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## Tuberculous meningitis in HIV-infected patients in Brazil: clinical and laboratory characteristics and factors associated with mortality

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### SUMMARY

**Background:** Tuberculous meningitis (TBM) is a growing problem in HIV-infected patients in developing countries, where there is scarce data about this co-infection. Our objectives were to analyze the main features and outcomes of HIV-infected patients with TBM.

**Methods:** This was a retrospective study of HIV-infected Brazilian patients admitted consecutively for TBM. All patients had *Mycobacterium tuberculosis* isolated from the cerebrospinal fluid (CSF). Presenting clinical and laboratory features were studied. Multivariate analysis was used to identify variables associated with death during hospitalization and at 9 months after diagnosis. Survival was estimated using the Kaplan–Meier method.

**Results:** We included 108 cases (median age 36 years, 72% male). Only 15% had fever, headache, and meningeal signs simultaneously. Forty-eight percent had extrameningeal tuberculosis. The median CD4+ cell count was 65 cells/ $\mu$ l. Among 90 cases, 7% had primary resistance to isoniazid and 9% presented multidrug-resistant strains. The overall mortality during hospitalization was 29% and at 9 months was 41%. Tachycardia and prior highly active antiretroviral therapy (HAART) were associated with 9-month mortality. The 9-month survival rate was 22% (95% confidence interval 12–43%).

**Conclusions:** Clinical and laboratory manifestations were unspecific. Disseminated tuberculosis and severe immunosuppression were common. Mortality was high and the 9-month survival rate was low. Tachycardia and prior HAART were associated with death within 9 months of diagnosis.

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## 1. Introduction

Tuberculous meningitis (TBM) is the most severe clinical presentation of tuberculosis and causes high mortality and morbidity, particularly in HIV-infected patients.<sup>1,2</sup> Despite recent medical advances, the early diagnosis of TBM continues to be difficult, and, in daily practice, clinical and cerebrospinal fluid (CSF) abnormalities usually determine the initiation of empirical treatment.<sup>3</sup> Data of large series from developing countries regarding confirmed TBM are scarce. This study was performed in order to describe the clinical presentation and CSF findings, as well as to identify the factors associated with mortality, in HIV-

infected patients with culture-proven TBM from a referral center in Sao Paulo, Brazil.

## 2. Materials and methods

We retrospectively analyzed data from the clinical records of all HIV-infected patients with a diagnosis of TBM admitted between March 1999 and December 2007 to the Emílio Ribas Institute of Infectious Diseases, Sao Paulo, Brazil. Our hospital is a 250-bed tertiary teaching center that serves a population of low socio-economic level from Sao Paulo State. All clinical records were reviewed for the period from TBM diagnosis to 9 months after diagnosis. HIV infection was diagnosed by enzyme-linked immunosorbent assay (ELISA) and confirmed by western blotting. The diagnosis of TBM was based on the presence of at least one culture showing growth of *Mycobacterium tuberculosis*

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in the CSF. We evaluated demographic (age, gender), clinical (signs and symptoms), and laboratory (CSF results, hemoglobin, cultures and susceptibility profile to *M. tuberculosis*) information using a standardized questionnaire. The neurologic status of patients was classified according to the British Medical Research Council (BMRC) staging system, which grades TBM as follows: grade I, patient with non-specific symptoms and signs, no clouding of consciousness, and no neurologic deficits; grade II, patient with lethargy or behavioral changes, meningeal irritation, or minor neurologic deficits such as cranial nerve palsies; and grade III, patient with stupor or coma, abnormal movements, seizures or severe neurologic deficits such as paresis.<sup>4</sup> CSF with the presence of pleocytosis (>5 cells/ $\mu$ l), high protein levels (>45 mg/dl), and low glucose levels (<45 mg/dl) was considered 'typical' of TBM. We defined primary drug resistance as resistance found in patients previously untreated with anti-tuberculosis drugs. Multidrug-resistant (MDR) tuberculosis was defined as a strain of *M. tuberculosis* with documented resistance in vitro to at least isoniazid and rifampin. Drug susceptibility testing data were retrieved from the registries of the Mycobacteriology Laboratory, Adolfo Lutz Institute, a reference laboratory in Sao Paulo, Brazil. Information on mortality was obtained from the clinical records.

