Discontinuation of Maintenance Therapy for Cryptococcal Meningitis in Patients with AIDS Treated with Highly Active Antiretroviral Therapy: An International Observational Study

Cristina Mussini,[1] Patrizio Pezzotti,[3] José M. Miró,[9] Esteban Martinez,[9] Juan Carlos Lopez Bernaldo de Quiros,[11] Paola Cinque,[6] Vanni Borghi,[1] Andrea Bedini,[1] Pere Domingo,[10] Pedro Cahn,[14] Philippe Bossi,[12] Andrea De Luca,[4] Antonella d'Arminio Monforte,[7] Mark Nelson,[13] Nneka Nwokolo,[13] Silvia Helou,[15] Ricardo Negroni,[15] Gaia Jacchetti,[8] Spinello Antinori,[7] Adriano Lazzarin,[6] Andrea Cossarizza,[2] Roberto Esposito,[1] Andrea Antinori,[5] and Judith A. Aberg[16] for the International Working Group on Cryptococcosis

[1]Clinic of Infectious and Tropical Diseases, University of Modena and Reggio Emilia, Azienda Policlinico, and [2]Department of Biomedical Sciences, University of Modena and Reggio Emilia, Modena, [3]Istituto Superiore di Sanità, and [4]Clinic of Infectious Diseases, Catholic University, and [5]National Institute for Infectious Diseases "L. Spallanzani," Rome, and [6]Clinic of Infectious Diseases, Università Vita e Salute, and [7]Clinic of Infectious Diseases, University of Milan and [8]Department of Infectious Diseases, Sacco Hospital, Milan, Italy; [9]Idibaps-Hospital Cliníc, University of Barcelona and [10]Hospital de la Santa Creu i Sant Pau, Barcelona, and [11]Infectious Diseases Unit, Hospital Gregorio Marañon, Madrid, Spain; [12]Department of Infectious Diseases, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [13]Chelsea and Westminster Hospital, London, United Kingdom; [14]Clinic of Infectious Diseases, Hospital J. A. Fernandez, and [15]Infectious Disease Hospital "F. J. Muñiz," Buenos Aires, Argentina; and [16]Department of Internal Medicine, Division of Infectious Disease, Washington University, St. Louis, Missouri

We conducted a retrospective, multicenter study evaluating the safety of discontinuing maintenance therapy for cryptococcal meningitis after immune reconstitution. Inclusion criteria were a previous definitive diagnosis of cryptococcal meningitis, a CD4 cell count of >100 cells/μL while receiving highly active antiretroviral therapy (HAART), and the subsequent discontinuation of maintenance therapy for cryptococcal meningitis. The primary end point was relapse of cryptococcal disease. As of July 2002, 100 patients were enrolled. When maintenance therapy was discontinued, the median CD4 cell count was 259 cells/μL and the median plasma virus load was <2.30 $\log_{10}$ copies/mL, and serum cryptococcal antigen was undetectable in 56 patients. During a median follow-up period of 28.4 months (range, 6.7–64.5; 262 person-years), 4 events were observed (incidence, 1.53 events per 100 person-years; 95% confidence interval, 0.42–3.92). Three of these patients had a CD4 cell count of >100 cells/μL and a positive serum cryptococcal antigen test result during the recurrent episode. In conclusion, discontinuation of maintenance therapy for cryptococcal meningitis is safe if the CD4 cell count increases to >100 cells/μL while receiving HAART. Recurrent cryptococcal infection should be suspected in patients whose serum cryptococcal antigen test results revert back to positive after discontinuation of maintenance therapy.

The advent of HAART has deeply affected not only the incidence of opportunistic infections, but also the recommendations for primary and secondary prophylaxis [1, 2]. Actually, it is possible to discontinue prophylactic regimens if the CD4 cell count increases to a value higher than that considered to indicate risk for the development of opportunistic infections before the availability of HAART [3–18]. The management of AIDS-associated cryptococcal meningitis (CM) likely

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Reprints or correspondence: Dr. Cristina Mussini, Clinic of Infectious and Tropical Diseases, University of Modena and Reggio Emilia, Azienda Policlinico, Via del Pozzo, 71- 41100 Modena, Italy (crimuss@unimo.it).

