Prevalence, Associated Factors, and Prognostic Determinants of AIDS-Related Toxoplasmic Encephalitis in the Era of Advanced Highly Active Antiretroviral Therapy

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Background. Characteristics, associated factors, and survival probability of toxoplasmic encephalitis (TE) in the era of advanced highly active antiretroviral therapy (HAART) have not been fully clarified.

Methods. Data for 205 individuals with acquired immunodeficiency syndrome (AIDS)–related TE were derived from the Italian Registry Investigative NeuroAIDS database, and the cases were studied longitudinally to evaluate prevalence, clinical characteristics, and survival. Moreover, the relationship between the occurrence of TE and exposure to antiretroviral therapy and to TE prophylaxis was evaluated.

Results. With an overall prevalence of 26%, TE represented the most frequent neurological disorder in the cohort. Female sex, severe immunodeficiency, and absence of primary TE prophylaxis significantly increased the risk of TE, and previous exposure to antiretroviral therapy reduced the probability of disease occurrence. Thirty-six percent of patients who had received antiretroviral therapy developed TE, although in most of these cases, the patient experienced failure of antiretroviral therapy. Of note, 66% of patients who had experienced antiretroviral therapy did not receive prophylaxis for TE at TE diagnosis.

The 1-year probability of that infection with human immunodeficiency virus (HIV) would progress or that death would occur after TE was 40% and 23%, respectively. Cognitive symptoms, low $CD4^+$ cell count, not receiving HAART after TE, and initiating HAART >2 months after TE diagnosis were all significantly associated with an increased probability of progression of HIV infection. Not receiving HAART after diagnosis negatively affected survival.

Conclusions. TE remains a highly prevalent disorder of the central nervous system, even in the late HAART era, particularly among severely immunosuppressed patients and in absence of prophylaxis. Considering that persons with TE have a high probability of early death, prophylaxis should be maintained in immunosuppressed patients who experience failure of antiretroviral therapy, and HAART should be initiated as soon as possible after TE diagnosis.

Toxoplasmic encephalitis (TE) is a life-threatening infection of the CNS that is typically observed in the later stages of HIV infection [1]. In the early 1990s, TE was the most prevalent focal brain disorder among HIV-infected patients, with a mean annual incidence of ~0.4–0.7 events per 100 person-years [2, 3] and occurring more frequently in patients with low $CD4^+$ cell

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counts [3]. In the years 1992–1996, because of the widespread use of prophylactic regimens, a decrease in epidemiological trends of disease was observed [3–5].

The advent of HAART has resulted in a reduction in the incidence of most opportunistic infections [6–8] and also in the incidence of CNS disorders, as confirmed by a recent European cohort study [5, 9–11]. Concerning TE, a trend towards a decreased incidence rate in the first years in which HAART was widely available, compared with the pre-HAART years, was reported in 2 large cohort studies [5, 12]. Of note is that TE prevalence among AIDS-related focal brain disorders appeared to stabilize during the HAART era, after a decrease was observed during the pre-HAART period [9].

Before the availability of HAART, injection drug use, previous AIDS-defining events, decreased $CD4^+$ cell count, lack of antiretroviral therapy, and lack of prophylaxis against infection with *Toxoplasma* species were all reported as being significantly associated with an increased risk of developing TE [3, 12]. At the beginning of the HAART era, lack of exposure to HAART and prophylaxis, as well as persistent $CD4^+$ cell depletion, significantly increased the risk of disease [12].

The proportion of TE-associated deaths decreased from 3.5% of all HIV infection–related deaths in 1992 to 1.9% in 1998, with a percentage reduction greater than that observed in HIV–related deaths overall [13]. Although the improvement in survival of HIV-infected patients due to HAART has largely been documented [14–16], specific evaluations about survival and associated factors in HIV-infected patients with TE have not been carried out until now.

The aim of the present study was to assess prevalence, clinical characteristics, and survival probability of patients with newly diagnosed cases of TE in the advanced HAART era. Moreover, the relationship between occurrence of TE and previous exposure to antiretroviral therapy and prophylaxis against infection with *Toxoplasma* species was evaluated.

