social, and psychological burden that severe obesity causes in a growing number of American youth. However, even longer-term (>10-year) follow-up will be necessary to track the persistence of the associated micronutrient deficiencies, as well as the emergence of other deficiencies and other unanticipated long-term complications. Only then will providers be fully informed for the counseling of adolescents and their families with regard to the benefits, risks, and timing of bariatric surgery.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Chemotherapy for Tuberculous Meningitis

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Tuberculous meningitis, the most destructive form of tuberculosis, continues to be associated with considerable mortality and morbidity; among children, it is the major cause of death resulting from tuberculosis. The consequences of tuberculous meningitis are yet again clearly shown in the article by Heemskerk et al. in this issue of the *Journal*.[1] This randomized, controlled study of tuberculous meningitis in Vietnamese adults, probably the largest ever undertaken, was carefully planned and executed and evaluated an intensified regimen that included both a higher dose of oral rifampin than the standard dose (15 mg per kilogram of body weight vs. 10 mg per kilogram) and the addition of levofloxacin to the standard regimen that has been used for almost 40 years. It is disappointing that there was no advantage associated with the use of this intensified treatment regimen, with regard to overall mortality (28%) and most measures of illness; indeed, the mortality associated with both the standard regimen and the intensified regimen, when clinical disease staging was taken into account, was no better than that associated with the standard therapy of isoniazid, para-aminosalicylic acid, and streptomycin that was used in treatment from 1952 to 1970.[2] Another recent trial, conducted in Indonesia and involving a much smaller number of patients with tuberculous meningitis, assessed treatment with another fluoroquinolone — moxifloxacin — at a standard dose of 400 mg and at a higher dose of 800 mg, as well as treatment with a higher rifampin dose (13 mg per kilogram) administered intravenously. The 6-month mortality associated with the lower and higher doses of moxifloxacin (42% and 63%, respectively) did not differ significantly from that associated with the regimen without moxifloxacin (45%); however, mortality was lower among patients who received the higher rifampin dose administered intravenously than among those who received the standard oral rifampin dose of 10 mg per kilogram (34% vs. 65%)[3]. Further exploration of higher doses of rifampin may yet lead to improvements in the outcome of tuberculous meningitis.

Coupled with the recent findings of the failure of fluoroquinolone treatment to contribute

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to the sterilization of lesions and to shorten the duration of treatment for pulmonary tuberculosis, these results are disappointing, and they suggest that although fluoroquinolones may replace isoniazid because of their good bactericidal activity and may assist in treating drug-resistant tuberculosis, they are not going to revolutionize the treatment of pulmonary tuberculosis or tuberculous meningitis. The usefulness of fluoroquinolones is also threatened by a rising prevalence of fluoroquinolone resistance among *Mycobacterium tuberculosis* isolates in many countries.[4] New antituberculosis drugs are at last becoming available, and they may in due course contribute to our management of tuberculous meningitis; however, it is unfortunate that the three drugs that are closest to wider clinical use — bedaquiline (TMC207), delamanid (OPC-67683), and pretomanid (PA-824) — are highly protein-bound and unlikely to have free penetration into cerebrospinal fluid (CSF), and the threat of adverse events will probably limit any increase in their dose.[5]

The results described above stand in stark contrast to those of our group in treating children with tuberculous meningitis in the Western Cape Province of South Africa. For close to 30 years, we have used a pragmatic regimen that takes into account the ability of the relevant drugs to penetrate into the CSF at more efficacious concentrations and the doses of the drugs needed to achieve these concentrations without undue toxic effects. With a combination of isoniazid (15 to 20 mg per kilogram), rifampin (20 mg per kilogram), pyrazinamide (40 mg per kilogram), and ethionamide (20 mg per kilogram), all given throughout 6 months of treatment, the most recent overall mortality among 184 children, with more than 80% of the children having stage 2 or 3 tuberculous meningitis (British Medical Council Research Council classification), was 3.8% — and the mortality was concentrated among children with stage 3 meningitis.[6] We also pay close attention to monitoring the presence of hydrocephalus and, depending on the type of hydrocephalus and degree of the associated raised intracranial pressure, manage this with a combination of furosemide and acetazolamide, with ventriculoperitoneal shunting in selected cases; all children also receive prednisone for the first month of treatment.

With regard to isoniazid, despite its good penetration into the CSF, the concentrations reached after administration of the usually recommended doses are lower than the concentrations in the blood, in both adults and children,[7] and this is particularly likely to be the case with faster *N*-acetyltransferase 2 isoniazid acetylators. It is also infrequently realized that isoniazid at concentrations approaching 5 μg per milliliter has an appreciable mutant-inhibition capacity, probably directed mainly at *inh*A mutants.[8] Ethionamide not only has good CSF penetration[7] but probably will retain activity in the presence of *kat*G mutants that confer isoniazid resistance. These facts are important in a world with an increasing prevalence of isoniazid resistance. Pyrazinamide also has good penetration into the CSF, and in the presence of isoniazid resistance it can have a substantial effect on relapse rates if administration is continued throughout the 6 months of treatment, reducing the rate of relapses in pulmonary tuberculosis to 1%, as compared with 7% if it is given for only 2 months.[9]

It has been cogently stated that the central nervous system is a "unique therapeutic compartment" that requires special consideration in the treatment of tuberculous meningitis.[10] The time has come to remember this when making recommendations regarding the drugs and doses to be used in chemotherapy for a disease as deadly as tuberculous meningitis.

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ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

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ABSTRACT

BACKGROUND

Tuberculous meningitis is often lethal. Early antituberculosis treatment and adjunctive treatment with glucocorticoids improve survival, but nearly one third of patients with the condition still die. We hypothesized that intensified antituberculosis treatment would enhance the killing of intracerebral *Mycobacterium tuberculosis* organisms and decrease the rate of death among patients.