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does not differ significantly from management of other AIDS-associated opportunistic infections, and HAART may, in fact, diminish the risk of recurrence once the infection has been adequately treated.

We studied persons with a diagnosis of CM whose CD4 count increased to >100 cells/μL while receiving HAART and who discontinued maintenance therapy to determine whether maintenance therapy for CM can be safely discontinued for patients with presumed immune reconstitution.

SUBJECTS, MATERIALS, AND METHODS

This is a multicenter retrospective study on the discontinuation of maintenance therapy for CM in subjects treated with HAART who had CD4 cell counts of >100 cells/μL before discontinuing antifungal therapy. CD4 cell counts were determined and plasma virus load assays were performed at each site. Cryptococcal antigens were detected in serum and CSF samples using commercially available latex agglutination systems. Case records of patients observed in 21 centers (listed in the study group section at the end of the text) were evaluated. Some of the cases reported in this article were previously reported [4, 17].

Inclusion and exclusion criteria. We included patients with HIV-1 infection who had a definitive diagnosis of $\geq$1 episode of CM when their CD4 cell count was <100 cells/μL, who received maintenance therapy, and who discontinued maintenance therapy after they attained a CD4 cell count of >100 cells/μL while receiving HAART. A diagnosis of CM was considered definitive if *Cryptococcus neoformans* was isolated from a CSF specimen or if there was a positive result of a CSF cryptococcal antigen titer or CSF india ink preparation study. Maintenance therapy was defined as treatment with any drug with known activity against *C. neoformans* at recommended standard doses and included fluconazole, itraconazole, and amphotericin B. HAART was defined as a combination of $\geq$3 antiretroviral agents. The decision to discontinue maintenance therapy was either an independent decision made by the patient or resulted from consultation between individual patients and their physicians.

End points. The primary end points of the study were a confirmed diagnosis of recurrence of CM, any evidence of cryptococcal disease, or death. Secondary end points were any new AIDS-defining illness [19], a decrease in the CD4 cell count to <100 cells/μL, and reinstitution of maintenance therapy.

Statistical analysis. All participants who underwent $\geq$1 follow-up evaluation after discontinuation of maintenance therapy were included in the analysis. The duration of follow-up was measured from the time of discontinuation to the date of the last visit or the date that a primary end point was reached. Incidences of CM and death related to this opportunistic infection were calculated for the period in which the patients were not receiving maintenance therapy. Events were assumed to have a Poisson distribution, and exact 95% CIs were calculated for the incidence of end points. SAS software, version 8.1 (SAS Institute), was used for statistical analysis.

RESULTS

Characteristics of Patients

A total of 100 patients were included in the study. The median duration of follow-up was 26.5 months (range, 12.7–76.8 months). The number of patients enrolled at each country and selected epidemiological and clinical characteristics of the study participants are shown in table 1. The median time from the first diagnosis of CM to the end of the observation period was 68.7 months (range, 23.9–113.7 months). The median duration of HAART before discontinuation of maintenance therapy was 26.1 months (range, 0.4–56.2 months). The median duration of maintenance therapy was 33.0 months (range, 2.0–90.7 months). The median time from the first CD4 cell count of >100 cells/μL to the discontinuation of maintenance therapy was 1 month (range, 0.4–40.4 months). In fact, clinicians or patients themselves decided to discontinue maintenance therapy for 54 patients (54.0%) within 1 month after the first CD4 cell count of >100 cells/μL, whereas, for the remaining 46 patients (46.0%), the median time was 13.7 months.

CD4 Cell Count, Plasma Virus Load, and Detection of Cryptococcal Antigen

Viroimmunological parameters and serum cryptococcal antigen data are shown in table 2. Twenty-five (61.0%) of the 41 patients with a positive serum cryptococcal antigen test result at time of antifungal therapy discontinuation continued to have positive results during the follow-up period (median titer, 1:128; range, 1:4–1:8192). Five (8.9%) of the 56 patients with a negative serum cryptococcal antigen result at the time of discontinuation had positive results during the follow-up period (titers were 1:512, 1:128, and 1:32 for 1 patient each and 1:16 for 2 patients). Maintenance therapy for CM was not restarted on the basis of the titer of serum cryptococcal antigen alone.