METHODS

Design of the study and diagnostic criteria. The Italian Registry Investigative NeuroAIDS (IRINA) study is a prospective multicenter study that involves 45 Italian infectious diseases centers that specialize in the treatment of HIV-infected patients. The main aim of the survey is to analyze epidemiological changes in and document the natural history of HIV-related neurological disorders in the era of HAART. The second aim of the IRINA study is to evaluate survival probability, baseline values, and longitudinal survival-associated factors in relationship to antiretroviral exposure before and after diagnosis of neurological disorders [17]. The study started in January 2000 and included all patients with HIV-related disorders of the CNS who were consecutively observed in the participating centers. For each case of neurological disease, the center is required to fill out a notification sheet with data that includes demographic and epidemiological variables, history of HIV infection and receipt of antiretroviral therapy, clinical and radiological characteristics, and diagnostic criteria. Every 6 months, a follow-up sheet is filled out with information regarding treatment outcome and survival.

Statistical analysis. The current study was based on all cases documented as part of the IRINA study from January 2000 through December 2002. To avoid selection bias, the analysis was restricted to persons experiencing a first episode of TE and to those with ≤ 1 concomitant CNS disorder. Diagnosis of TE was performed in agreement with the 1993 Centers for Disease Control and Prevention (CDC) classification, and both histological and presumptive diagnoses were accepted. Presumptive diagnosis was based on compatible clinical and/or neuroradiological signs, serological test results positive for *Toxoplasma* species, or response to specific therapy [18].

The association between the presence of TE and demographic, clinical, and radiological characteristics was explored by 2×2 contingency tables and was estimated calculating ORs with 95% CIs. Statistical significance was tested by Fisher's exact test or by univariate logistic regression analysis. A multivariable logistic regression model that included all significant covariates found by univariate analysis was used to calculate adjusted ORs and to detect factors predictive of TE.

To analyze the effect of exposure to antiretroviral therapy, patients were stratified in 2 groups according to exposure to antiretroviral treatment. The first group included patients who were antiretroviral therapy naive at TE diagnosis, and the second group included patients who were receiving HAART at TE diagnosis or had experienced antiretroviral therapy. Differences between the 2 groups were assessed using 1-way analysis of variance or Fisher's exact test and logistic regression, as appropriate, for continuous and categorical variables, respectively. Survival probabilities were estimated using the Kaplan-Meier method and log-rank test. A Cox proportional hazards model was employed to define crude and adjusted relative hazards associated with death and clinical progression of disease. The multivariable model was adjusted for baseline and time-dependent covariates that significantly influenced survival and clinical progression on univariate analysis. All P values $\leq .05$ were considered to be statistically significant. Statistical analysis was performed using the software package SPSS, version 11.0.1 (SPSS).

RESULTS

Prevalence and characteristics of TE. From January 2000 through December 2002, of the 805 persons with CNS disorders documented by the IRINA study, 211 (26.2%) had a first episode of TE. Of these, 205 patients without other concomitant CNS disorders were included in the analysis. A bioptic or au-

Table 1. Demographic, clinical, epidemiological, and radiological features of patients with and without toxoplasmic encephalitis (TE).

Variable	Patients with TE (n = 205)	Patients without TE (n = 568)	P
Male sex	135 (66.0)	438 (77.1)	.002
Age, mean years ± SD	39 ± 7.5	41 ± 9.5	<.001
Transmission group			
IDU	76 (37.1)	268 (47.2)	.012
MSM	24 (11.7)	61 (10.7)	
Heterosexual	83 (40.5)	263 (28.7)	
Other/unknown	22 (10.7)	76 (13.4)	
Previous AIDS-defining events	55 (26.8)	187 (32.9)	.114
$CD4^+$ cell count, mean cells/μL ± SD	69 ± 82	135 ± 170	<.001
Plasma HIV RNA load, mean $\log_{10}$ copies/mL ± SD	4.68 ± 1.13	4.40 ± 1.32	.005
Prophylaxis against TE	35 (17.1)	171 (30.6)	<.001
Cognitive symptoms	94 (45.9)	357 (62.9)	<.001
Focal signs	149 (72.7)	262 (46.1)	<.001
Abnormal mental status	69 (33.6)	156 (27.5)	.074
Cerebral atrophy	31 (15.1)	244 (43.0)	<.001
White matter involvement	60 (29.3)	316 (56.5)	<.001
Single lesion	61 (29.7)	71 (32.6)	.674
Contrast enhancement	194 (94.6)	115 (20.2)	<.001
Mass effect	159 (77.5)	67 (11.8)	<.001
History of antiretroviral therapy	76 (37.1)	293 (52.0)	<.001
Receipt of antiretroviral therapy at diagnosis	50 (24.4)	207 (36.4)	.002