METHODS

We performed a randomized, double-blind, placebo-controlled trial involving human immunodeficiency virus (HIV)–infected adults and HIV-uninfected adults with a clinical diagnosis of tuberculous meningitis who were admitted to one of two Vietnamese hospitals. We compared a standard, 9-month antituberculosis regimen (which included 10 mg of rifampin per kilogram of body weight per day) with an intensified regimen that included higher-dose rifampin (15 mg per kilogram per day) and levofloxacin (20 mg per kilogram per day) for the first 8 weeks of treatment. The primary outcome was death by 9 months after randomization.

RESULTS

A total of 817 patients (349 of whom were HIV-infected) were enrolled; 409 were randomly assigned to receive the standard regimen, and 408 were assigned to receive intensified treatment. During the 9 months of follow-up, 113 patients in the intensified-treatment group and 114 patients in the standard-treatment group died (hazard ratio, 0.94; 95% confidence interval, 0.73 to 1.22; P=0.66). There was no evidence of a significant differential effect of intensified treatment in the overall population or in any of the subgroups, with the possible exception of patients infected with isoniazid-resistant *M. tuberculosis*. There were also no significant differences in secondary outcomes between the treatment groups. The overall number of adverse events leading to treatment interruption did not differ significantly between the treatment groups (64 events in the standard-treatment group and 95 events in the intensified-treatment group, P=0.08).

CONCLUSIONS

Intensified antituberculosis treatment was not associated with a higher rate of survival among patients with tuberculous meningitis than standard treatment. (Funded by the Wellcome Trust and the Li Ka Shing Foundation; Current Controlled Trials number, ISRCTN61649292.)

ARLY TREATMENT WITH ANTITUBERCU-losis chemotherapy and adjunctive treatment with glucocorticoids reduce the rate of death and disability from tuberculous meningitis, but the disease still kills or disables almost half the patients with the condition.[1,2] The current guidelines recommend treatment with four antituberculosis drugs for at least the first 2 months of therapy, followed by treatment with two drugs (rifampin and isoniazid) for an additional 7 to 10 months.[3,4] However, these recommendations are based on data from pulmonary tuberculosis and do not take into account the differential ability of antituberculosis drugs to penetrate the brain.

Rifampin is considered to be a critical drug in tuberculosis treatment, but concentrations of the drug in cerebrospinal fluid (CSF) are less than 30% of the concentration in plasma.[5-7] In pulmonary tuberculosis, an increase in the oral dose of rifampin from 10 to 13 mg per kilogram of body weight had an acceptable side effect profile and led to a 65% increase in plasma concentrations of the drug.[8] A recent randomized comparison of higher-dose intravenous rifampin (approximately 13 mg per kilogram per day) versus a standard oral dose (10 mg per kilogram per day) in 60 Indonesian adults with tuberculous meningitis showed that mortality among patients who received the higher intravenous dose was 50% lower than that among patients who received the standard dose.[9]

Fluoroquinolones are active antituberculosis agents with good penetration of the blood–brain barrier.[10] For example, the concentration of levofloxacin in CSF reaches 70% of the concentration in plasma, and the drug has early bactericidal activity approaching that of isoniazid.[10-12] A randomized study involving Vietnamese adults with tuberculous meningitis suggested that the initial addition of levofloxacin to a standard four-drug antituberculosis regimen improved the survival rate, especially among patients who were treated before the onset of coma.[10] We therefore sought to test the hypothesis that intensified antituberculosis treatment — with higher-dose rifampin (15 mg per kilogram per day) and the addition of levofloxacin (20 mg per kilogram per day) for the first 8 weeks of treatment — would result in lower rates of death and disability from tuberculous meningitis than the rates with the currently recommended regimen.

METHODS

STUDY POPULATION AND SETTING

We recruited study participants from two centers in Ho Chi Minh City, Vietnam: Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease and the Hospital for Tropical Diseases. These 500-bed hospitals serve the local community and act as tertiary referral centers for patients with severe tuberculosis (Pham Ngoc Thach Hospital) or infectious diseases (Hospital for Tropical Diseases) in southern Vietnam.

A full description of the methods has been published elsewhere[13] and is provided in the protocol, available with the full text of this article at NEJM.org. Adults (≥18 years of age) with a clinical diagnosis of tuberculous meningitis (at least 5 days of meningitis symptoms, nuchal rigidity, and CSF abnormalities) were eligible to enter the trial. Patients were subsequently classified as having definite, probable, or possible tuberculous meningitis or an alternative condition, in accordance with published diagnostic criteria[14] (Table S1 in the Supplementary Appendix, available at NEJM.org). Patients could not enter the trial if they had received more than 7 days of antituberculosis drugs for the current infection; if they were known or suspected to be pregnant; if they had known or suspected hypersensitivity to or unacceptable side effects from fluoroquinolones or rifampin; if multidrug-resistant tuberculosis was known (on the basis of previous sputum drug susceptibility test results or Xpert MTB/RIF assay [Cepheid]) or suspected to be present; or if the plasma creatinine concentration was more than three times the upper limit of the normal range (for males, >360 μmol per liter [4.07 mg per deciliter], and for females, >300 μmol per liter [3.39 mg per deciliter]), if the plasma bilirubin concentration was more than 2.5 times the upper limit of the normal range (total bilirubin >42.5 mmol per liter), or if the plasma aspartate or alanine aminotransferase level was more than five times the upper limit of the normal range (>185 U per liter or >200 U per liter, respectively).

