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Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults

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ABSTRACT

BACKGROUND

Adjunctive glucocorticoids are widely used to treat human immunodeficiency virus (HIV)–associated tuberculous meningitis despite limited data supporting their safety and efficacy.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial involving HIV-positive adults (≥18 years of age) with tuberculous meningitis in Vietnam and Indonesia. Participants were randomly assigned to receive a 6-to-8-week tapering course of either dexamethasone or placebo in addition to 12 months of antituberculosis chemotherapy. The primary end point was death from any cause during the 12 months after randomization.

RESULTS

A total of 520 adults were randomly assigned to receive either dexamethasone (263 participants) or placebo (257 participants). The median age was 36 years; 255 of 520 participants (49.0%) had never received antiretroviral therapy, and 251 of 484 participants (51.9%) with available data had a baseline CD4 count of 50 cells per cubic millimeter or less. Six participants withdrew from the trial, and five were lost to follow-up. During the 12 months of follow-up, death occurred in 116 of 263 participants (44.1%) in the dexamethasone group and in 126 of 257 participants (49.0%) in the placebo group (hazard ratio, 0.85; 95% confidence interval, 0.66 to 1.10; P=0.22). Prespecified analyses did not reveal a subgroup that clearly benefited from dexamethasone. The incidence of secondary end-point events, including cases of immune reconstitution inflammatory syndrome during the first 6 months, was similar in the two trial groups. The numbers of participants with at least one serious adverse event were similar in the dexamethasone group (192 of 263 participants [73.0%]) and the placebo group (194 of 257 participants [75.5%]) (P=0.52).

CONCLUSIONS

Among HIV-positive adults with tuberculous meningitis, adjunctive dexamethasone, as compared with placebo, did not confer a benefit with respect to survival or any secondary end point. (Funded by the Wellcome Trust; ACT HIV ClinicalTrials.gov number, NCT03092817.)

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*A full list of the ACT HIV investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Tuberculous meningitis is a serious complication caused by *Mycobacterium tuberculosis*. This condition is especially common in human immunodeficiency virus (HIV)–positive persons; mortality among such persons can exceed 50% despite effective antituberculosis chemotherapy.[1-4]

Death and neurologic sequelae from tuberculous meningitis are associated with intracerebral inflammation.[5] Attempts to improve outcomes by controlling inflammation with adjunctive glucocorticoids were first reported in 1952.[6] In 2004, a trial involving 545 Vietnamese adolescents and adults showed that adjunctive dexamethasone reduced mortality from tuberculous meningitis,[3] although the benefit was uncertain in the 98 HIV-positive persons enrolled in the trial.

Before the current trial, the number of HIV-positive adults with tuberculous meningitis who had ever been enrolled in trials of adjunctive glucocorticoids remained at 98. A systematic review and meta-analysis of glucocorticoids for tuberculous meningitis concluded that their benefit in HIV-positive persons was uncertain.[7] However, many treatment guidelines recommend glucocorticoids for everyone with tuberculous meningitis, regardless of HIV status.[8-10] Trials of adjunctive glucocorticoids involving HIV-positive persons with other forms of tuberculosis and other opportunistic infections highlight the potential risks of this approach. Glucocorticoids have been associated with an increased risk of HIV-associated cancers, especially Kaposi's sarcoma,[11,12]; among patients with HIV-associated cryptococcal meningitis, adjunctive dexamethasone was associated with increased risks of death, disability, and adverse events.[13]

Adjunctive glucocorticoids are widely used for the treatment of HIV-associated tuberculous meningitis, but with little evidence of their safety or efficacy. We therefore conducted a double-blind, randomized, placebo-controlled trial (Adjunctive Corticosteroids for Tuberculous Meningitis in HIV-Positive Adults [ACT HIV]) to determine whether adjunctive dexamethasone would reduce mortality among HIV-positive adults with tuberculous meningitis.