NOTE. Data are no. (%) of patients, unless otherwise indicated. IDU, injection drug user; MSM, man who has sex with men

toptic diagnosis of TE was obtained in 4.4% of cases, and a presumptive diagnosis, made according to CDC criteria [18], was obtained in 95.6%. Neuroimaging diagnosis was made on the basis of CT and MRI findings in 66 (32.2%) of the patients, CT findings alone in 97 (47.3%), and MRI findings alone in 42 (20.5%). Of the 568 patients classified as not having TE, only 67 (11.8%) had a mass effect, and 56 of these patients received a diagnosis of an alternative CNS disorder that was confirmed by accepted criteria. In particular, the diagnoses were progressive multifocal leukoencephalopathy (5 cases), primary CNS lymphoma (26), cytomegalovirus encephalitis (1), cerebral criptococcosis (6), CNS tuberculosis (4), and systemic non-Hodgkin lymphoma with CNS involvement (5); 9 other disorders were diagnosed, including neurosyphilis (1 case), meningiomas (2), intracerebral hematoma (2), brain astrocitoma (2), and pyogenic abscess (2). In the remaining 11 patients, an encephalopathy of unknown origin, defined by the absence of diagnostic criteria for the other disorders and by a defined neuroradiological pattern, was described. Of these 11 patients, 5 had a $CD4^+$ cell count of $\geqslant$200 cells/μL and a neuroimaging pattern not suggestive of TE. Of the remaining 6 patients with $CD4^+$ cell counts of <200 cells/μL, only 2 had serological test results positive for *Toxoplasma* species; however, in both cases, TE has been reasonably excluded on the basis of clinical and radiological findings and follow-up. Comparisons between the demographic, clinical, virological, and neuroradiological characteristics of patients with TE and patients without TE are reported in table 1.

Baseline demographic, epidemiological, virological, clinical, and radiological features for all patients, stratified according to previous exposure to antiretroviral therapy, are reported in table 2. Previous exposure to antiretroviral therapy was found in 76 (36%) of the patients. Among patients who had experienced antiretroviral therapy, 10 (13%) had received nucleoside reverse-transcriptase inhibitor monotherapy or double therapy, with a median duration of exposure of 9 months (interquartile range (IQR), 2–24 months), and 66 (87%) had received HAART, with a median duration of exposure of 24 months ([IQR], 6–45 months). At neurological diagnosis, 44 (66%) of the patients were receiving HAART, and 22 (34%) had discontinued antiretroviral therapy. Virological parameters strongly differed between the antiretroviral therapy–experienced and the antiretroviral therapy–naive groups (table 2). Among patients in the experienced group, an undetectable virus load in plasma and a $CD4^+$ cell count >200 cells/μL at TE diagnosis were found in 11% and 12% of patients, respectively. Patients in the ex-

Table 2. Demographical, epidemiological, and clinical characteristics of 205 patients at diagnosis of toxoplasmic encephalitis (TE), by history of antiretroviral (ART) exposure.

Variable	All patients (n = 205)	ART-naive patients (n = 129)	ART-experienced patients (n = 76)
Male sex	135 (66.0)	84 (65.1)	51 (67.1)
Age, median years (IQR)	38 (34–43)	38 (33–43)	38 (35–42)
HIV transmission route			
IDU	76 (37.1)	40 (31.0)[a]	36 (47.4)[a]
MSM	24 (11.7)	15 (11.6)	9 (11.8)
Heterosexual	83 (40.5)	58 (45.0)	25 (32.9)
Other/unknown	22 (10.7)	16 (12.4)	6 (7.9)
Previous AIDS defining events	55 (26.8)	12 (9.4)[b]	43 (56.6)[b]
$CD4^+$ cell count, median cells/μL (IQR)	34 (15–101)	32 (15–73)[a]	45 (16–124)[a]
Plasma HIV RNA load, median $\log_{10}$ copies/mL (IQR)	5.0 (4.4–5.4)	5.1 (4.7–5.5)[b]	4.5 (2.7–5.2)[b]
TE prophylaxis	35 (17.1)	10 (7.8)[b]	25 (32.8)[b]
Clinical characteristics			
Cognitive symptoms	94 (45.9)	59 (45.7)	35 (46.1)
Focal signs	149 (72.7)	97 (75.8)	52 (68.4)
Meningeal symptoms	16 (7.8)	11 (8.6)	5 (6.6)
Abnormal mental status	69 (33.6)	48 (37.5)	21 (27.6)
Neuroradiological characteristics			
Cerebral atrophy	31 (15.1)	17 (13.9)	14 (18.4)
White matter involvement	60 (29.3)	42 (32.8)	18 (23.7)
Single lesion	61 (29.7)	35 (27.3)	26 (34.2)
Multiple lesions	141 (68.7)	91 (71.9)	50 (65.8)
Contrast enhancement	194 (94.6)	119 (93.0)	75(98.7)
Mass effect	159 (77.5)	101 (79.0)	58 (76.3)

NOTE. Data are no. (%) of patients, unless otherwise indicated. IDU, injection drug user; IQR, interquartile range; MSM, man who has sex with men.