At our institution, the treatment of tuberculosis in HIV-infected patients follows the guidelines of the Ministry of Health of Brazil.<sup>5</sup> Therefore, the initial TBM treatment is 2 months of daily oral isoniazid (10 mg/kg), rifampin (10 mg/kg) and pyrazinamide (35 mg/kg), followed by 7 months of oral isoniazid and rifampin at the same dosages. Corticosteroids were used for 1–2 months (prednisone 1 mg/kg/day).

Continuous variables were described with medians and ranges; categorical variables were described with numbers and percentages. Variables with < 20% missing values were imputed using simple imputation (EM method from SPSS; SPSS Inc., Chicago, IL, USA). Variables were compared with the Wilcoxon rank sum test or Fisher's exact test, as appropriate. The primary outcome was death during hospitalization. The secondary outcome was death within 9 months of presentation. We evaluated patient characteristics associated with the primary and secondary outcomes. The Cox proportional hazards model was used as the primary model. Variables associated with the outcome with a *p*-value of  $\leq 0.5$  in the univariate analysis were included in the multivariate analysis. Variables associated with the outcome with a *p*-value of  $\leq 0.05$  in the multivariate analysis remained in the model. Survival distribution was estimated using the Kaplan–Meier method. The comparison of survival between the different subject groups was performed by log-rank test. Overall, a *p*-value of  $\leq 0.05$  denoted a statistical association. SPSS 11.0 was used for all calculations. The study was approved by the ethical and scientific boards of the Emílio Ribas Institute of Infectious Diseases.

### 3. Results

#### 3.1. Clinical and laboratory characteristics

Of the 108 cases included in the study, 78 (72%) were male and the median age was 36 years. Sixty-three (58%) patients presented a history of prior tuberculosis, six of them with neurological involvement. Sixty-three (61%) of 103 patients with available information had previously used at least one antiretroviral combination, and 36 (51%) of 71 patients with available information were using antiretrovirals at the time of admission. In hospital, 52 (48%) patients were diagnosed with concomitant extrameningeal tuberculosis: 35 cases with pulmonary involvement, 11 with

lymphatic involvement, and six cases with blood involvement (defined by growth of *M. tuberculosis* in cultures of blood samples). The main clinical and laboratory features of the patients are showed in Table 1.

The classic triad of fever, headache, and meningeal signs was described in only 16 (15%) patients. Fever and headache were simultaneously present in 65 (60%) cases. The CSF cell count (total leukocyte count,  $\times 10^6/l$ ) was categorized as follows:  $\leq 5$  (normal) = 20 (19%) patients; 6–100 = 28 (26%) patients; 101–500 = 45 (42%) patients; >500 = 15 (14%) patients. The CSF patterns identified are shown in Table 2. The 'typical' CSF alterations of TBM were observed in 69 patients (64%). In addition, only 13% showed none or only one altered CSF parameter. In Tables 1 and 2, the number of patients with information available is specified where information was missing for at least one patient. There was missing information for the following variables: extrameningeal tuberculosis for one patient (1%), computed tomography (CT) abnormalities for eight (7%), prior highly active antiretroviral therapy (HAART) for five (5%), HAART at admission for 37 (34%), CD4 at baseline for 10 (9%), CSF:serum glucose ratio for 16 (15%), in-hospital death for one (1%), follow-up of in-hospital death for four (4%), and follow-up within 9 months for three (3%). All analyses were done with those patients with complete information.

Drug susceptibility testing was done only for isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. The test results for isoniazid, rifampin, and pyrazinamide were available in 90 cases and for ethambutol and streptomycin in 77. Fifty-four (60%) patients were not resistant to any drug. Twenty-one (23%) patients had resistance to isoniazid, 10 (11%) to rifampin, and five (6%) to streptomycin. No resistance to pyrazinamide and ethambutol was found. Seven (8%) patients presented primary resistance to isoniazid. Of the eight (9%) patients with MDR tuberculosis, six had a history of prior tuberculosis and two presented this resistance pattern at the first clinical manifestation of tuberculosis. No patient had extensively drug-resistant tuberculosis (XDR-TB).