Incidence of Primary End Points

No events occurred during a median period of 26.1 months (220 person-years) when patients were taking both HAART and maintenance therapy for CM. The incidence during that period was 0% (95% CI, 0–1.67 cases per 100 person-years). After discontinuation of maintenance therapy, during a period of observation of 262 person-years (median, 28.4 months; range, 6.7–64.5 months), 2 cases of CM and 2 extrameningeal cryptococcal infections were diagnosed. The incidence of relapse of cryptococcal infection was 1.53 cases per 100 person-

Table 1. Demographic and clinical characteristics of 100 HIV-infected adults who were receiving HAART and who discontinued maintenance therapy for cryptococcal meningitis.

Characteristic	Value
Country of origin	
Italy	35 (35.0)
Spain	21 (21.0)
Argentina	16 (16.0)
Great Britain	16 (16.0)
France	3 (3.0)
United States	9 (9.0)
Sex	
Male	84 (84.0)
Female	16 (16.0)
HIV exposure group	
Injection drug users	34 (34.0)
Men who have sex with men	40 (40.0)
Heterosexuals	19 (19.0)
Other	7 (7.0)
Age at first diagnosis of cryptococcal meningitis, median years (range)	33.6 (15.2–56.7)
Maintenance therapy for cryptococcal meningitis	
Fluconazole	93 (93.0)
Itraconazole	4 (4.0)
Liposomal amphotericin B	3 (3.0)
Relapse of cryptococcal meningitis before HAART	12 (12.0)
Time from last episode of cryptococcal meningitis to HAART initiation, median months (range)	6.62 (0.0–49.0)
Antiretroviral therapy naive at HAART initiation	39 (39.0)
Antiretroviral therapy received at the time of CD4 cell count of >100 cells/μL	
Indinavir	39 (39.0)
Nelfinavir	14 (14.0)
Ritonavir	2 (2.0)
Nevirapine	17 (17.0)
Efavirenz plus 2 NRTIs	12 (12.0)
Ritonavir-lopinavir plus 2 NRTIs	9 (9.0)
Amprenavir plus 2 NRTIs	1 (1.0)
Abacavir plus 2 NRTIs	3 (3.0)
Saquinavir plus 2 NRTIs	3 (3.0)
Time from last episode of cryptococcal meningitis to discontinuation of maintenance therapy, median months (range)	36.7 (4.4–91.6)
Time from HAART initiation to discontinuation of maintenance therapy, median months (range)	26.1 (3.2–56.2)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

years (95% CI, 0.42–3.92 cases per 100 person-years; $P = .08$, compared with the period when patients were receiving maintenance therapy).

Case Reports

Patient 1. A 39-year-old man discontinued maintenance therapy for CM and primary PCP prophylaxis 42 months after commencing HAART and 58 months after diagnosis of CM. At the time that prophylaxis was discontinued (16 months after a CD4 cell count of >100 cells/μL was attained), the CD4 cell count was 185 cells/μL (13% of the total lymphocyte count), the plasma virus load was <200 copies/mL, and the serum cryptococcal antigen test result was negative. Two months later, he was admitted to the hospital because of fever and dyspnea. A chest radiograph revealed bilateral interstitial infiltrates. Serum and CSF cryptococcal antigen titers were 1:2048, but the results of blood and CSF cultures were negative. CSF chemistry findings were normal. Examination of a bronchoalveolar lavage (BAL) specimen failed to recover any pathogens. The CD4 cell count was 136 cells/μL, and the plasma virus load was 7810 copies/mL. The patient was successfully cured with a full course of trimethoprim-sulfamethoxazole and amphotericin B.