[a] $P < .05$

[b] $P < .01$, by Fisher's exact test and 1-way analysis of variance for categorical and continuous variables, as appropriate.

perienced group identified injection drug use as the HIV transmission route more frequently (OR, 2.00; 95% CI, 1.11–3.59), were more likely to have experienced a previous AIDS-defining event (OR, 12.70; 95% CI, 6.01–26.82), and were more likely to have been exposed to prophylaxis against TE (OR, 6.07; 95% CI, 2.71–13.58). Prevalence of TE, stratified according to exposure to antiretroviral therapy, as well by $CD4^+$ cell count and virus levels in plasma, is shown in figure 1.

Factors associated with TE. The relationship between the risk of developing TE and different baseline factors is shown in table 3. Male sex, previous exposure to antiretroviral therapy, and higher $CD4^+$ cell count at neurological diagnosis significantly decreased the probability of TE according to multivariate logistic regression analysis. The presence of lesions with contrast enhancement or with mass effect was associated with a significantly higher risk of TE diagnosis, and detection of white matter abnormalities was related to a decreased risk of disease. Age, HIV transmission route, previous diagnosis of AIDS, plasma HIV RNA load, and neurological features did not affect the risk of TE occurrence.

TE prophylaxis was received by 35 (17%) of 205 patients. Of note, as many as 31 (66%) of 47 patients who had experienced antiretroviral therapy and who had $CD4^+$ cell counts of <100 cells/μL were not receiving prophylaxis at the time of TE diagnosis, even though 54% of them were currently prescribed HAART. As shown in table 3, receipt of TE prophylaxis independently reduced the risk of developing TE in the multivariate model.

TE follow-up. During the first 6 months after TE diagnosis, the median duration of exposure to HAART was 150 days (IQR, 79–180 days). At 6 months, improvement and/or resolution of disease was observed in 76% of patients during clinical examination and in 73.2% of patients according to CT and MRI findings. The 6-month mean ($\pm$SD) change in HIV RNA load was -2.1 ± 1.7 $\log_{10}$ copies/mL, and the mean ($\pm$SD) increase in $CD4^+$ cell count was 141.9 ± 118.2 cells/μL (table 4).

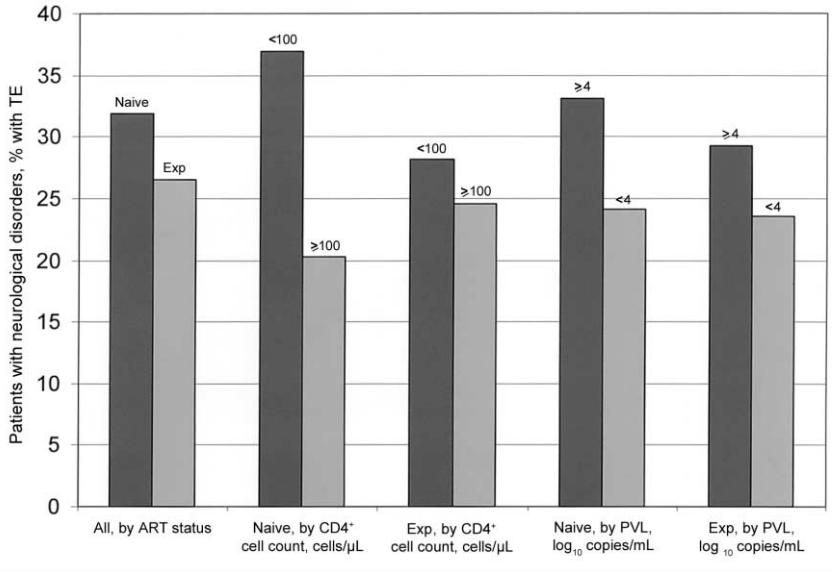

Figure 1. Prevalence of toxoplasmic encephalitis (TE) among patients with neurological disorders, by history of exposure to antiretroviral therapy (ART), $CD4^+$ cell count, and plasma HIV RNA load (PVL) at onset of neurological disorder. Exp, patients with history of exposure to ART; naive, patients with no history of exposure to ART.