**Table 1**

Clinical and laboratory characteristics of 108 HIV-infected patients with confirmed tuberculous meningitis

Variable	Patients (N = 108)
Age, median (range) years	36 (6–53)
Male, n (%)	78 (72)
Symptoms at presentation, n (%)	
Headache	82 (76)
Nausea	41 (38)
Altered mentation	38 (35)
Focal deficit	17 (16)
Seizures	12 (11)
Signs at presentation, n (%)	
Fever	84 (78)
Meningeal signs	20 (19)
Hepatomegaly	25 (23)
Splénomegaly	16 (15)
Adenopathy	10 (9)
BMRC severity grade, n (%)	
I	40 (37)
II	43 (40)
III	25 (23)
Extrameningeal tuberculosis, n (%) (N = 107)	52 (48)
Prior TB, n (%)	63 (58)
CT abnormalities, n (%) (N = 100)	55 (55)
Prior HAART, n (%) (N = 103)	63 (61)
HAART at admission, n (%) (N = 71)	36 (51)
Hemoglobin level, median (range) mg/dl	11 (6–16.9)
CD4+ cell count, median (range) cells/ $\mu$ l (N = 98)	65 (2–624)

BMRC, British Medical Research Council staging system; TB, tuberculosis; CT, computed tomography scan; HAART, highly active antiretroviral therapy.

**Table 2**

Cerebrospinal fluid findings of 108 HIV-infected patients with confirmed tuberculous meningitis

	Patients (N = 108)
CSF findings, median (range)	
Total leukocyte count, $\times 10^6/l$	160 (1–2880)
Neutrophils	44 (0–100)
Lymphocytes	49 (0–100)
Monocytes	7 (1–43)
CSF glucose (mg/dl)	29 (7–117)
CSF:blood glucose ratio (N=92)	0.27 (0.06–1.01)
Protein (mg/dl)	171 (19–1249)
CSF patterns, n (%)	
3 altered parameters	69 (64)
2 altered parameters	25 (23)
Glucose and protein	7
Total leukocyte count and protein	15
Total leukocyte count and glucose	3
1 altered parameter	10 (9)
Total leukocyte count	2
Glucose	2
Protein	6
None	4 (4)

We compared the clinical and laboratory characteristics among patients with and without HAART use on admission. Nausea (11 (33%) vs. 20 (57%) cases,  $p = 0.03$ ), focal deficit (nine (25%) vs. two (6%) cases,  $p = 0.03$ ), and prior HAART use (23 (64%) vs. 25 (71%) cases,  $p = 0.004$ ) were more frequent in the group with HAART use on admission. In addition, the median (range) CD4 cell count was similar among patients with and without HAART use on admission (76 (11–624) vs. 70 (2–237) cells/ $\mu l$ ,  $p = 0.4$ ).

#### 4. Characteristics associated with mortality

Also, the text states earlier that “There was missing information for the following variables: in-hospital death for one (1%), follow-up of in-hospital death for four (4%), and follow-up within 9 months for three (3%).” This would then give 44/105=42% (remove 3 missing 9-month follow-up) or 44/101=44% (remove 3 missing 9-month follow-up and 4 missing in-hospital follow-up).

Is 41% correct? 44/108 gives 41%, however removing 7 cases lost to follow-up gives 44/101=44%.

The overall mortality during hospitalization was 29% (31 patients) and the overall 9-month mortality was 41% (44 patients), excluding the seven cases that were lost to follow-up. Among MDR cases, the mortality during hospitalization was 38% (three patients) and the overall 9-month mortality was 71% (five patients), excluding one patient who was lost to follow-up. Headache (hazard ratio (HR) 0.4, 95% confidence interval (CI) 0.2–0.8,  $p = 0.01$ ), nausea/vomiting (HR 0.3, 95% CI 0.1–0.8,  $p = 0.01$ ), and hemoglobin  $< 8$  mg/dl (HR 3.2, 95% CI 1.2–8.4,  $p = 0.02$ ) were associated with death during hospitalization in the univariate analysis. Isoniazid resistance (HR 1.0, 95% CI 0.4–2.5,  $p = 0.9$ ) and MDR tuberculosis (HR 0.9, 95% CI 0.3–3.0,  $p = 0.8$ ) were not associated with death during hospitalization in the univariate analysis. None of the variables remained associated when included in the multivariate model (Table 3). However, CSF glucose  $< 45$  mg/dl (HR 3.2, 95% CI 0.9–10.8,  $p = 0.06$ ) presented a borderline association.