Patient 2. A 32-year-old man discontinued maintenance therapy for CM 12 months after HAART was commenced, 26 months after CM was diagnosed, and 9 months after a CD4 cell count of >100 cells/μL was attained. His CD4 cell count was 405 cells/μL (25% of the total lymphocyte count), his plasma virus load was <200 copies/mL, and the serum cryptococcal antigen test result was negative. Eleven months after stopping maintenance therapy, the patient had an elevated lactose dehydrogenase level (1019 U/L). He was asymptomatic. The CD4 cell count was 465 cells/μL (31% of the total lymphocyte count), and the plasma virus load was <200 copies/mL. A CT scan of the body revealed a splenic mass. The patient had several transient motor deficits mimicking ischemic attacks. MRI of the brain revealed small nodules (diameter, 1–2 mm) on the cranial floor. CSF chemistry and pressure findings were normal. The results of CSF and serum cryptococcal antigen tests were negative. Results of blood, BAL, and CSF cultures were negative. A diagnostic splenectomy was performed, and the histopathological diagnosis revealed *C. neoformans*. Culture was not performed. The patient was successfully treated with liposomal amphotericin B.

Patient 3. A 43-year-old man discontinued maintenance therapy for CM 9 months after HAART was started, 14 months after CM was diagnosed, and 8 months after a CD4 cell count of >100 cells/μL was attained. The patient's CD4 cell count was 236 cells/μL, his plasma virus load was 122,000 copies/mL, and a serum cryptococcal antigen test was not performed. One year later, the patient was admitted to the hospital with weakness, stupor, and headache. CT of the brain revealed multiple ring-enhancing lesions with surrounding edema. A CSF examination revealed only a protein level of 250 mg/μL and a lymphocyte count of 6 lymphocytes/μL. The CSF cryptococcal antigen titer was 1:512, and CSF culture yielded *C. neoformans*. The patient's CD4 cell count was 46 cells/μL (13% of the total lymphocyte count), and his plasma virus load was <200 copies/mL. The patient was treated with amphotericin B, sulfadiazine, and pyr-

Table 2. Viroimmunological parameters and detection of cryptococcal antigen in patients who discontinued maintenance therapy for cryptococcal meningitis.

Characteristic	Recurrent cryptococcal meningitis		Cryptococcal antigen detected at discontinuation of maintenance therapy		Cryptococcal antigen detected at last visit	
	No (n = 96)	Yes (n = 4)	Negative (n = 56)	Positive (n = 41)	Negative (n = 67)	Positive (n = 30)
Interval since last episode of cryptococcosis, months	68.76 (23.89–113.71)	41.66 (41.23–92.88)	71.85 (26.41–113.71)	66.17 (23.89–97.77)	70.83 (26.41–113.71)	62.62 (23.89–95.08)
Duration of HAART before discontinuation of maintenance therapy, months	26.15 (3.20–56.18)	10.97 (9.23–41.56)	24.85 (3.40–55.33)	26.64 (3.55–56.18)	25.00 (3.33–55.33)	28.22 (3.25–56.18)
At discontinuation of maintenance therapy						
CD4 cell count, cells/μL	260 (100–1231)	236 (185–279)	274 (100–668)	239 (102–1231)	260 (100–668)	260 (100–1231)
Plasma HIV load, $\log_{10}$ copies/mL	2.30 (1.60–6.30)	2.30 (1.70–5.09)	2.30 (1.60–5.27)	1.90 (1.60–6.30)	2.30 (1.60–6.00)	2.30 (1.60–6.34)
At last visit						
CD4 cell count, cells/μL	372 (7–1510)	…[a]	400 (7–837)	321 (8–1510)	384 (7–837)	283 (24–1510)
Plasma HIV load, $\log_{10}$ copies/mL (range)	1.76 (1.30–5.67)	2.30 (1.70–2.30)	1.90 (1.30–5.67)	1.88 (1.60–5.49)	1.90 (1.60–5.67)	1.70 (1.30–5.49)

NOTE. Data are median (range).

[a] The individual values for the 4 patients who experienced a recurrent episode of cryptococcosis were 13, 465, 46, and 536 cells/μL.

imethamine. The patient died of respiratory failure 4 months after hospital admission. An autopsy was not performed.