On multivariable logistic regression analysis, the probability of achieving 6-month clinical improvement and/or resolution of disease was significantly lower in the antiretroviral therapy–experienced patients than in the antiretroviral therapy–naive patients (OR, 0.25; 95% CI, 0.16–0.39), even after adjusting for $CD4^+$ cell count, HIV RNA load, abnormal mental status, number of brain lesions, prophylaxis against *Toxoplasma* species, and duration of exposure to HAART after TE diagnosis.

Survival analysis. After a median follow-up period of 365 days (IQR, 180–545 days), a total of 34 patients (16.1%) died, and 25 (73.5%) of these patients died during the first 6 months of follow-up. In 22 cases, death was related to TE. During

Table 3. Baseline factors associated with the risk of developing toxoplasmic encephalitis (TE) by univariate or multivariate logistic regression analysis in 805 patients with neurological disorders.

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age ⩾35 years	0.56 (0.38–0.81)	.003	0.97 (0.51–1.87)	.93
Sex, male vs. female	0.57 (0.40–0.81)	.002	0.47 (0.25–0.88)	.02
Transmission route, sexual transmission vs. IDU/unknown	1.68 (1.22–2.31)	.002	1.23 (0.72–2.11)	.45
ART status at TE diagnosis, experienced vs. naive	0.55 (0.39–0.76)	<.001	0.49 (0.26–0.91)	.02
History of TE prophylaxis	0.47 (0.31–0.71)	<.001	0.47 (0.24–0.90)	.02
Cognitive symptoms	0.50 (0.36–0.69)	<.001	0.72 (0.40–1.29)	.28
Focal signs	3.19 (2.24–4.52)	<.001	1.08 (0.61–1.92)	.79
Meningeal symptoms	0.37 (0.22–0.65)	<.001	0.46 (0.20–1.05)	.06
Cerebral atrophy	0.23 (0.15–0.35)	<.001	0.78 (0.29–1.54)	.47
Contrast enhancement	85.79 (42.65–172.54)	<.001	30.45 (13.29–69.72)	<.001
Mass effect	26.59 (17.51–40.37)	<.001	5.17 (2.88–9.08)	<.001
White matter involvement	0.33 (0.23–0.46)	<.001	0.57 (0.33–0.98)	.04
$CD4^+$ cell count, cells/μL at TE diagnosis[a]	0.79 (0.72–0.87)	<.001	0.85 (0.75–0.97)	.01
Plasma HIV RNA load, $\log_{10}$ copies/mL at TE diagnosis[b]	1.20 (1.05–1.38)	.009	1.03 (0.81–1.30)	.83

NOTE. IDU, injection drug use.

[a] For each increase in the $CD4^+$ cell count of 50 cells/μL.

[b] For each increase in the plasma HIV RNA load of 1.0 $\log_{10}$ copies/mL.

Table 4. Changes in CD4⁺ cell count and HIV RNA load and the clinical outcomes for 205 patients with toxoplasma encephalitis (TE), by antiretroviral therapy (ART) status.

Variable	All patients (n = 205)	ART–naive patients (n = 129)	ART–experienced patients (n = 76)	P[a]
Increase in CD4⁺ cell count, mean cells/μL ± SD	141.9 ± 118.2	158.2 ± 122.6	116.1 ± 107.1	.06
Change in plasma HIV RNA load, mean $\log_{10}$ copies/mL ± SD	−2.1 ± 1.7	−2.81 ± 1.37	−0.97 ± 1.70	<.001
Clinical improvement and/or resolution of TE at 6 months after diagnosis, % of patients	76.0	87.5	58.1	<.001

[a] P values compare the ART-naive group with the ART-experienced group by 1-way analysis of variance for mean changes in CD4⁺ cell count and HIV RNA load and by Fisher's exact test for frequency of 6-month clinical improvement and/or resolution of TE.

follow-up, there were 24 patients who experienced new AIDS-defining events. The 1-year probability of clinical progression of disease (i.e., the probability of experiencing a new AIDS-related event or death) was 40%. According to the multivariate Cox model, only the presence of cognitive symptoms was independently associated with an increased risk of HIV-related disease progression, whereas a CD4⁺ cell count ⩾100 cells/μL and receipt of HAART after TE diagnosis (a time-dependent covariate) were both associated with a reduced risk (table 5). According to multivariate Cox regression, patients who initiated HAART within 2 months after TE diagnosis had a significantly decreased probability of HIV-associated disease progression, compared with those who delayed therapy (relative hazard, 0.36; 95% CI, 0.15–0.86).