METHODS

TRIAL DESIGN AND CONDUCT

The trial methods, conduct, and analysis are described in the published protocol[14] and statistical analysis plan,[15] which are also available with the full text of this article at NEJM.org. The trial was designed and conducted by the investigators, supported by Oxford University Clinical Research Unit Clinical Trials Units in Vietnam and Indonesia. The funder (Wellcome Trust) had no role in the design or conduct of the trial. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

TRIAL SITES AND PARTICIPANTS

We recruited participants from the Hospital for Tropical Diseases and Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease in Ho Chi Minh City, Vietnam, and from Dr. Cipto Mangunkusumo National Reference Hospital and Persahabatan National Respiratory Referral Hospital in Jakarta, Indonesia. Participants were 18 years of age or older, were HIV-positive (either newly or previously diagnosed), and had received a clinical diagnosis of tuberculous meningitis (≥5 days of meningitis symptoms and cerebrospinal fluid [CSF] abnormalities), with antituberculosis chemotherapy either planned or started by the attending physician. Participants were classified as having definite, probable, or possible tuberculous meningitis, according to published criteria (Table S1 in the Supplementary Appendix, available at NEJM.org).[16] Persons were ineligible if another brain infection was suspected, if antituberculosis chemotherapy had been received for more than 6 consecutive days before enrollment, if systemic glucocorticoids had been received for more than 3 consecutive days before enrollment, or if systemic glucocorticoids were considered to be mandatory or contraindicated for any reason.

TRIAL OVERSIGHT

Written informed consent to enter the trial was obtained from all the participants or a relative if they were incapacitated. If capacity returned, consent was obtained from the participant. Trial approvals were obtained from local and national ethics and regulatory authorities in Vietnam and Indonesia and from the Oxford Tropical Research Ethics Committee in the United Kingdom (Text S1 in the Supplementary Appendix). An independent data monitoring committee reviewed data at 6-month intervals until 303 participants had undergone randomization and annually thereafter.

RANDOMIZATION AND TRIAL GROUPS

Participants were randomly assigned in a 1:1 ratio to receive dexamethasone or placebo, with stratification according to participating site and modified Medical Research Council (MRC) tuberculous meningitis severity grade.[17] Participants with grade I disease had a score on the Glasgow Coma Scale of 15 (range, 3 to 15, with higher scores indicating better status) with no focal neurologic signs; those with grade II disease had either a score of 11 to 14 or a score of 15 with focal neurologic signs; and those with grade III disease had a score of 10 or less. The randomization list was computer-generated on the basis of randomly permuted blocks of 4 and 6 (probability, 0.75 and 0.25, respectively). Randomization of the participants was performed by trained clinical staff, with 24-hour availability, using Web-based software.

TRIAL INTERVENTIONS

All the participants received standard-of-care antituberculosis chemotherapy and antiretroviral therapy (ART) according to national guidelines (Text S2). In participants who had not previously received ART, ART was started approximately 6 to 8 weeks after the initiation of antituberculosis chemotherapy. All the participants were randomly assigned to receive dexamethasone or placebo; the dexamethasone regimen followed the regimen previously shown to reduce mortality from tuberculous meningitis (Text S3).[3] Blinded trial-substance packages (fully made-up and labeled packs) contained either dexamethasone or matching placebo. All the participants and investigators were unaware of the trial-group assignments. Participants with grade II or III disease received intravenous administration for 4 weeks (0.4 mg per kilogram of body weight per day for the first week, 0.3 mg per kilogram per day for the second week, 0.2 mg per kilogram per day for the third week, and 0.1 mg per kilogram per day for the fourth week) and then oral administration for 4 weeks, starting at 4 mg per day and decreasing by 1 mg each week. Participants with grade I disease received intravenous administration for 3 weeks (0.3 mg per kilogram per day for the first week, 0.2 mg per kilogram per day for the second week, and 0.1 mg per kilogram per day for the third week) and then oral administration for 3 weeks, starting at 3 mg per day and decreasing by 1 mg each week. Adherence to dexamethasone or placebo was ensured with the use of supervised intake for inpatients and encouraged by detailed instructions at discharge; adherence checks were performed at follow-up visits or through telephone calls.