Patient 4. A 31-year-old man discontinued maintenance therapy for CM 20 months after a CD4 cell count of >100 cells/μL was attained and 31 months after CM was diagnosed. The patient's CD4 cell count was 536 cells/μL (13.2% of the total lymphocyte count), his plasma virus load was <50 copies/mL, and the results of a serum cryptococcal antigen test were negative. One month later, he had fever, cough, and headache. The findings of a physical examination were normal. The serum cryptococcal antigen titer result became positive (titer, 1:256), but blood and CSF culture results were negative. CT of the body revealed mediastinal, periaortic, and abdominal lymph nodes. Histological examination of a lymph node specimen revealed the presence of *C. neoformans.* Culture was not performed. The patient was successfully treated with oral fluconazole.

Secondary End Points

Apart from those described above, no other deaths or AIDS-related events occurred during the observation period. Five patients (5%) had a confirmed CD4 cell count of <100 cells/μL; for 4 of these patients, the CD4 cell count was attributed to discontinuation of antiretroviral treatment. One of the patients developed CM, whereas maintenance therapy for CM was reinitiated for the remaining 4 patients.

DISCUSSION

This study demonstrates that persons with CM taking HAART have a lower risk of relapse when the CD4 cell count increases to >100 cells/μL, even in the absence of antifungal maintenance therapy. For comparison, in the pre-HAART era, without antifungal maintenance therapy, 50%–60% of the patients experienced a relapse of this opportunistic infection during 1 year of follow-up [20–21]. However, in the present study, only 4 events in 262 person-years occurred. This suggests that the observed CD4 cell recovery during HAART is associated with protection against recurrent cryptococcal meningitis and that it appears to be safe to withdraw maintenance therapy for cryptococcosis in HIV-infected individuals who have presumed immune reconstitution while receiving HAART.

Of note, 3 of 4 patients with recurrent cases had a negative serum cryptococcal antigen test result at the time of discontinuation of antifungal therapy. The cryptococcal antigen test is a sensitive and relatively specific indicator of CNS cryptococcosis. Active cryptococcal infection may be present in some patients with positive cryptococcal antigen test results but negative fungal culture results. Recent recommendations have been to presumptively treat any HIV-infected person who has a positive cryptococcal antigen test result and a negative culture result, regardless of the presence or absence of clinical symptoms [22]. There have been several studies noting the lack of clinical utility in serial monitoring of serum and/or CSF cryptococcal antigen, but none of the studies have ever addressed the scenario of an antigen test result becoming negative and later turning positive [23–26]. In the absence of such data, it would seem prudent to consider this to be either a recurrent disease or reinfection with *C. neoformans.* We are unaware of any other reports describing the reversion of a negative serum cryptococcal antigen test result to a positive result. This was the case for 2 of the patients who had recurrent episodes of cryptococcal infection. This is a completely new scenario—in fact, before the HAART era, it was common to say, "*semel Cryptococcus, semper Cryptococcus*" (i.e., "once you have had *Cryptococcus* infection, you will always have it"). After the advent of HAART, and on the basis of the results of the present study, one could conclude that *C. neoformans* infection may be completely eradicated or remain latent in most patients, but it may relapse or a patient may develop a new infection. Our study leads us to reinforce the indication for close monitoring of the CD4 cell count in patients who discontinue maintenance therapy. Indeed, patient 3 had a rapid and unpredictable decrease in the CD4 cell count, despite having an undetectable plasma virus load, which, in the absence of prophylactic regimens, allowed the onset of opportunistic infection.

After the advent of the HAART era, some observational and randomized trials [27, 28] reported the onset of opportunistic infections in patients with CD4 cell counts greater than what is considered at risk. This is also the case for 3 of the 4 patients we describe who had a relapse of CM.

When interpreting the results of this study, 2 main limitations should be considered. First, because of the retrospective, observational nature of the study, we cannot exclude the possibility that persons with more-stable disease were overrepresented. Because the present study, which had a large sample size, demonstrated that recurrent episodes of CM are possible, a large, randomized trial from countries where it is endemic is warranted. Nevertheless, a randomized trial conducted in Thailand with a small sample size reported the absence of any recurrent episodes in the discontinuation arm after 1 year of follow-up [18]. The second limit to our study is that it does not directly address the issue of when maintenance therapy for CM can safely be discontinued. The most recent guidelines suggest to wait until 3–6 months after the first CD4 cell count of >100 cells/μL is attained [29]. In the present study, one-half of the patients discontinued therapy soon after the CD4 cell count increased to >100 cells/μL, and none of these patients had a recurrent episode. On the contrary, all events occurred in patients who discontinued antifungal maintenance therapy after they had had a CD4 cell count of >100 cells/μL for $\geq$6 months. A possible explanation is that these patients may have

had specific immune defects against *C. neoformans* that are not routinely assessed in clinical laboratories [30]. Another possibility that we cannot exclude is reinfection.