STUDY OVERSIGHT

Written informed consent to participate in the study was obtained from all patients or from their relatives if the patient could not provide consent. The trial was approved by the Oxford

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Tropical Research Ethics Committee, the institutional review board at the Hospital for Tropical Diseases and at Pham Ngoc Thach Hospital, and the ethics committee of the Ministry of Health, Vietnam. An independent data and safety monitoring board reviewed the data after 6 months, 1 year, 2 years, and 3 years. The Xpert MTB/RIF assays used in the study were purchased. The rifampin and its matching placebo, as well as some of the levofloxacin, was purchased from Mekophar and Sanofi, respectively. Some of the levofloxacin and all of the levofloxacin matching placebo were donated by Sanofi. Neither Mekophar nor Sanofi played a part in the design, implementation, or analysis of the study, including manuscript preparation, or in the decision to submit the results for publication. All the authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol.

LABORATORY INVESTIGATIONS

CSF specimens were stained and cultured with the use of standard methods for pyogenic bacteria, fungi, and mycobacteria and were tested with an Xpert MTB/RIF assay. Isolates of *Mycobacterium tuberculosis* were tested for susceptibility to isoniazid, rifampin, ethambutol, and streptomycin by means of the mycobacterial growth indicator tube method.[15] All patients were tested for antibodies to human immunodeficiency virus (HIV) and hepatitis C and for the presence of hepatitis B surface antigen. CD4 cell counts were measured for all HIV-infected adults as soon as possible after randomization.

STUDY TREATMENT

All patients received standard oral antituberculosis treatment, which consisted of isoniazid (5 mg per kilogram per day; maximum, 300 mg per day), rifampin (10 mg per kilogram per day), pyrazinamide (25 mg per kilogram per day; maximum, 2 g per day), and ethambutol (20 mg per kilogram per day; maximum, 1.2 g per day) for 3 months, followed by rifampin and isoniazid at the same doses for an additional 6 months. Patients who had previously received treatment for tuberculosis also received streptomycin (20 mg per kilogram per day; maximum, 1 g per day) for the first 3 months. All patients received adjunctive treatment with dexamethasone for the first 6 to 8 weeks of treatment, as described previ-

ously.[16] Intensified treatment consisted of the standard 9-month regimen with the addition for the first 8 weeks of treatment of a weight-based dose of rifampin (5 mg per kilogram per day, to achieve a total dose of 15 mg per kilogram per day) and of levofloxacin (20 mg per kilogram per day) (Table S2 in the Supplementary Appendix). Adherence to treatment was ensured with the use of supervised drug intake for inpatients, encouraged by detailed instructions at discharge, and measured by pill counts at the monthly follow-up visits. For patients infected with *M. tuberculosis* that was resistant to rifampin, isoniazid, or both, treatment was adjusted in accordance with local practices and the susceptibility of the organism.

HIV-infected patients received antiretroviral therapy in accordance with Vietnamese guidelines. Antiretroviral therapy that was started before enrollment was continued unless it was contraindicated for use with rifampin. If the antiretroviral therapy regimen that the patient was receiving at the time of enrollment included nevirapine, that drug was switched to efavirenz. For patients who had not previously received antiretroviral therapy, the therapy was started after 8 weeks of antituberculosis therapy.[17] Cotrimoxazole prophylaxis (960 mg per day) was given to all patients who had CD4 cell counts below 200 per cubic millimeter.

RANDOMIZATION AND CONCEALMENT OF STUDY-GROUP ASSIGNMENTS

Patients were stratified at study entry according to site, HIV infection status, and the modified British Medical Research Council criteria (MRC grade).[18] MRC grade 1 indicates a Glasgow coma score of 15 (on a scale of 3 to 15, with lower scores indicating reduced levels of consciousness) with no neurologic signs, grade 2 a score of 11 to 14 (or a score of 15 with focal neurologic signs), and grade 3 a score of 10 or lower. Patients were randomly assigned in a 1:1 ratio to receive either standard or intensive antituberculosis treatment according to a computer-generated randomization list, with randomization in variable block sizes of 4 and 6.

The study pharmacist prepared visually matched pills in identical, sequentially numbered treatment packs according to the randomization list for dispensation in sequential order as patients were recruited. All the participants,

enrolling physicians, and investigators remained unaware of the treatment assignments until the last patient completed follow-up. The attending physicians were responsible for enrolling the participants and for ensuring that the study drug was given from the correct treatment pack. Daily monitoring of all inpatients by one of the investigators ensured uniform management between the study sites and accurate recording of clinical data in individual study notes.

OUTCOME ASSESSMENTS

The condition of the patients was reviewed daily until discharge from the hospital for assessment of clinical progress and neurologic and drug-related adverse events. After discharge, monthly visits were scheduled for clinical evaluation and laboratory monitoring until the completion of treatment at 9 months.

The primary outcome was death by 9 months after randomization. The secondary outcomes included neurologic disability at 9 months, time to the first new neurologic event or death, and serious adverse events. The disability outcome was assessed with the use of the "simple questions" score (based on the answers to two yes-or-no questions regarding the patient's dependency on others in daily activities and whether the illness has left the patient with any other problems) and the modified Rankin score (a disability score that ranges from 0 [no symptoms] to 5 [totally dependent on others]) and was classified as "good outcome," "intermediate outcome," "severe disability," or "death," as described previously.[16,17,19] Patients were assessed at 2, 6, and 9 months after randomization; the worst score from either questionnaire was taken as the outcome. If the 9-month disability assessment was missing, the previous assessment was used instead. New neurologic events were defined as the occurrence of any of the following: cerebellar symptoms; monoplegia, hemiplegia, paraplegia, or tetraplegia; seizures; cranial nerve palsy; or a decrease in Glasgow coma score of 2 or more points for 2 or more days from the highest previously recorded score.

