_{10}$ copies/mL in the continuation arm. The median time from the first available $CD4^+$ T cell count <200 cells/mm^3 to the first $CD4^+$ T cell count >200 cells/mm^3 was 18.0 months. The median time between the first $CD4^+$ T cell count >200 cells/mm^3 and enrollment was 8.4 months. At enrollment, the median $CD4^+$ T cell count was 324 cells/mm^3 for the discontinuation arm and 336 cells/mm^3 for the continuation arm, with a $CD4^+$ T percentage of 16.8% and 17.3%, respectively; the median plasma viral load was <2.70 $\log_{10}$ copies/mL in both arms of the study.

Incidence of primary end points. The median duration of follow-up was 6.36 months (210 patient-years) for patients randomized to the discontinuation arm and 6.12 months (209 patient-years) for the continuation arm. Seventy-five patients (21.1%) in the discontinuation arm and 60 patients (17.0%) in the continuation arm had a follow-up of longer than 1 year. The incidence of the primary end points is presented in table 2. As mentioned in Patients and Methods, no cases of definitive *P. carinii* pneumonia were diagnosed, or even suspected, among the 708 patients. In the 243 patients with positive serum IgG antibodies to *T. gondii,* no cases of toxoplasmic encephalitis were diagnosed during follow-up. The upper 99% Poisson confidence limits for incidence were 2.5 per 100 patient-years for *P. carinii* pneumonia and 7.3 per 100 patient-years for toxoplasmic encephalitis in both arms of the study. Univariate and multivariate relative hazards of progressing to *P. carinii* pneumonia, toxoplasmic encephalitis, and death related to these infections were not estimable because of the absence of events.

Incidence of secondary end points. None of the patients had an AIDS-defining event during follow-up (i.e., events reported in stage C of the CDC HIV classification). Nine patients (4 in the discontinuation arm and 5 in the continuation arm of the study) had an event that was considered indicative of CDC stage B: 1 patient per arm had oral candidiasis; 1 patient per arm had cervical intraepithelial dysplasia; and 2 patients in the discontinuation arm and 3 in the continuation arm had herpes zoster. Univariate and adjusted relative hazards for patients who discontinued prophylaxis, compared with those who continued prophylaxis, did not significantly differ from unity (data not shown).

Twenty-eight patients (7.9%) in the discontinuation arm and 18 (5.1%) in the continuation arm developed a bacterial infection during the follow-up period, but the incidence-rate ratio was not significantly different from unity ($P = .15$). Specifically, 19 patients developed bronchitis (12 in the discontinuation arm), 9 developed pneumonia (4 in the discontinuation arm), 3 developed sinusitis (2 in the discontinuation arm), 3 developed urinary tract infections (2 in the discontinuation arm), 4 developed bacterial abscesses (1 in the discontinuation arm), 3 developed sepsis (2 in the discontinuation arm), 2 developed otitis (both in the discontinuation arm), 2 developed pharyngitis (both in the discontinuation arm), and 1 developed cholecystitis

(in the discontinuation arm). When restricting the analysis to patients who were undergoing TMP-SMZ prophylaxis, an univariate and an adjusted relative hazard of 0.85 was found for patients who were continuing prophylaxis, but this hazard was not significantly different from unity ($P = .65$).

Patients who interrupted the study and deaths. A total of 20 patients interrupted the study. Specifically, 7 patients in the continuation arm decided to discontinue prophylaxis, 1 patient in the discontinuation arm decided to continue prophylaxis, 11 patients were lost to follow-up, and 1 had to restart prophylaxis during chemotherapy. Five patients died (3 in the discontinuation arm and 2 in the continuation arm of the study): 1 patient who had non–Hodgkin's lymphoma died of pulmonary aspergillosis, 1 died of tongue cancer, 1 patient with a previous diagnosis of progressive multifocal leukoencephalopathy died of sepsis, 1 died of leukemia, and 1 died of myeloma.

Immunologic and virologic time trends during follow-up. The distribution of $CD4^+$ T cell counts and viral loads at the time of starting HAART and during the follow-up period (by arm of the study) are shown in figures 1 and 2, respectively. At 6 months from enrollment, the median $CD4^+$ T cell count was 330 cells/mm^3 in the discontinuation arm and 340 cells/mm^3 in the continuation arm ($P = .88$); the median viral load was 2.70 $\log_{10}$ copies/mL in both arms of the study ($P = .96$).

For 23 patients (14 in the discontinuation arm and 9 in the continuation arm of the study), the $CD4^+$ T cell count had decreased to <200 cells/mm^3 on 2 consecutive measurements in 1 month, with an estimated cumulative probability (at 6 months from enrollment) of 10.0% and of 11.5% for those in the discontinuation arm and in the continuation arm, respectively. A total of 55 patients (24 in the discontinuation arm and 31 in the continuation arm) had a single $CD4^+$ T cell count <200 cells/mm^3, with an estimated cumulative probability (at 6 months from enrollment) of 4.1% and of 2.0% for those in the discontinuation arm and in the continuation arm, respectively.