In conclusion, the present study indicates that it may be considered safe to discontinue maintenance therapy for CM after HAART and a CD4 count >100 cells/μL. Nevertheless, patients should be carefully monitored for a sudden decrease in the CD4 cell count in order to reintroduce prophylactic regimens. Moreover, it may be of utility to measure a serum cryptococcal antigen value at the time that antifungal therapy is discontinued, and it may be prudent to empirically treat patients whose negative results revert to positive. Finally, patients should receive clear advice regarding this risk and should be monitored closely for the onset of any new symptoms, such as headache or fever.

THE INTERNATIONAL WORKING GROUP ON CRYPTOCOCCOSIS

Members. Anna Maria Cattelan (Clinic of Infectious Diseases, Padova, Italy); Roberto Manfredi and Francesco Chiodo (Clinic of Infectious Diseases, University of Bologna, Italy); Luca Guerra (Department of Infectious Diseases, Bologna, Italy); Libera Maria Vaira (Department of Infectious Diseases, Monza, Italy); Rinaldo Roda and Florio Ghinelli (Department of Infectious Diseases, Ferrara, Italy); Patrizia Orlandi and Massimo Arlotti (Department of Infectious Diseases, Rimini, Italy); Antonietta Cargnel, Gaia Jachetti, and Marco Fasan (Department of Infectious Diseases, Milan, Italy); Paola Mele, Bruna Pasticci, Franco Baldelli, and Giuliano Stagni (Clinic of Infectious Diseases, Perugia, Italy); Marco Moroni and Giuliano Rizzardini (Department of Infectious Diseases, Busto Arsizio, Italy); Maria Alessandra Ursitti and Giacomo Magnani (Department of Infectious Diseases, Reggio Emilia, Italy); Andrea De Luca, Adriana Ammassari, and Roberto Cauda (Clinic of Infectious Diseases, Catholic University, Rome); Alessandra Govoni and Andrea Antinori (National Institute for Infectious Diseases, "L. Spallanzani," Rome); Esteban Martínez, José M. Miró, Felipe García-Alcaide, Anna Milinkovic, José Bernardo Pérez-Cuevas, María Eugenia Valls, Miguel Angel García-Viejo, José Mallolas, and José M. Gatell (Idibaps-Hospital Clinic, University of Barcelona, Barcelona, Spain); Juan Carlos Lopez Bernaldo de Quiros, J. Cosin, P. Miralles, J. Berenguer, and B. Padilla (Infectious Diseases Unit, Hospital Gregorio Marañon, Madrid); Cristina Mussini, Vanni Borghi, Andrea Bedini, and Roberto Esposito (Clinic of Infectious and Tropical Diseases, Modena, Italy); Paola Cinque and Adriano Lazzarin (Università Vita e Salute, Milan, Italy); Pere Domingo (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain); Pedro Cahn and Omar Sued (Clinic of Infectious Diseases, Hospital J.A. Fernandez, Buenos Aires, Argentina); Philippe Bossi and Christine Katlama (Maladies Infectieuses et Tropicales, Groupe Hospitalier Pitié-Salpêtrière, Paris, France); Antonella d'Arminio Monforte, Spinello Antinori, and Mauro Moroni (Clinic of Infectious Diseases, University of Milan, Italy); Mark Nelson, Nneka Nwokolo, and Brian Gazzard (Chelsea and Westminster Hospital, London, United Kingdom); Martin Fisher (Department of Infectious Diseases, Brighton, United Kingdom); Silvia Helou and Ricardo Negroni (Infectious Disease Hospital "F. J Muñiz," Buenos Aires, Argentina); and Judith Aberg (Department of Internal Medicine, Division of Infectious Disease, Washington University, St. Louis, Missouri).

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