Headache (HR 0.5, 95% CI 0.2–0.9,  $p = 0.01$ ), tachycardia (HR 6.2, 95% CI 2.1–18.1,  $p < 0.01$ ), and CD4+ cell count  $< 100$  cells/ $\mu l$  (HR 2.5, 95% CI 1.1–5.7,  $p = 0.03$ ) were associated with death within 9 months after TBM diagnosis in the univariate analysis. Prior HAART (HR 2.1, 95% CI 1.0–4.1,  $p = 0.04$ ), BMRC III vs. I + II (HR 1.9, 95% CI 1.0–3.5,  $p = 0.06$ ), and hemoglobin  $< 8$  mg/dl (HR 2.7, 95% CI 1.0–8.4,  $p = 0.04$ ) were marginally associated with death within 9

**Table 3**

Patient characteristics associated with death during hospitalization in the multivariate analysis of 108 HIV-infected patients with confirmed tuberculous meningitis

Characteristic	Multivariate HR (95% CI)	p-Value
Age (years)	1.1 (1.0–1.1)	0.2
Headache	0.7 (0.2–2.7)	0.6
Nausea/vomiting	0.3 (0.1–1.2)	0.09
Tachycardia	2.4 (0.2–28.9)	0.06
Meningism	1.5 (0.2–13.8)	0.7
BMRC III vs. I + II	2.4 (0.7–8.0)	0.2
Prior HAART	1.7 (0.5–6.2)	0.4
CD4+ cell count $< 100$ cells/ $\mu l$	2.4 (0.5–10.4)	0.3
Hemoglobin level $< 8$ g/dl	1.4 (0.2–10.9)	0.7
Resistance to isoniazid	0.6 (0.2–2.1)	0.4
CSF glucose $< 45$ mg/dl	9.8 (1.0–94.3)	0.05

HR, hazard ratio; CI, confidence interval; BMRC, British Medical Research Council staging system; HAART, highly active antiretroviral therapy; CSF, cerebrospinal fluid.

**Table 4**

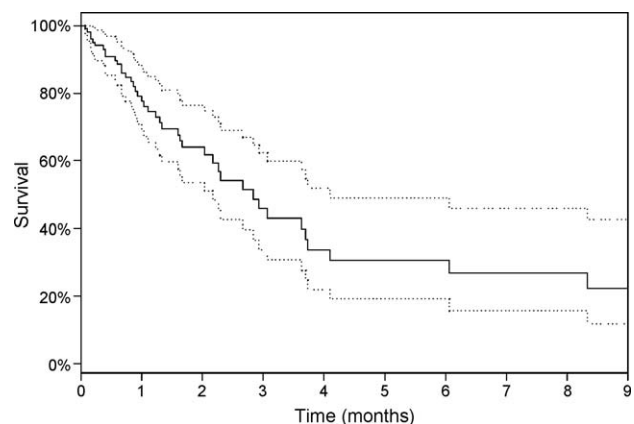
Patient characteristics associated with death within 9 months after diagnosis of tuberculous meningitis in the multivariate analysis of 108 HIV-infected patients

Characteristic	Multivariate HR (95% CI)	p-Value
Age (years)	1.0 (1.0–1.1)	0.3
Headache	0.8 (0.3–2.5)	0.8
Nausea/vomiting	0.8 (0.3–2.0)	0.6
Tachycardia	9.8 (1.4–69.5)	0.02
Meningism	1.9 (0.5–7.3)	0.3
BMRC III vs. I + II	1.4 (0.5–3.8)	0.5
Prior HAART	3.2 (1.1–9.6)	0.04
CD4+ cell count $< 100$ cells/ $\mu l$	2.6 (0.8–9.0)	0.1
Hemoglobin level $< 8$ g/dl	2.4 (0.4–15.1)	0.4
Resistance to isoniazid	1.2 (0.4–3.1)	0.8
CSF glucose $< 45$ mg/dl	3.2 (0.9–10.8)	0.06

HR, hazard ratio; CI, confidence interval; BMRC, British Medical Research Council staging system; HAART, highly active antiretroviral therapy; CSF, cerebrospinal fluid.

months after TBM diagnosis in the univariate analysis. Isoniazid resistance (HR 0.4, 95% CI 0.1–1.8,  $p = 0.3$ ) and MDR tuberculosis (HR 1.1, 95% CI 0.4–2.8,  $p = 0.9$ ) were not associated with death within 9 months of diagnosis in the univariate analysis. Tachycardia (HR 9.8, 95% CI 1.4–69.5,  $p = 0.02$ ) and prior HAART (HR 3.2, 95% CI 1.1–9.6,  $p = 0.04$ ) remained associated when included in the multivariate model (Table 4). However, CSF glucose  $< 45$  mg/dl (HR 3.2, 95% CI 0.9–10.8,  $p = 0.06$ ) presented only a borderline association.