STATISTICAL ANALYSIS

We calculated that with a sample size of at least 750 patients, including a minimum of 350 HIV-infected patients, the trial would have 80% power to detect a 10-percentage-point lower 9-month risk of death among patients receiving the intensified treatment than among those receiving the standard treatment (30% vs. 40%, corresponding to a target hazard ratio of 0.7) in the overall population and a 15-percentage-point lower risk of death in the subgroup of HIV-infected patients (50% vs. 65%), at a two-sided 5% significance level.
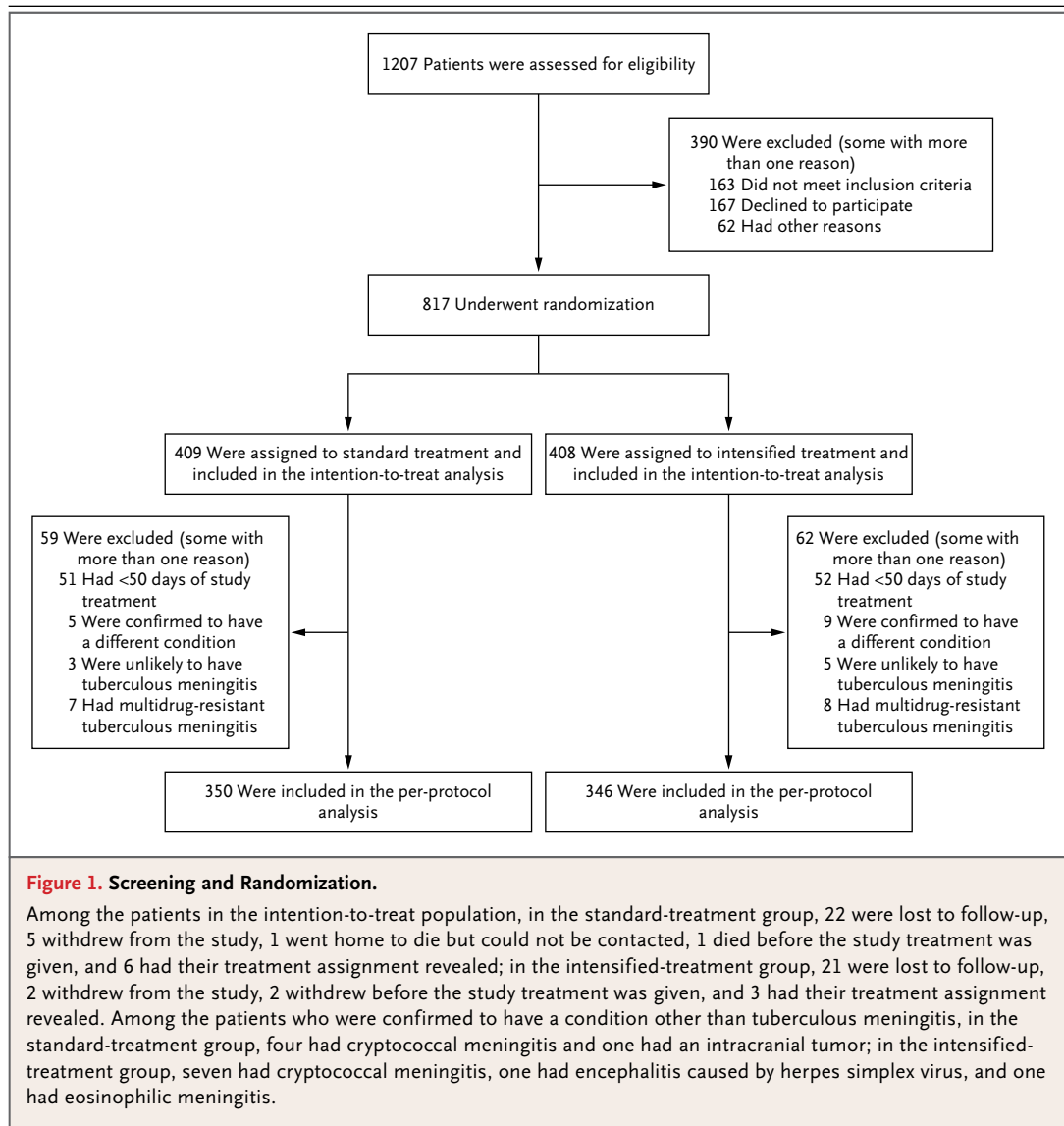
The statistical analysis followed the protocol[13] and the statistical analysis plan (see the Supplementary Appendix). The primary outcome was analyzed in all patients and in prespecified subgroups, with the analysis based on the Cox proportional-hazards model with stratification according to HIV infection status and MRC grade. The ordinal disability score was compared between the two study groups with a proportional-odds logistic-regression model with adjustment for HIV infection status and MRC grade. Secondary time-to-event outcomes were analyzed in the same way as the primary outcome. Additional prespecified multivariable Cox regression analyses and analyses of the disability score were based on multiple imputation of missing covariates and disability outcomes, as detailed in the statistical analysis plan.

The primary analysis population was the intention-to-treat population, which included all patients who underwent randomization. The analysis of the primary outcome was repeated in the per-protocol population, which did not include patients with unlikely tuberculous meningitis or an alternative diagnosis according to the diagnostic criteria,[14] patients with multidrug-resistant infections, or patients who received less than 50 days of treatment with the study drug for reasons other than death. All statistical analyses were performed with the statistical software R, version 3.1.2.[20]

RESULTS

STUDY POPULATION

From April 18, 2011, through June 18, 2014, a total of 817 adult patients were randomly assigned to receive standard antituberculosis treatment plus either placebo (409 patients; standard-treatment group) or additional rifampin and levofloxacin (408 patients; intensified-treatment group). A total of 53 patients (28 in the standard-treatment group and 25 in the intensified-treatment group) did not complete follow-up for reasons other than death.