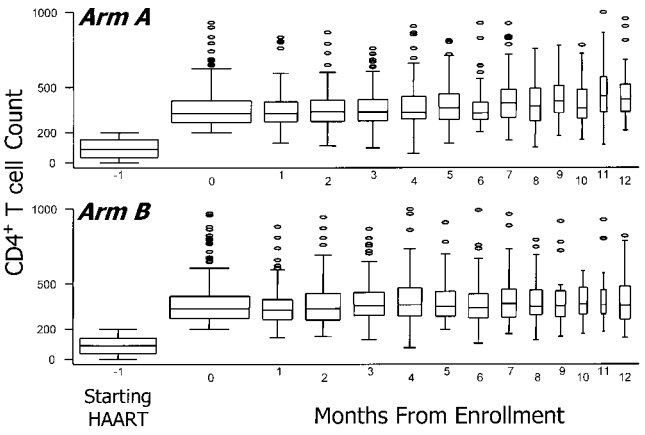

Figure 1. Box-and-whiskers plots of $CD4^+$ T cell counts (cells/mm^3) by arm of the study and by no. of months from enrollment. Boxes at each time unit extend from the 25th percentile ($x_{[25]}$) to the 75th percentile ($x_{[75]}$) (i.e., the interquartile range [IQR]); lines inside the boxes represent the median values. Lines emerging from the boxes (i.e., the "whiskers") extend to the upper and lower adjacent values. Upper adjacent value is defined as the largest data point, $\leqslant x_{[75]} + 1.5 \times \text{IQR}$; lower adjacent value is defined as the smallest data point, $\geqslant x_{[25]} - 1.5 \times \text{IQR}$. Observed values that are more extreme than the adjacent values, if any, are individually plotted *(circles)*. Widths of the boxes are proportional to the no. of observations available at each time unit. Month −1 indicates the time at which highly active antiretroviral therapy (HAART) was begun. *Arm A,* Discontinuation arm. *Arm B,* Continuation arm.

Discussion

The present randomized, controlled trial shows that there was no increase in the risk of developing *P. carinii* pneumonia or toxoplasmic encephalitis among HIV-infected patients whose $CD4^+$ T cell counts increased to >200 cells/mm^3 after beginning HAART after discontinuing prophylaxis for these infections. In particular, the upper 99% confidence limit of the incidence of *P. carinii* pneumonia for patients randomized to discontinuing prophylaxis was 2.5 per 100 patient-years, which is very similar to that obtained in controlled clinical trials employing TMP-SMZ as primary prophylaxis [17, 18]. Several recent observational studies [11–13] have addressed the issue of discontinuing primary prophylaxis in patients who are being treated with potent combination antiretroviral therapy and whose $CD4^+$ T cell counts have increased to >200 cells/mm^3 [19, 20], and none of these studies has reported cases of *P. carinii* pneumonia or toxoplasmic encephalitis after discontinuation. On the basis of these results, the US Public Health Service/Infectious Diseases Society of America modified its guidelines for the prevention of opportunistic infections in HIV-infected patients [21]. According to the new guidelines, clinicians can consider discontinuing prophylaxis for patients with a $CD4^+$ T cell count >200 cells/mm^3, although discontinuation is not strictly recommended. In our opinion, the results of the present trial, especially because they were obtained after a randomized design, indicate that primary prophylaxis for *P. carinii* pneumonia and for toxoplasmic encephalitis can be safely discontinued in patients with a sustained increase in $CD4^+$ T cell count to >200 cells/mm^3. This conclusion is also supported by that fact that no cases of *P. carinii* pneumonia or toxoplasmic encephalitis were observed during the 6 months after the completion of the trial.

The results of this trial also allow us to draw additional conclusions. The fact that no events were detected, despite a previous prolonged phase of immunosuppression, indicates that HAART can induce significant immunologic improvement, even in patients with advanced HIV-1 infection. The recovery of $CD4^+$ T cells was quite stable over time in both arms of the study, suggesting that prophylaxis could potentially be suspended for a long period of time. In fact, although $CD4^+$ T cell counts decreased to <200 cells/mm^3 in some patients, in