The estimated median survival time was 3 months (95% CI 2–4 months). The Kaplan–Meier estimates of the probability of survival



**Figure 1.** Kaplan–Meier graph showing the probability of survival of HIV-infected patients with tuberculous meningitis (dotted lines are 95% confidence intervals).

were 46% (95% CI 34–62%) at 3 months, 31% (95% CI 19–49%) at 6 months, and 22% (95% CI 12–43%) at 9 months. Figure 1 shows the overall cumulative probability of survival of patients with TBM.

## 5. Discussion

The present study retrospectively assessed the clinical and laboratory features and factors associated with mortality in 108 HIV-infected patients with culture-positive TBM in Sao Paulo, Brazil. Overall, the mortality during hospitalization was 29% and within 9 months was 41%. Only tachycardia and prior HAART use were associated with death within 9 months in the multivariate analysis.

Tuberculosis is a prevalent and challenging problem in developing countries, including Brazil, and TBM is the most frequent neurologic complication. In our setting, TBM constitutes the third most frequent neurologic opportunistic condition and it is only exceeded by cerebral toxoplasmosis and cryptococcal meningoencephalitis.<sup>6,7</sup> In addition, TBM represents the second most frequent cause of opportunistic meningitis in AIDS patients in Brazil.<sup>8</sup>

TBM continues to cause high mortality rates in HIV-infected patients, particularly those in developing countries, due in part to late diagnosis. The clinical presentation is usually non-specific and similar to other neurologic opportunistic infections such as cryptococcosis, neurosyphilis, and bacterial meningitis. Therefore, a high index of suspicion should always be maintained, and computerized tomography and lumbar puncture (in the absence of contraindications) should be performed.

In clinical practice, determining the initiation of anti-tuberculous agents is challenging, especially in resource-limited settings, where diagnosis tools such as PCR are usually unavailable. In this regard, considering that only 15% of cases presented the classic triad of fever, headache, and meningeal signs, it is necessary to take advantage of CSF findings. Approximately 64% of our cases presented the 'typical' CSF alterations of TBM, a pattern previously well defined in the literature.<sup>9</sup> In these cases, the presence of clinical symptoms and the exclusion of other etiologies of meningitis should lead to a prompt initiation of anti-tuberculous treatment. On the other hand, the presence of none or only one altered parameter, observed in 13% of our cases, should call for a more conservative approach, always considering each clinical context. Interestingly, 18% of cases presented a normal total leukocyte count and 5% of cases had only high protein and low glucose simultaneously. The absence of pleocytosis has previously been described in 11–16% of HIV-infected patients with TBM.<sup>10,11</sup> In the present study, approximately 50% of cases had extraneural tuberculosis, occurring particularly in the lung. Similarly, previous studies have reported the isolation of *M. tuberculosis* from extraneural samples in 55–77% of cases,<sup>12,13</sup> confirming the high rate of disseminated tuberculosis in HIV-infected patients. Furthermore, an intensive investigation of extrameningeal tuberculosis should be performed in all possible cases of TBM.

In the present series, 9% of patients had MDR TBM and most of them (75%) presented a history of previous tuberculosis. A study performed in a hospital that assists a marginalized population, reported 42 (42%) patients with MDR TBM among 101 HIV-infected patients with TBM, and 43% of cases had previously undergone incomplete treatment or were taking anti-tuberculous drugs at the time of TBM diagnosis.<sup>12</sup> Another study reported 30 (9%) patients with MDR TBM among 350 patients (HIV-positive and -negative) with TBM. The frequency of cases with a history of tuberculosis treatment among the HIV-infected patients with MDR TBM was high (89%).<sup>14</sup> Another study showed 10 (6%) patients with MDR TBM among 180 patients (HIV-positive and -negative) with TBM; in this study, HIV infection was independently associated

with MDR TBM.<sup>15</sup> Considering the high prevalence of MDR TBM in developing countries and that MDR TBM is strongly predictive of death,<sup>15</sup> it is necessary to consider the history of previous tuberculosis treatment in all HIV-infected patients with a suspicion of TBM, and to highlight the need to evaluate the susceptibility profile in order to choose the best anti-tuberculous treatment.