END POINTS

The primary end point was death from any cause during the 12 months after randomization. Secondary end points were neurologic disability (defined by a score on the modified Rankin scale of 3 to 5) (Table S2) at 12 months, neurologic immune reconstitution inflammatory syndrome (IRIS) during the first 6 months, and the following end points assessed over 12 months after randomization: first new neurologic event or death, new acquired immunodeficiency syndrome (AIDS)–defining event or death, HIV-associated cancer, use of open-label glucocorticoid treatment for any reason, shunt surgery, and serious adverse events.[15]

ASSESSMENTS AND INVESTIGATIONS

Participants underwent clinical assessments at baseline; at days 3, 7, 10, 14, 21, and 30; and monthly until month 12. Assessment included the score on the Glasgow Coma Scale, modified MRC disease-severity grade, and details of clinical and adverse events and other interventions. Participants were monitored daily while in the hospital, and serious adverse events were reported to local and national regulators. In participants for whom systemic glucocorticoids were considered to be necessary by the treating clinician after randomization, dexamethasone or placebo was discontinued (with doses already received remaining blinded) and glucocorticoids were commenced.

Baseline blood tests included full blood count; levels of sodium, potassium, creatinine, alanine transaminase (ALT), and bilirubin; hepatitis B and C; CD4 count; and HIV viral load. Lumbar CSF was sampled at baseline and tested for pyogenic bacteria (gram stain and culture) and cryptococcal antigen. At least 6 ml of CSF (if available) was used for Ziehl–Neelsen smear microscopy, either Xpert MTB/RIF or Xpert MTB/RIF Ultra, and mycobacterial culture (mycobacteria growth indicator tube [MGIT]) according to standard procedures.[18] Phenotypic drug-susceptibility testing was performed with the use of a BACTEC MGIT SIRE kit (Becton, Dickinson).[18]

STATISTICAL ANALYSIS

On the basis of previous trials,[3,19] we assumed a target hazard ratio for death (dexamethasone group vs. placebo group) of 0.69 and a 9-month mortality of 40% in the dexamethasone group. We estimated that 520 HIV-positive participants with tuberculous meningitis would be required for the trial to have 80% power at a two-sided 5% significance level, with allowance for 5% loss to follow-up.

Unless otherwise stated, the analysis followed a prespecified published plan (Texts S4 and S5).[15] Briefly, intention-to-treat and per-protocol analyses were performed for the primary and secondary end points. The intention-to-treat population included all the participants who underwent randomization, even if no dexamethasone or placebo was received. The per-protocol population included all the participants who underwent randomization excluding those who subsequently did not meet the inclusion criteria or who met exclusion criteria at enrollment, those with a final diagnosis other than tuberculous meningitis, and those who received either less than 7 days of dexamethasone or placebo or less than 30 days of antituberculosis chemotherapy for reasons other than death.

Baseline characteristics were summarized according to trial group for the intention-to-treat and per-protocol populations. The primary analysis was a Cox proportional-hazards regression model with trial group as the only covariate.[15] We assessed between-group differences in six prespecified subgroups defined according to MRC disease-severity grade, diagnostic category (definite, probable, or possible tuberculous meningitis), *LTA4H* genotype (Text S6), antituberculosis-drug resistance, ART status at enrollment, and CD4 count. We repeated analyses with adjustment for MRC disease-severity grade. Neurologic disability at 12 months was compared with the use of proportional-odds logistic regression. All other secondary end points were compared with the use of Cox proportional-hazards models and cumulative event probabilities (nonparametric Kaplan–Meier estimates, and Aalen–Johansen estimates in case death was a competing risk). No correction for multiple testing was made, and confidence intervals should not be interpreted as results from hypothesis tests. The number of participants with any serious adverse event was compared by means of a chi-square test. Data were analyzed with the use of R software, version 4.1.1 (R Core Team, 2021).[20]