The 1-year estimated survival probability after TE diagnosis was 77%. Analyzing the risk of death with use of the multivariable Cox model, the presence of abnormal mental status was the only variable that was independently associated with an increase in the risk of death, and receipt of HAART after diagnosis was the only factor that was independently associated with a decrease in the risk of death (table 5). Kaplan-Meier curves displaying the probability of progression to AIDS or death and to death alone according to prognostic variables are shown in figure 2.

DISCUSSION

The results of our study indicate that, even in the late HAART era, TE is still the most prevalent CNS disorder, accounting for approximately one-fourth of all documented cases in both antiretroviral-treated and untreated HIV-infected persons. This is in accordance with the finding that the prevalence of this disorder among patients with focal brain lesions has remained unchanged since the first years of the HAART era [9], even though a reduction of incidence has been reported [5, 12]. This apparent discordance between prevalence data and incidence

Table 5. Crude and adjusted relative hazards (RHs) for clinical progression of disease and for death alone for 205 patients with toxoplasma encephalitis (TE), by univariate or multivariate Cox regression analysis.

	Univariate analysis		Multivariate analysis	
Variable	RH (95% CI)	P	RH (95% CI)	P
Predictors of HIV progression				
Cognitive symptoms	1.92 (1.12–3.25)	.02	1.78 (1.00–3.14)	.05
Abnormal mental status	2.08 (1.21–3.57)	.008	1.55 (0.88–2.75)	.13
CD4⁺ cell count ⩾100 cells/μL	0.33 (0.13–0.82)	.02	0.40 (0.15–1.02)	.05
Multifocal lesions vs. single lesion	1.94 (1.00–3.77)	.05	1.33 (0.67–2.64)	.42
Receipt of HAART after diagnosis	0.22 (0.11–0.47)	<.001	0.28 (0.13–0.61)	.001
Predictors of death				
Cognitive symptoms	2.18 (1.09–4.36)	.03	1.62 (0.76–3.43)	.21
Abnormal mental status	2.65 (1.35–5.20)	.005	2.26 (1.10–4.64)	.03
Plasma HIV RNA load ⩾4 $\log_{10}$ copies/mL[a]	1.62 (1.00–2.62)	.05	1.38 (0.84–2.28)	.20
Receipt of HAART after TE diagnosis	0.19 (0.08–0.45)	<.001	0.21 (0.08–0.54)	.001

NOTE. Clinical progression was defined as occurence of a new AIDS-defining event or death. Only variables that were significantly associated with TE diagnosis on univariate Cox regression analysis were included in the multivariate model.

[a] For each increase in the plasma HIV RNA load of 1.0 $\log_{10}$ copies/mL.