Figure 1. Screening and Randomization.

Among the patients in the intention-to-treat population, in the standard-treatment group, 22 were lost to follow-up, 5 withdrew from the study, 1 went home to die but could not be contacted, 1 died before the study treatment was given, and 6 had their treatment assignment revealed; in the intensified-treatment group, 21 were lost to follow-up, 2 withdrew from the study, 2 withdrew before the study treatment was given, and 3 had their treatment assignment revealed. Among the patients who were confirmed to have a condition other than tuberculous meningitis, in the standard-treatment group, four had cryptococcal meningitis and one had an intracranial tumor; in the intensified-treatment group, seven had cryptococcal meningitis, one had encephalitis caused by herpes simplex virus, and one had eosinophilic meningitis.

A total of 121 patients (59 in the standard-treatment group and 62 in the intensified-treatment group) were not included in the per-protocol population. A condition other than tuberculous meningitis was diagnosed in 14 patients (5 in the standard-treatment group and 9 in the intensified-treatment group), and 8 patients (3 in the standard-treatment group and 5 in the intensified-treatment group) were deemed unlikely to have tuberculous meningitis. A total of 103 patients received less than 50 days of treatment with the study regimens for reasons other than death, and 15 of these patients were determined to have multidrug-resistant tuberculous meningi-

tis (Fig. 1). We assessed adherence to the 8-week intervention, and 4.0% of the participants (33 of 817, 19 in the standard-treatment group and 14 in the intensified-treatment group) were judged to be nonadherent (<100% medication doses received).

BASELINE CHARACTERISTICS

The characteristics of the patients at baseline were balanced between the two treatment groups, with the exception of sodium concentrations in plasma (lower in the intensified-treatment group), the frequency of a previous episode of tuberculosis (higher in the intensified-treatment group),

Table 1. Characteristics of the Patients at Enrollment.*

Characteristic	Standard Regimen (N = 409)	Intensified Regimen (N = 408)	All Patients (N = 817)
Male sex — no. (%)	278 (68.0)	282 (69.1)	560 (68.5)
Median age (IQR) — yr	35 (30–47)	35 (29–45)	35 (29–46)
MRC grade — no. (%)†			
1	160 (39.1)	158 (38.7)	318 (38.9)
2	178 (43.5)	179 (43.9)	357 (43.7)
3	71 (17.4)	71 (17.4)	142 (17.4)
HIV-infected — no. (%)	174 (42.5)	175 (42.9)	349 (42.7)
Median CD4 count (IQR) — cells/mm³‡	38 (15–82)	38 (14–113)	38 (14–101)
Diagnostic category — no. (%)§			
Definite tuberculous meningitis	201 (49.1)	206 (50.5)	407 (49.8)
Probable tuberculous meningitis	109 (26.7)	105 (25.7)	214 (26.2)
Possible tuberculous meningitis	91 (22.2)	83 (20.3)	174 (21.3)
Unlikely to be tuberculous meningitis	3 (0.7)	5 (1.2)	8 (1.0)
Confirmed other condition	5 (1.2)	9 (2.2)	14 (1.7)
Resistance category			
Drug-susceptibility test results available — no.	156	166	322
No isoniazid or rifampin resistance — no. (%)¶	107 (68.6)	113 (68.1)	220 (68.3)
Isoniazid monoresistance — no. (%)	41 (26.3)	45 (27.1)	86 (26.7)
Rifampin monoresistance — no. (%)	1 (0.6)	0	1 (0.3)
Multidrug resistance — no. (%)	7 (4.5)	8 (4.8)	15 (4.7)

* No characteristic differed significantly between the study groups (P≤0.05 at baseline according to Fisher's exact test for categorical data or the Wilcoxon rank-sum test for continuous data), with the exception of sodium concentration (P=0.004), frequency of a previous episode of tuberculosis (P=0.045), total white-cell count in the cerebrospinal fluid (P=0.006), and lymphocyte percentage in the cerebrospinal fluid (P=0.01); the complete list of baseline characteristics is provided in Table S3 in the Supplementary Appendix. IQR denotes interquartile range.

† Medical Research Council (MRC) grade 1 indicates a Glasgow coma score of 15 (on a scale of 3 to 15, with lower scores indicating reduced levels of consciousness) with no neurologic signs, grade 2 a score of 11 to 14 (or 15 with focal neurologic signs), and grade 3 a score of 10 or less.

‡ CD4 cell counts were assessed only in HIV-infected patients. Data were missing for 30 patients in the standard-treatment group and for 25 patients in the intensified-treatment group.

§ Diagnostic categories were assigned according to the consensus case definition.[14] Patients whose condition was unlikely to be tuberculous meningitis had a score of less than 6 on the scale based on the consensus case definition (maximum score, 20) (see Table S1 in the Supplementary Appendix). Confirmation of another condition was made only on the basis of microbiologic evidence.

¶ Isoniazid monoresistance is defined as resistance to isoniazid but not to rifampin. Multidrug resistance is defined as resistance to at least isoniazid and rifampin. In all categories, resistance to other drugs may be present.

total white-cell count in the CSF (higher in the intensified-treatment group), and lymphocyte percentage in the CSF (lower in the intensified-treatment group) (Table 1, and Table S3 in the Supplementary Appendix). A total of 68.5% of the patients were men, the median age of the patients was 35 years, and the median duration of illness was 15 days. A majority of the patients had mild-to-moderate illness; only 17.4% had MRC grade 3 illness at enrollment. A total of 42.7% of patients were infected with HIV. Using the published diagnostic criteria,[14] we defined 49.8% of the patients as having definite tuberculous meningitis, 26.2% as having probable tuberculous meningitis, and 21.3% as having possible tuberculous meningitis. Among the patients with culture-confirmed disease, 26.7% had isoniazid-resistant infection, and 4.7% had multi-

drug-resistant infection. The baseline clinical characteristics of the patients according to MRC illness severity grade are provided in Table S4 in the Supplementary Appendix.