The present study is the first to show the high resistance profile of TBM in HIV-infected patients in Sao Paulo. An official report using data of a survey from 1997 indicates that the prevalence of primary resistance to isoniazid and rifampin in the general population of Brazil is low (1.1%).<sup>16</sup> Current national guidelines recommend therapeutic schemes with three drugs for initial pulmonary tuberculosis and TBM in HIV-infected patients.<sup>5,17</sup> In contrast, studies performed in HIV-infected patients from Sao Paulo have found values of primary resistance to isoniazid of 6.9–7.1% and MDR resistance of 11.6–16.6%.<sup>18,19</sup> We consider that this information taken together with our results showing that 7% of HIV-infected patients with TBM presented primary resistance to isoniazid, suggests that the use of three drugs should be revisited in our setting. Therefore, it appears reasonable to include ethambutol until susceptibility tests are available. Updated epidemiologic surveys will give a more definite answer to this issue.

TBM is a fatal disease without treatment, causing death in 30–69% of cases<sup>20,21</sup> despite anti-tuberculous treatment, and HIV-infection significantly reduces the survival rate.<sup>1</sup> In the present study, the overall mortality during hospitalization was 29% and the overall 9-month mortality was 41%. Higher rates of mortality in AIDS-related TBM have been described in other studies. A study from Zimbabwe reported an in-hospital mortality of 67% in 21 HIV-infected patients with confirmed TBM.<sup>22</sup> A recent survey from Argentina reported that the global mortality during hospitalization among 101 HIV-infected patients with confirmed TBM was 63%.<sup>12</sup> Another study from Vietnam with patients recruited to a randomized controlled trial, reported that the 9-month mortality rate among 96 HIV-infected patients with definite, probable, or possible TBM was 65%.<sup>1</sup> In contrast to most resource-limited settings, we speculate that the availability of HAART in Brazil probably improved the long-term prognosis, at least in a subset of our patients. However, TBM continues to cause high mortality and represents a life-threatening disease, as shown by the estimated median survival time of 3 months and estimate of the probability of survival at 9 months of 22% in our study.

In addition, the specific clinical and laboratory profiles of the patients included in each study seem to explain the differences in mortality rates. For example, a previous study has reported 81% of patients with BMRC II and III, 42% of MDR strains, and 63% in-hospital mortality.<sup>12</sup> In contrast, in patients with a similar degree of immunodeficiency, our study reported 64% of cases classified as BMRC II and III, 9% of MDR strains, and 29% of in-hospital mortality.

The patients included in our study had some features that appear to have contributed to maintaining the high rates of TBM mortality, despite the availability of a reasonable infrastructure in our hospital: HIV status, inclusion of only culture-positive cases, frequency of disseminated tuberculosis, rates of MDR resistance, and extended (e.g., anemia, malnutrition) and severe immunosuppression (e.g., low CD4+ cell count).<sup>1,9,12,14,15</sup> In addition, it is possible that the usual limitations of access to healthcare in developing countries could be an additional reason for the delayed presentation that we observed in our patients, who were predominantly persons of low socio-economic level. Although we did not retrieve the median length of clinical symptoms before admission, we believe that this was prolonged. This fact was recently reported in patients with bacterial

meningitis from an area with a high prevalence of HIV infection in Malawi.<sup>23</sup>

Data on prognostic factors of TBM in HIV-infected patients are scarce. Factors independently associated with death in AIDS-related TBM include BMRC grade III,<sup>1</sup> BMRC grade II or III, CD4+ cell count <50 cells/ $\mu$ l, and MDR strains.<sup>12</sup> Tuberculous drug resistance (when not MDR) is an uncertain influence on outcome. Some preliminary unpublished data from Vietnam suggest that the outcome of isoniazid-resistant TBM is worse than for the fully sensitive disease (Guy Thwaites, personal communication). However, in the present study we did not find this association.