RESULTS

TRIAL POPULATION

From May 25, 2017, to April 29, 2021, a total of 520 adults were randomly assigned to receive either dexamethasone or placebo. Eleven participants (2.1%) did not complete 12 months of follow-up owing to withdrawal from the trial (6 participants) or loss to follow-up (5 participants). An additional 22 participants received dexamethasone or placebo for fewer than 7 days. Overall, 33 participants (6.3%) were excluded from the per-protocol population (Fig. 1). We did not calculate an overall estimate of adherence to dexamethasone or placebo.

BASELINE CHARACTERISTICS

Participant characteristics at baseline were balanced between the trial groups (Table 1 and Table S3) and were broadly representative of populations of persons with tuberculous meningitis (Table S4). The median age of the participants was 36 years (interquartile range, 30 to 41). Disease was generally mild or moderate (447 of 520 participants [86.0%] with grade 1 or 2 disease). A total of 186 of 520 participants (35.8%) had newly diagnosed HIV, 255 of 520 (49.0%) had not previously received ART, and 251 of 484 (51.9%) had CD4 counts of 50 cells per cubic millimeter or less. The antituberculosis chemotherapy regimens at enrollment included rifampin in 478 of 514 participants (93.0%), isoniazid in 485 of 514 (94.4%), pyrazinamide in 471 of 514 (91.6%), and ethambutol in 364 of 514 (70.8%). Multidrug resistance was identified in 16 participants (10 in the dexamethasone group and 6 in the placebo group) and treated according to national guidelines.

PRIMARY END POINT

Death occurred in 116 of 263 participants (44.1%) in the dexamethasone group and in 126 of 257 participants (49.0%) in the placebo group (hazard ratio, 0.85; 95% confidence interval [CI], 0.66 to 1.10; P=0.22) (Fig. 2A and 2B and Table 2). Similar results were observed with adjustment for MRC disease-severity grade (Table S5). A beneficial effect of dexamethasone was not observed in any prespecified subgroup in the