PRIMARY OUTCOME

During 9 months of follow-up, 113 patients in the intensified-treatment group and 114 patients in the standard-treatment group died (hazard ratio, 0.94; 95% confidence interval [CI], 0.73 to 1.22; P=0.66) (Fig. 2). There was no evidence of a differential effect of intensified treatment in the overall population or in any of the prespecified subgroups, although there was a suggestion of benefit of intensified treatment for patients with isoniazid-resistant infections (P=0.06) (Table 2). The probability of overall survival according to treatment group in the per-protocol population and MRC-grade groups is shown in Figures S1 and S2 in the Supplementary Appendix.

A Cox regression analysis (Table S5 in the Supplementary Appendix) identified the following factors as predictors of poor survival: more severe neurologic compromise at treatment initiation, as indicated by a higher MRC grade (hazard ratio for grade 2 vs. grade 1, 2.41; 95% CI, 1.70 to 3.42; hazard ratio for grade 3 vs. grade 1, 6.31; 95% CI, 4.36 to 9.12); HIV infection (hazard ratio, 2.53; 95% CI, 1.90 to 3.36); and multidrug-resistant or rifampin-resistant infection (hazard ratio, 4.72; 95% CI 2.41 to 9.24) or infection with unknown drug resistance (hazard ratio as compared with no isoniazid or rifampin resistance, 1.76; 95% CI, 1.27 to 2.45). In HIV-infected patients, a higher CD4 cell count was associated with reduced mortality (hazard ratio per increase of 100 cells per cubic millimeter, 0.62; 95% CI, 0.44 to 0.87).

SECONDARY OUTCOMES AND ADVERSE EVENTS

There was no evidence of a differential effect of intensified treatment on any of the prespecified secondary outcomes (Table S6 in the Supplementary Appendix). Overall, there was no significant difference between the treatment groups with regard to clinical adverse events, apart from a higher frequency of seizures in the intensified-treatment group than in the standard-therapy group (23 vs. 11 patients, P=0.04), as well as a higher frequency of vision impairment in the intensified-treatment group (14 vs. 4, P=0.02)

(Table 3). Signs of drug allergy were more frequent in the intensified-treatment group than in the standard-therapy group (occurring in 30 patients vs. 17 patients); however, this difference did not reach significance (P=0.052). The difference between the study groups in the number of adverse events leading to interruptions in antituberculosis treatment also did not reach significance (64 events in the standard-treatment group vs. 95 in the intensified-treatment group, P=0.08) (Table S7 in the Supplementary Appendix). There were more interruptions due to jaundice in the intensified-treatment group than in the standard-treatment group (in 19 vs. 7 patients, P=0.02). Additional laboratory abnormalities are listed in Table S5 in the Supplementary Appendix. There were significantly more patients with grade 3 or grade 4 increases in bilirubin level in the intensified-treatment group than in the standard-treatment group (49 vs. 31, P=0.04), as well as significantly more patients with grade 3 or 4 hyponatremia (112 vs. 81, P=0.01) (Table S8 in the Supplementary Appendix). The median duration of the initial hospitalization was 31 days in the intensified-treatment group and 30 days in the standard-treatment group. A total of 11 patients (4 in the standard-treatment group and 7 in the intensified-treatment group) had a prolongation of the corrected QT interval above the critical threshold of 500 msec (calculated with the use of the Framingham formula) at any time between baseline and 4 weeks of treatment.

DISCUSSION

In this pragmatic, randomized, double-blind, placebo-controlled trial involving adults with tuberculous meningitis, intensified antituberculosis treatment was not associated with a higher rate of survival than the rate with standard treatment. The results contradict the findings of previous studies that suggested that an increase in rifampin dose[9] and the addition of a fluoroquinolone to the standard regimen[10] may improve the outcome in patients with tuberculous meningitis.

A limitation of our study was that we tested a regimen rather than the contribution of individual drugs. A factorial design may have enabled the latter but would have led to the need for a prohibitively large sample size.[21] However, our

Figure 2. Kaplan–Meier Curves for Overall Survival According to Treatment Group and HIV Infection Status.

In accordance with the statistical analysis plan, all deaths in the database were included in the final analysis; this included two deaths on days 274 and 275. Because the 9-month follow-up visit was on days 270 through 272 for most patients, the numbers of patients at risk on days 274 and 275 were low, which accounts for the sharp decrease in the Kaplan–Meier curves at the end of the study period.

A **All Patients**

No. at Risk										
Standard	409	342	322	315	298	293	290	286	284	222
Intensified	408	353	328	313	305	295	288	283	379	225

B **HIV-Uninfected Patients**

No. at Risk										
Standard	235	208	202	200	192	189	188	186	186	151
Intensified	233	211	200	195	189	183	182	181	179	148

C **HIV-Infected Patients**

No. at Risk										
Standard	174	134	120	115	106	104	102	100	98	71
Intensified	175	142	128	118	116	112	106	102	100	77

negative findings suggest that neither a higher dose of rifampin nor a higher dose of levofloxacin improves tuberculous meningitis treatment.