In this study, we identified some variables associated with 9-month mortality in a multivariate model: tachycardia and prior HAART use. Most of our patients had severe immunosuppression and reported previous antiretroviral therapy use. In addition, the median CD4 cell count was similar among patients with and without HAART use on admission. Thus, prior HAART use and further discontinuation or irregular use seem to be the more likely explanations for the unexpected finding of prior HAART use and unfavorable outcome. The loss of opportunity to use HAART has previously been described in other neurologic complications and represents a current challenge in Brazil, a developing country which has had a free and universal access program for HAART since 1996.<sup>24,25</sup>

Although we did not identify an association between anemia and mortality, hemoglobin levels are a known risk factor for death in patients with HIV<sup>26,27</sup> and TB infection.<sup>28</sup> A study has reported that the hematocrit level is independently associated with death in HIV-infected patients with TBM.<sup>1</sup> Anemia is a surrogate marker for poor general health in HIV-infected patients from developing countries, and it is frequently described in patients with neurological diseases.<sup>22,23</sup>

We identified a borderline association between CSF glucose levels and in-hospital and 9-month mortality. In accordance with this, the presence of hypoglycorrhachia has been correlated with the more advanced stages of TBM.<sup>9</sup>

This retrospective study has several limitations. These include the absence of a standardized history and neurological examination that could have resulted in misclassification of patients with regard to neurologic symptoms and signs; the lack of a complete neurological evaluation at discharge; the absence of an adequate registry of follow-up data, precluding any inference about therapeutic aspects (for example, to compare schemes with three vs. four anti-tuberculous agents, schemes with and without corticosteroids, and timing and type of antiretrovirals given). In addition, we included only culture-proven cases and therefore our results are only applicable to patients who met these strict diagnosis criteria. Although this is a large series of patients with TBM for a single institution, the relatively small sample size may have compromised the power to detect significant associations between patient characteristics and mortality. Finally, we were not able to identify information about potential cases of TBM in the setting of immune reconstitution inflammatory syndrome. Only prospective studies could answer this challenging question.

In this series of TBM in HIV-infected patients, the clinical presentation was unspecific, disseminated tuberculosis was common, mortality was high, and most patients had severe immunosuppression. Tachycardia and prior HAART use were independently associated with death within 9 months of TBM diagnosis.

#### Ethical approval

The study was approved by the ethical and scientific boards of the Emilio Ribas Institute of Infectious Diseases.

#### Conflict of interest

No conflict of interest to declare.