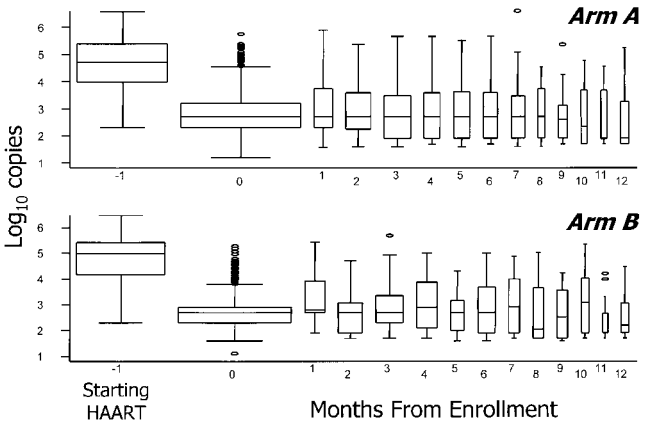

Figure 2. Box-and-whiskers plots of plasma human immunodeficiency virus (HIV) viral load ($\log_{10}$ copies/mL) by arm of the study and by no. of months from enrollment. Boxes at each time unit extend from the 25th percentile ($x_{[25]}$) to the 75th percentile ($x_{[75]}$) (i.e., interquartile range [IQR]); lines inside the boxes represent the median values. Lines emerging from the boxes (i.e., the "whiskers") extend to the upper and lower adjacent values. Upper adjacent value is defined as the largest data point, $\leq x_{[75]} + 1.5 \times \text{IQR}$; lower adjacent value is defined as the smallest data point, $\geq x_{[25]} - 1.5 \times \text{IQR}$. Observed values that are more extreme than the adjacent values, if any, are individually plotted *(circles)*. Widths of the boxes are proportional to the number of observations available at each time unit. Month −1 indicates the time at which highly active antiretroviral therapy (HAART) was begun. *Arm A,* Discontinuation arm. *Arm B,* Continuation arm.

most cases the second measurement did not confirm this decrease, and only a few patients had to restart prophylaxis because of a stable decrease. Of the drugs currently used for preventing *P. carinii* pneumonia and toxoplasmic encephalitis, TMP-SMZ is considered to be the most likely to protect against a variety of bacterial infections [22, 23]. In our trial, we estimated a relative hazard of developing bacterial infections of 0.85 when comparing patients who continued prophylaxis with TMP-SMZ with those who discontinued use of this drug. This hazard, although not statistically significant, is similar in magnitude to that reported by Buskin et al. [23], which suggested that continued prophylaxis in patients with an immune response induced by HAART could have beneficial effects on secondary outcomes such as bacterial infections. However, the magnitude of this protective effect is probably not sufficient to justify the continuation of prophylaxis.

In conclusion, although the results of this trial support those of previous observational studies regarding the safety of discontinuing primary prophylaxis for *P. carinii* pneumonia and toxoplasmic encephalitis in patients treated with HAART whose $CD4^+$ T cell counts increased to >200 cells/mm^3, additional issues still need to be addressed. First, as in the previously mentioned observational studies, most patients in this trial had a median viral load that was below the level of detection at enrollment in the study. Observational data from clinical trials on antiretroviral therapy have shown that baseline viral load and reductions in viral load during therapy appear to influence the risk of developing several opportunistic infections—independent of the $CD4^+$ T cell count [24]. Additional data are needed to assess the value of discontinuing primary prophylaxis in patients who exhibit a sustained increase in $CD4^+$ T cell count after HAART but who also exhibit a persistently detectable HIV plasma viremia [25]. Although our trial was not designed to explore this end point and could not provide a concrete answer relative to this issue, in the nearly one-third of the patients whose viral load was detectable at enrollment, no events were observed.

A second issue that remains to be addressed is the finding that a few events, both those that are HIV related and those that are not, occurred in HIV-positive patients from both arms of the study. To assess whether or not these events are independent risk factors for the future development of *P. carinii* pneumonia or toxoplasmic encephalitis, a longer period of follow-up is required. Finally, functional analyses are urgently required to ascertain whether or not the newly formed $CD4^+$ T cells are capable of recognizing antigens from *P. carinii, T. gondii,* or other opportunistic agents and possibly to analyze the life span of protective clones. Such functional analysis could be crucial in identifying the moment at which prophylaxis has to be restarted or in recognizing those patients who need to continue prophylaxis because of a defective immune reconstitution.

Changes in Opportunistic Prophylaxis (CIOP) Study

The following institutions and investigators participated in the CIOP study. Scientific Committee: Cristina Mussini, Alessandra Govoni, Vanni Borghi, Nicola Mongiardo, Andrea Antinori, Patrizio Pezzotti, Andrea De Luca, Francesco Chiodo, Antonella d'Arminio Monforte, Lucio Bonazzi, Ercole Concia, Alessandra Ursitti, Teresa Bini, Roberto Esposito, Andrea Cossarizza, and Bruno De Rienzo.