There are a number of possible explanations for our results. It is possible that the oral rifampin dose used in our study (15 mg per kilogram per day) did not increase the intracerebral drug concentrations sufficiently to enhance bacterial killing. Recent data suggest that much higher doses of rifampin (up to 35 mg per kilogram per day) may have an acceptable side-effect profile and may be necessary to significantly increase the killing of *M. tuberculosis* in pulmonary tuberculosis.[22] Furthermore, oral administration probably results in substantially lower rifampin concentrations in plasma than does intravenous administration of equivalent doses.[23] Some reports have suggested that the relative benefit of rifampin in the treatment of tuberculous meningitis may be modest in the presence of effective mycobacterial killing by isoniazid.[24] The main role of rifampin in the treatment of pulmonary tuberculosis is probably to shorten the treatment duration rather than to enhance early mycobacterial killing.[25,26] In contrast, fluoroquinolones have enhanced the early sterilization of sputum but have not allowed the duration of therapy to be shortened, because of unacceptable increases in disease relapses.[27-29] Previous studies have shown that fluoroquinolones either have no effect on the outcome of tuberculous meningitis[9] or confer a possible benefit in patients with mild disease.[10] A pharmacokinetic and pharmacodynamic analysis involving the patients recruited for our trial may help address these possibilities.

An intensified antituberculosis regimen may, however, benefit patients infected with isoniazid-resistant *M. tuberculosis*. The way in which this finding should influence clinical practice is un-
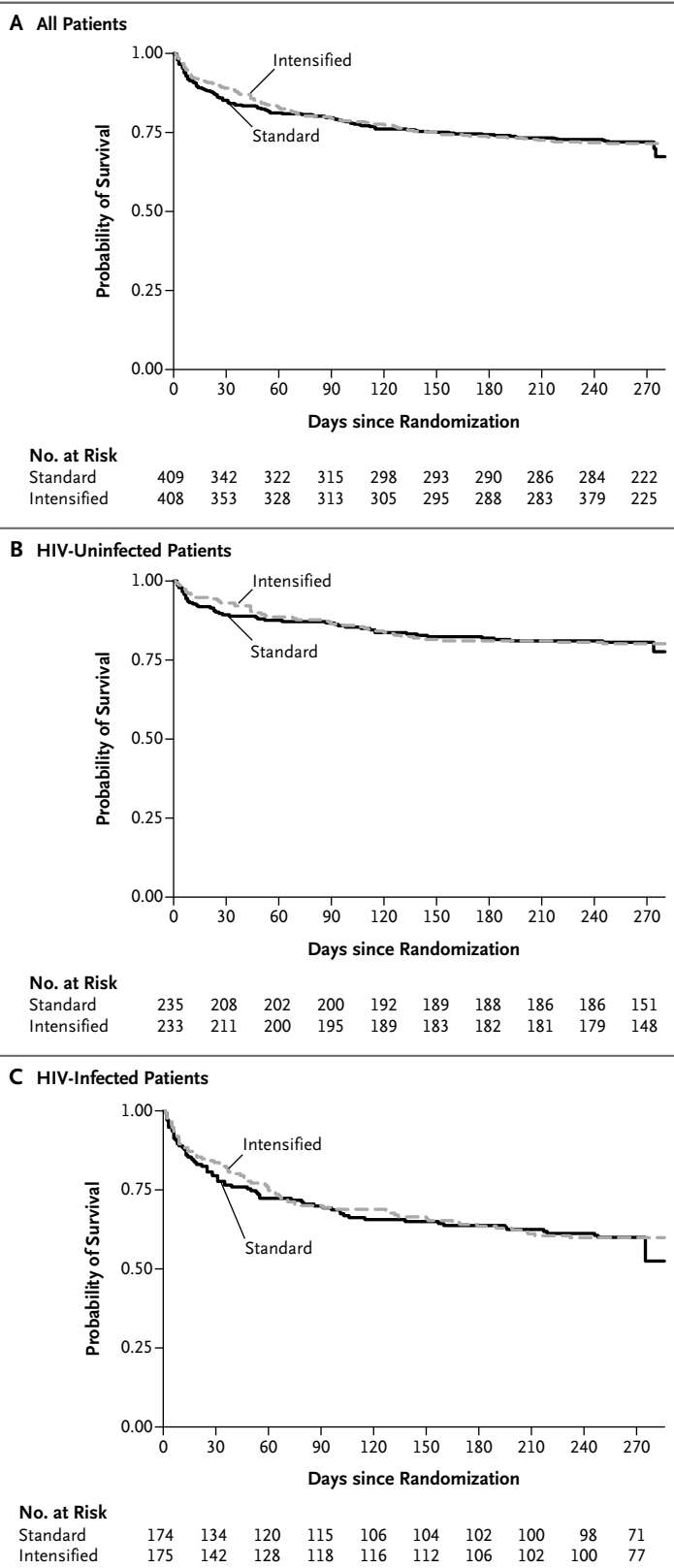
Table 2. Survival during the 9-Month Study Period.