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#### References

- Thwaites GE, Duc Bang N, Huy Dung N, Thi Quy H, Thi Tuong Oanh D, Thi Cam Thoa N, et al. The influence of HIV infection on clinical presentation, response to treatment, and outcome in adults with tuberculous meningitis. *J Infect Dis* 2005;**192**:2134–41.
- Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2005;**351**:1741–51.
- Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *Lancet* 2002;**360**:1287–92.
- British Medical Research Council. Streptomycin treatment of tuberculous meningitis. *Lancet* 1948;**1**:582–96.
- Ministério da Saúde do Brasil. Recomendações para terapia anti-retroviral em adultos e adolescentes infectados pelo HIV–2007/2008. Available at: <http://www.aids.gov.br> (accessed October 2008).
- Oliveira JF, Greco DB, Oliveira GC, Christo PP, Guimarães MD, Oliveira RC. Neurological disease in HIV-infected patients in the era of highly active antiretroviral treatment: a Brazilian experience. *Rev Soc Bras Med Trop* 2006;**39**:146–51.
- Vidal JE, Penalva de Oliveira AC, Fink MC, Pannuti CS. AIDS-related progressive multifocal leukoencephalopathy: a retrospective study in a referral center in Sao Paulo, Brazil. *Rev Inst Med Trop S Paulo* 2008;**50**:209–12.
- Trujillo JR, Jaramillo-Rangel G, Ortega-Martinez M, Penalva de Oliveira AC, Vidal JE, Bryant J, et al. International NeuroAIDS: prospects of HIV-1 associated neurological complications. *Cell Res* 2005;**15**:962–9.
- Zuger A. Tuberculosis. In: Scheld WM, Whitley RJ, Marra CM, editors. *Infections of the central nervous system*. 3rd ed., Philadelphia: Lippincott-Raven; 2004. p. 441–60.
- Laguna F, Adrados M, Ortega A, Gonzales-Lahiz JM. Tuberculosis meningitis with acellular cerebrospinal fluid in AIDS patients. *AIDS* 1992;**6**:1165–7.
- Berenguer J, Moreno S, Laguna F, Vicente T, Adrados M, Ortega A, et al. Tuberculous meningitis in patients infected with the human immunodeficiency virus. *N Engl J Med* 1992;**326**:668–72.
- Cecchini D, Ambrosioni J, Brezzo C, Corti M, Rybko A, Perez M, et al. Tuberculous meningitis in HIV-infected patients: drug susceptibility and clinical outcome. *AIDS* 2007;**21**:373–4.
- Karstaedt AS, Valtchanova S, Barriere R, Crewe-Brown HH. Tuberculous meningitis in South African urban adults. *Q J Med* 1998;**91**:743–7.
- Patel VB, Padayatchi N, Bhigjee AI, Allen J, Bhagwan B, Moodley AA, et al. Multidrug-resistant tuberculosis meningitis in KwaZulu-Natal, South Africa. *Clin Infect Dis* 2004;**38**:851–6.
- Thwaites GE, Lan NT, Dung NH, Quy HT, Oanh DT, Thoa NT, et al. Effect of antituberculosis drug resistance on response to treatment and outcome in adults with tuberculous meningitis. *J Infect Dis* 2005;**192**:79–88.
- Braga JU, Barreto AM, Werneck AM, Hijjar MA. Inquérito Epidemiológico da resistência às drogas usadas no tratamento da tuberculose no Brasil, 1995–97—Parte III: principais resultados. *Boletim da Campanha Nacional Contra a Tuberculose (Rio de Janeiro)* 2003;**11**:76–81.
- Castelo Filho A, Kritski AL, Barreto AW, Lemos ACM, Ruffi no Netto A, Guimarães CA, et al. II Consenso Brasileiro de tuberculose: diretrizes brasileiras para tuberculose 2004. *J Bras Pneumol* 2004;**30**(Suppl 1):1–56.
- Pinto WP, Hadad DJ, Silva Telles MA, Ueki SY, Palaci M, Basile MA, et al. Tuberculosis and drug resistance among patients seen at an AIDS reference center in Sao Paulo, Brazil. *Int J Infect Dis* 2001;**5**:93–100.
- Rozman LM, Santo AH, Rozman MA. *Mycobacterium tuberculosis* drug resistance in HIV patients in Baixada Santista, Sao Paulo, Brazil. *Cad Saude Publica* 2007;**23**:1051–9.
- Thwaites G, Hien TT. Tuberculous meningitis: many questions, too few answers. *Lancet Neurol* 2005;**4**:160–70.
- Trachtenberg JD, Kambugu AD, McKellar M, Semitala F, Mayanja-Kizza H, Samore MH, et al. The medical management of central nervous system infections in Uganda and the potential impact of an algorithm-based approach to improve outcomes. *Int J Infect Dis* 2007;**11**:524–30.
- Hakim JG, Gangaidzo IT, Heyderman RS, Mielke J, Mushangi E, Taziwa A, et al. Impact of HIV infection on meningitis in Harare, Zimbabwe: a prospective study of 406 predominantly adult patients. *AIDS* 2000;**14**:1401–7.
- Scarborough M, Gordon SB, Whitty CJ, French N, Njalale Y, Chitani A, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *N Engl J Med* 2007;**357**:2441–50.

24. Vidal JE, Hernandez AV, de Oliveira AC, Dauar RF, Barbosa SP, Focaccia R, et al. Cerebral toxoplasmosis in HIV-positive patients in Brazil: clinical features and predictors of treatment response in the HAART era. *AIDS Patient Care STDs* 2005;**19**:840–8.
25. Marins JR, Jamal LF, Chen SY, Barros MB, Hudes ES, Barbosa AA, et al. Dramatic improvement in survival among adult Brazilian AIDS patients. *AIDS* 2003;**17**:1675–82.
26. Lundgren JD, Mocroft A. Anemia and survival in human immunodeficiency virus. *Clin Infect Dis* 2003;**37**(Suppl 4):297–303.
27. Moore RD, Keruly JC, Chaisson RE. Anemia and survival in HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;**1**:29–33.
28. Klautau GB, Kuschnaroff TM. Clinical forms and outcome of tuberculosis in HIV-infected patients in a tertiary hospital in Sao Paulo – Brazil. *Braz J Infect Dis* 2005;**6**:464–7.