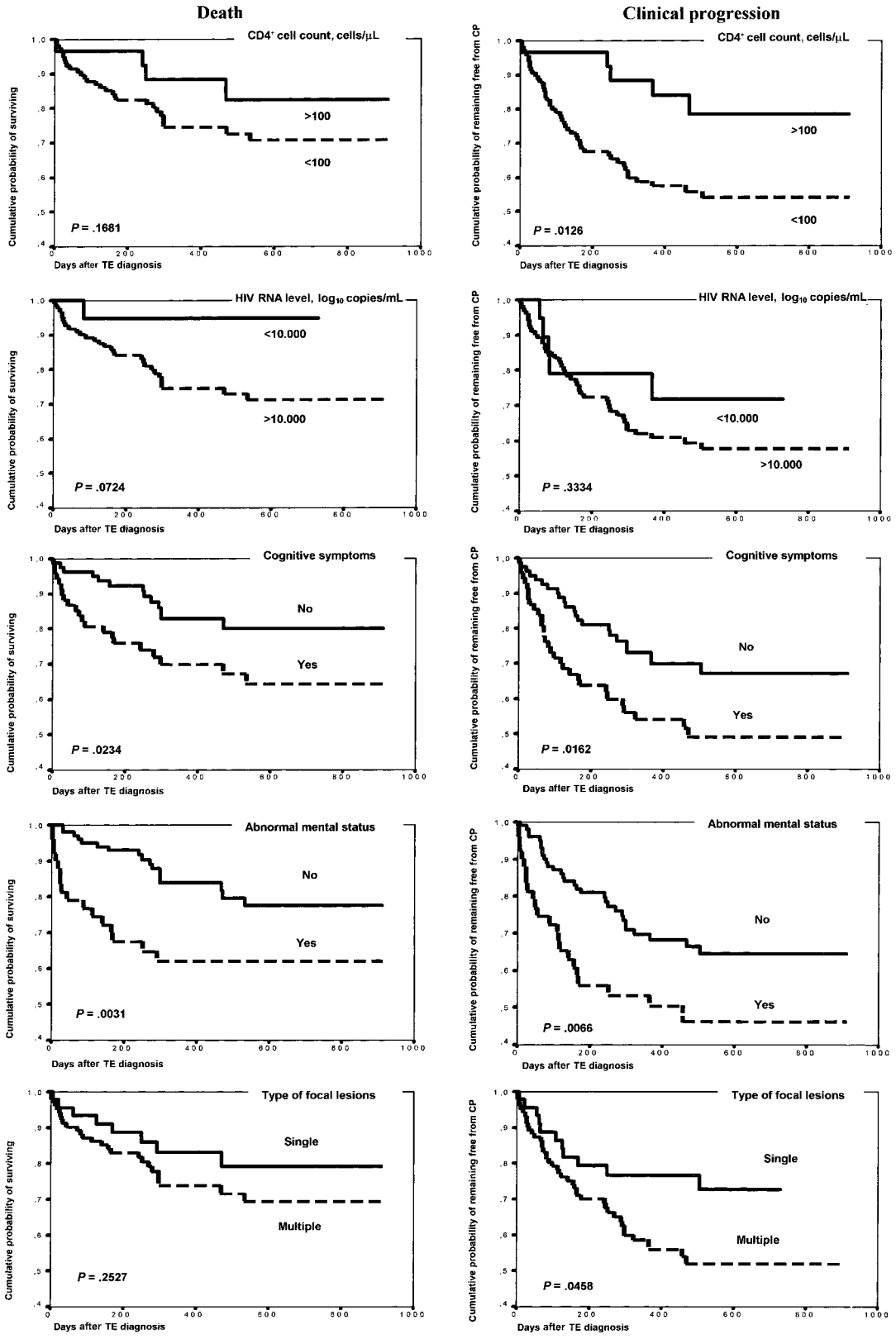

Figure 2. Kaplan-Meier estimated cumulative probability of surviving (left column) and of remaining free from clinical progression (CP) *(right column)* in patients with toxoplasmic encephalitis (TE) by the main baseline prognostic factors ($CD4^+$ cell count, plasma HIV RNA load, presence of cognitive symptoms, abnormal mental status, and single or multiple focal brain lesions). CP was defined as any new AIDS-defining event or death. Significance was tested with the log-rank test.

data may be accounted for by a smaller decrease in the incidence of TE, compared with other neurological disorders [5]. Considering that 36% of TE episodes occurred in persons with previous exposure to antiretrovirals, patients who had experienced antiretroviral therapy had a 50% reduction in risk of developing TE. This effect was independent of HIV RNA load and $CD4^+$ cell count, confirming that the protective effect of HAART against clinical progression is not simply related to virological success [19]. Nevertheless, plasma virus levels were comparably high and $CD4^+$ cell count was consistently low both in antiretroviral-naive and in antiretroviral-experienced patients, suggesting that the failure of treatment with antiretrovirals is the main determinant when TE occurs in patients receiving HAART. The fact that only 25% of patients developed TE during the first 6 months of HAART (data not shown) seems to suggest that the early risk due to incomplete recovery of the immune system [20, 21] might not have represented a relevant issue in our cohort.

A recent large prospective cohort study [12] showed that lack of exposure to antiretroviral therapy and immunosuppression markers were strong predictors of TE occurrence. In the present study, we found that, for each 50-cell decrease in $CD4^+$ cell count, there was a 30% increase in the risk of TE occurrence, independent of antiretroviral exposure. It has been suggested that a reduced risk of TE in the presence of HAART-induced recovery of the immune system is associated with a restoration of specific immune responses against *Toxoplasma gondii* [22]. This observation has relevant implications for therapeutic strategies, in particular for patients who remain strongly immunodeficient despite HAART and are therefore still susceptible to opportunistic infections [12, 23].

The efficacy of primary prophylaxis in preventing TE is well known [24–26]. In a comparative study by calendar years [12], primary prophylaxis reduced the risk of TE by 46% in the early HAART era. The present study confirmed the efficacy of primary prophylaxis in prevention of TE, with a 53% reduction of the risk of TE occurrence. These results emphasize that, even in the era of HAART, TE prophylaxis will remain a main factor in reducing disease occurrence [8, 27]. Prophylaxis should be discontinued in HAART-treated patients only when a sustained rise in $CD4^+$ cell count is detected [8, 28–32]; we observed that only 34% of antiretroviral-experienced patients with a $CD4^+$ cell count <100 cells/μL were receiving TE prophylaxis at diagnosis. On the basis of these data, survey studies about physician adherence to guidelines for the prevention of opportunistic infections in the HAART era may be advisable.