Subgroup	Standard Regimen (N = 409)	Intensified Regimen (N = 408)	Hazard Ratio (95% CI)	P Value	P Value for Heterogeneity*
	no. of deaths/total no. of patients				
Intention-to-treat population	114/409	113/408	0.94 (0.73–1.22)	0.66	
Per-protocol population	94/350	93/346	0.91 (0.68–1.21)	0.52	
MRC grade					0.69
1	25/160	21/158	0.82 (0.46–1.46)	0.49	
2	50/178	52/179	1.07 (0.72–1.57)	0.74	
3	39/71	40/71	0.87 (0.56–1.36)	0.55	
HIV infection status					0.74
Uninfected	46/235	45/233	1.00 (0.66–1.51)	1.00	
Infected†	68/174	68/175	0.91 (0.65–1.27)	0.57	
Previous tuberculosis					0.82
No	89/347	78/324	0.91 (0.67–1.23)	0.53	
Yes	25/62	35/84	0.99 (0.59–1.67)	0.97	
Receiving antituberculosis treatment at enrollment‡					0.02
No	36/150	49/149	1.38 (0.89–2.12)	0.15	
Yes	78/259	64/259	0.74 (0.53–1.03)	0.07	
Diagnostic category§					0.93
Definite tuberculous meningitis	56/201	55/206	0.90 (0.62–1.31)	0.57	
Probable tuberculous meningitis	30/109	33/105	1.10 (0.66–1.83)	0.71	
Possible tuberculous meningitis	28/91	25/83	0.94 (0.54–1.63)	0.82	
Resistance category					0.04
No or other resistance	22/107	30/113	1.54 (0.88–2.71)	0.13	
Isoniazid resistance	16/41	11/45	0.45 (0.20–1.02)	0.06	
Rifampin or multidrug resistance	6/8	5/8	0.63 (0.15–2.69)	0.53	

* Heterogeneity was tested with a likelihood ratio test for an interaction term between the subgroup variable and the randomly assigned treatment group. As prespecified, the Cox regression was stratified according to MRC grade and HIV infection status.
† Among the patients who were not receiving antiretroviral therapy at enrollment, 49 of 114 patients (43%) in the intensified-treatment group died (30 of them in the first 8 weeks), and 44 of 115 patients (38%) in the standard-treatment group died (29 of them in the first 8 weeks). Among the patients who were receiving antiretroviral therapy at enrollment, 19 of 61 patients (31%) in the intensified-treatment group died (9 of them in the first 8 weeks), and 24 of 59 patients (41%) in the standard-treatment group died (18 of them in the first 8 weeks).
‡ Patients were not eligible to enter the trial if they had received more than 7 days of antituberculosis treatment before enrollment. The median duration of antituberculosis treatment was 4 days (interquartile range, 2 to 5).
§ A total of 22 patients with unlikely tuberculous meningitis or a confirmed other condition were not included.

certain, given that the detection of isoniazid resistance usually requires bacterial culture and often takes many weeks. The development of rapid molecular tests that can reliably detect isoniazid resistance in cerebrospinal fluid may aid in early diagnosis and treatment adjustments. However, empirical intensification of treatment regimens may be warranted in patients who are at high risk for isoniazid-resistant infection or in settings with a high prevalence of isoniazid-resistant bacteria.

The overall mortality in our population was lower than that anticipated on the basis of previous reports. This may be due to a combination of earlier diagnosis (38.9% of patients had MRC grade 1 disease at randomization), increased availability of second-line drugs for drug-resistant infections, and improved management of

Table 3. Clinical Grade 3 and 4 Adverse Events.*

Adverse Event	Standard Regimen (N=409)	Intensified Regimen (N=408)	P Value†
	no. of patients (%)		
Any event	229 (56.0)	240 (58.8)	0.44
Neurologic event	155 (37.9)	173 (42.4)	0.20
Deterioration of consciousness	89 (21.8)	90 (22.1)	0.93
Headache	30 (7.3)	36 (8.8)	0.44
Hemiplegia	21 (5.1)	31 (7.6)	0.16
Paraplegia	9 (2.2)	10 (2.5)	0.82
Urinary retention	12 (2.9)	10 (2.5)	0.83
Cranial-nerve palsies	11 (2.7)	13 (3.2)	0.69
Seizures	11 (2.7)	23 (5.6)	0.04
Vision impairment	4 (1.0)	14 (3.4)	0.02
Hepatotoxicity	28 (6.8)	17 (4.2)	0.12
Jaundice	17 (4.2)	29 (7.1)	0.07
Respiratory event	18 (4.4)	18 (4.4)	1.00
Event requiring mechanical ventilation	10 (2.4)	14 (3.4)	0.42
Signs of drug allergy	17 (4.2)	30 (7.4)	0.052
Cardiologic events	14 (3.4)	13 (3.2)	1.00
Diarrhea	7 (1.7)	5 (1.2)	0.77
Vomiting	13 (3.2)	18 (4.4)	0.37
Severe abdominal pain	12 (2.9)	5 (1.2)	0.14
Fever	8 (2.0)	9 (2.2)	0.81
Hemorrhage or anemia	16 (3.9)	17 (4.2)	0.86
Other hematologic event	4 (1.0)	3 (0.7)	1.00
New AIDS-defining illness	6 (1.5)	10 (2.5)	0.33
Gastrointestinal bleeding	3 (0.7)	1 (0.2)	0.62
Other gastrointestinal symptoms	3 (0.7)	9 (2.2)	0.09
Renal event	2 (0.5)	3 (0.7)	0.69
Urinary symptoms	0	1 (0.2)	0.50
Dermatologic symptoms	5 (1.2)	6 (1.5)	0.77
Peripheral edema	0	4 (1.0)	0.06
Musculoskeletal symptoms	3 (0.7)	3 (0.7)	1.00
Exhaustion	2 (0.5)	4 (1.0)	0.45
Other	14 (3.4)	12 (2.9)	0.84

* In total, 446 adverse events occurred in the standard-treatment group and 534 adverse events occurred in the intensi-fied-treatment group (P=0.09, by the Wilcoxon rank-sum test). AIDS denotes acquired immunodeficiency syndrome.
† P values were calculated with the use of Fisher's exact test.

HIV infection. Although the results of our study do not support a change in the currently recommended treatment regimens for tuberculous meningitis, enhanced antituberculosis treatment with higher doses of first-line antituberculosis drugs, including intravenous rifampin, or the newer antituberculosis drugs bedaquiline and delamanid, still require investigation. In the

meantime, the key determinants of survival from this dangerous infection are earlier diagnosis and treatment.

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