Participating clinical centers: Policlinico Bari, Istituto Malattie Infettive (G. Angarano and N. Ladisa); Ospedali Riuniti Bergamo, Divisione Malattie Infettive (G. Gavazzeni and G. P. Gregis); Ospedale Maggiore Bologna, Divisione di Malattie Infettive (F. Gritti and B. Cannella); Policlinico S. Orsola Bologna, Istituto Malattie Infettive (F. Chiodo and C. Beltrami); Spedali Civili Brescia, Istituto Malattie Infettive (G. Carosi and G. Casari); Ospedale Regionale Bolzano, Divisione Malattie Infettive (P. Mian and R. Pristerà); Ospedale Garibaldi Catania, I Divisione Malattie Infettive (P. Di Gregorio and S. Galvagna); Arcispedale S. Anna Ferrara, Unità Operativa Malattie Infettive (F. Ghinelli and L. Sighinolfi); Azienda Ospedaliera Careggi Firenze, Unità Operativa Malattie Infettive (F. Leoncini and G. Rogasi); Presidio Ospedaliero M. Bufalini Cesena, Unità Operativa Malattie Infetttive (A. Stagno and S. Brighi);

Ospedale Morgagni Forlì, Modulo di Malattie Infettive (C. Cancellieri and F. Allegrini); Ospedale San Martino Genova, Divisione di Malattie Infettive (F. Rizzo and M. Camera); Istituto Gaslini Genova, Istituto Malattie Infettive (D. Bassetti and M. Marturano); Ospedale Maggiore Lodi, Reparto di Malattie Infettive (I. Arcidiacono); Ospedale Vecchio Monza, Divisione di Malattie Infettive (L. Cremoni and L. M.Vaira); Ospedale L. Sacco Milano, Istituto di Malattie Infettive (M. Moroni, A. d'Arminio Monforte, T. Bini, G. Moscatelli, and B. Castelnuovo); Ospedale L. Sacco Milano, II Divisione Malattie Infettive (A. Cargnel, P. Meraviglia, C. Atzori, and E. Angeli); Ospedale L. Sacco Milano, I Divisione Malattie Infettive (F. Milazzo and M. Cohen); Ospedale Carlo Poma Mantova, Divisione Malattie Infettive (A. Scalzini and S. Miccolis); Policlinico Modena, Clinica Malattie Infettive (B. De Rienzo and C. Mussini); Ospedale Civile Massa, Unità Operativa Infettive (P. Almi and L. Matini); Ospedale Cotugno Napoli, IV Divisione (R. Pempinello and M. Gargiulo); Azienda Ospedaliera Padova, Divisione Malattie Infettive (P. Cadrobbi, F. Meneghetti, and A. M. Catellan); Policlinico Monteluce Perugia, Istituto Malattie Infettive (S. Pauluzzi, M. B. Pasticci, P. Mele, and S. Guerrieri); Ospedale S. Chiara di Cisanello Pisa, Divisione Malattie Infettive (M. Della Santa and E. Savalli); Azienda Ospedaliera Parma, Divisione Malattie Infettive (F. Fiaccadori and C. Calzetti); Ospedale S. Maria delle Croci Ravenna, Divisione Malattie Infettive (S. Ranieri and P. Bassi); Arcispedale S. Maria Nuova Reggio Emilia, Divisione Malattie Infettive (L. Bonazzi and A. Ursitti); Ospedale Infermi Rimini, Divisione Malattie Infettive (R. Ciammarughi and G. Moscatelli); Presidio Ospedaliero Rovigo, Divisione Malattie Infettive (M. Carretta and G. Masiero); IRCCS L. Spallanzani Roma (III Divisione: A. Antinori and M. Maddaluno; IV Divisione: P. Narciso and C. Carvelli; II Divisione: F. Palmieri and N. Petrosillo); Policlinico Gemelli Roma, Istituto Malattie Infettive (L. Ortona, A. De Luca, E. Tamburrini, and R. Murri); Ospedale S. Corona Pietra Ligure, Divisione Malattie Infettive (G. Riccio and G. Varagona); Ospedale S. Chiara Trento, Divisione Malattie Infettive (F. Branz and C. Paternoster); Ospedale A. di Savoia Torino, Divisione Malattie Infettive (M. L. Soranzo and A. Macor); Ospedale di Circolo Varese, Divisione Malattie Infettive (D. Torre); Ospedali Civili Riuniti Venezia, Divisione Malattie Infettive (E. Raise and S. Pasquinucci); Ospedale S. Bortolo Vicenza, Divisione Malattie Infettive (F. De Lalla and L. Timillero); Ospedale Borgo Trento Verona, Istituto Malattie Infettive (E. Concia, M. Solbiati, and M. Trevenzoli); and Hôpital Pitié Salpêtrière Paris, Département des Maladies Infectieuses (C. Katlama and C. Olivier).

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