We could not entirely account for the increased risk of TE observed in women independent from HAART exposure, virological markers, and TE prophylaxis. Female sex has been associated with lower HIV loads in plasma, but significant sex-based differences in rates of disease progression have been excluded [33, 34]. Furthermore, a higher rate of discontinuation of therapy because of toxicity or likely poor adherence was observed in HIV-infected women starting antiretroviral therapy [35], even though sex was not generally associated with adherence to HAART in most studies [36]. Female sex as a factor increasing the risk of TE should be elucidated further.

Survival analysis showed that TE occurrence still represents a poor prognostic determinant in the natural history of HIV-infected persons, even in the era of HAART. In our cohort, the estimated 1-year probabilities of showing HIV disease progression or death were 40% and 23%, respectively. This finding is consistent with that observed among patients with AIDS and multiple adverse prognostic factors in a large cohort of antiretroviral-naive patients starting HAART [37]. It is reasonable to assume that, even though HAART remains the main prognostic determinant in patients with advanced disease and severe immunodeficiency [15, 38], TE-specific mortality had a relevant role in negatively affecting survival, accounting for more than two-thirds of all deaths. However, in our study, starting HAART after TE diagnosis was associated with a strong reduction of the risk of clinical progression of disease and death, and this is consistent with the dramatic improvement in survival rates observed in patients with advanced disease when adjusted for HAART adherence and appropriate care [39]. Considering the calendar years of the present study, it is conceivable that our cohort could have benefited from the improvements in antiretroviral regimens and HAART management that have been observed in recent years for HIV-infected persons with very advanced disease [40].

We further observed a significant benefit of early initiation of HAART after TE diagnosis. In fact, a 3-fold reduction in the risk of developing a new AIDS-defining event or death in patients who started HAART within the first 2 months after diagnosis of a neurological disorder has been found. An unresolved question, raised in the past several years, concerned the appropriate timing for initiation of HAART in patients with opportunistic diseases. Even though a potential benefit in treating certain AIDS-related conditions has been shown [41, 42], relevant concerns relative to the toxicity of multiple-drug regimens and poor adherence have supported delaying the initiation of HAART until after the acute phase of most opportunistic diseases. Even though we are not able to determine the optimum timing for starting HAART after TE diagnosis, it seems that early initiation of HAART leads to a survival benefit.

Some limitations of this study need to be mentioned. First, classification bias could not be entirely excluded because TE diagnoses were formulated by the treating physician at the participating center. However, diagnostic criteria were standardized in the study design, according to updated literature, and the methods that were employed were specified in each notification sheet. The Coordinating Center revised all notified sheets and

certified the appropriate definition criteria employed, and all discordant cases were excluded. A second limitation of the study was that information about serological testing for *Toxoplasma* species was only included among the diagnostic criteria of TE and was not specifically required on the notification sheet for other diagnoses. The lack of this finding may have affected a complete evaluation of prophylaxis data. Nevertheless, previous data showed that only 3%–6% of patients with TE had negative results of serological tests [43], and this could have minimized possible bias in the analysis. Furthermore, previous data suggest that, in the Italian population, the rate of primary infection with *Toxoplasma* species did not increase as a result of an increase in the rate of AIDS [44], as confirmed by the very low prevalence of detection of IgM-specific antibody response in HIV-infected people. On the basis of these considerations, we think that a lack of serological testing for infection with *Toxoplasma* species would not have significantly influenced the accuracy of the epidemiological data in our study.

Finally, we cannot estimate the exact prognostic impact of TE on survival because of a lack of control subjects with advanced HIV infection who did not have neurological disease. However, prevalent data allow more-accurate comparative analyses within a group of subjects who are homogeneous for clinical selection criteria, and this method is more appropriate for acquiring clinical information.

In conclusion, TE remains the most prevalent cause of HIV-associated neurological disorders, even in the late HAART era, with an increased risk of disease observed in antiretroviral-naive patients. Severe immunodeficiency and a lack of TE prophylaxis were confirmed as main determinants of TE occurrence, independent of whether HAART was received. Moreover, even if receipt of HAART after diagnosis with a neurological disorder markedly reduced the risk of clinical progression and death—particularly if started early in the course of neurological disease—TE survival remained poor, mainly for early specific mortality. Because TE was associated with a high probability of early death, all strategies to avoid TE occurrence, such as not delaying HAART until there is a high risk of clinical progression and maintaining prophylaxis in immunosuppressed patients for whom HAART has failed, should be considered [45–47].

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