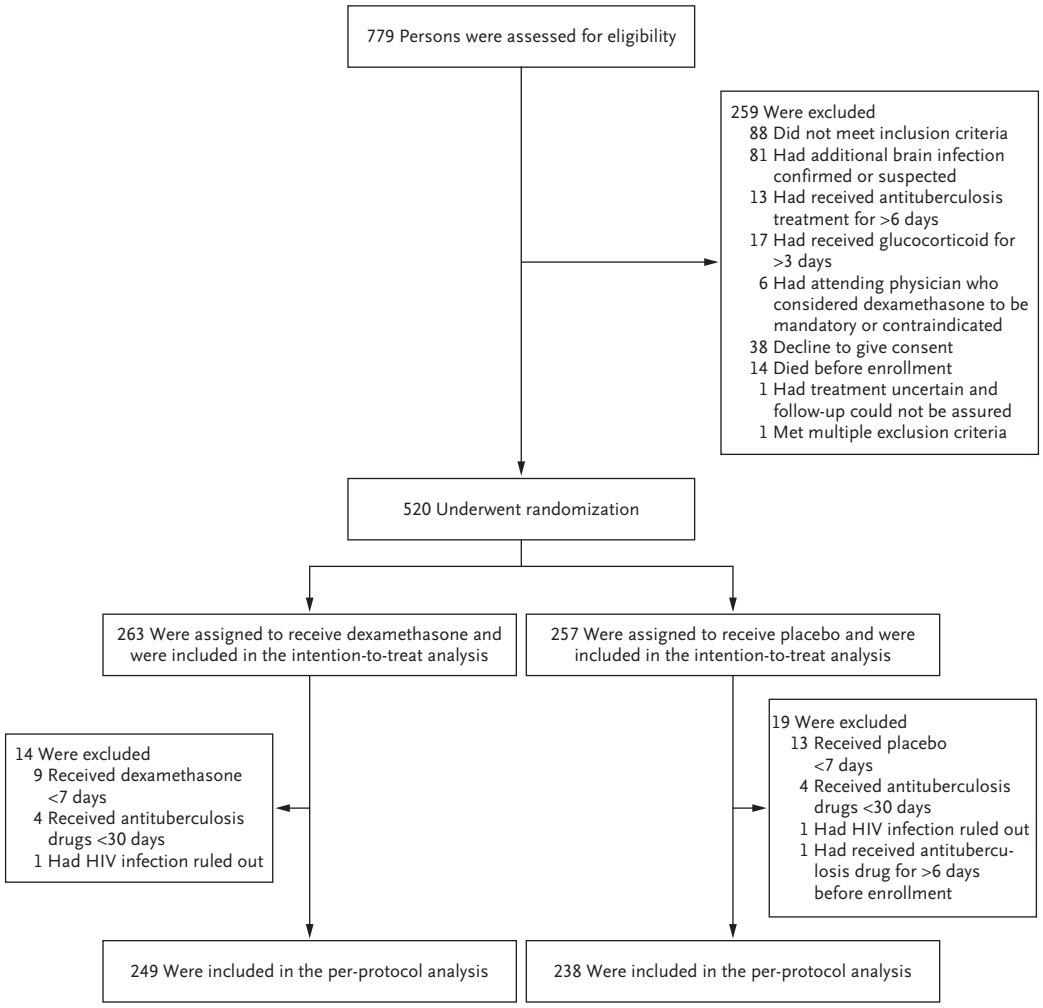

Figure 1. Screening, Enrollment, and Randomization.

Among the participants in the intention-to-treat population, in the dexamethasone group, two were lost to follow-up and five withdrew from the trial before 12 months, whereas in the placebo group, three were lost to follow-up and one withdrew from the trial before 12 months. The participants who were excluded after randomization because they received dexamethasone or placebo for less than 7 days or received antituberculosis drugs for less than 30 days do not include the participants who died before receiving these substances for the specified intervals. HIV denotes human immunodeficiency virus.

intention-to-treat population (Table 2 and Figs. S2 through S8) and was not observed in the per-protocol population or subgroups of that population (Tables S5 and S6 and Fig. S9).

SECONDARY END POINTS

The incidence of secondary end-point events was similar in the two trial groups in both the intention-to-treat and the per-protocol populations (Tables S7 and S8). In the dexamethasone and placebo groups, there was a similar likelihood of neurologic disability (odds ratio, 1.31; 95% CI, 0.80 to 2.14), new neurologic events or death (hazard ratio, 0.85; 95% CI, 0.67 to 1.08), and AIDS-defining events or death (hazard ratio, 0.87; 95% CI, 0.68 to 1.12) (Table S9).

Among participants who had not previously received ART, the median time to initiation of ART was 31 days (interquartile range, 15 to 53) in 81 participants who received dexamethasone and 36 days (interquartile range, 16 to 61) in 66 participants who received placebo. Neurologic

Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

Characteristic	Total (N=520)	Dexamethasone (N=263)	Placebo (N=257)
Median age (IQR) — yr	36 (30–41)	36 (29–41)	36 (30–42)
Male sex — no. (%)	396 (76.2)	208 (79.1)	188 (73.2)
Diagnostic category — no. (%)†			
Definite tuberculous meningitis	212 (40.8)	108 (41.1)	104 (40.5)
Probable tuberculous meningitis	253 (48.7)	129 (49.0)	124 (48.2)
Possible tuberculous meningitis	52 (10.0)	24 (9.1)	28 (10.9)
Not tuberculous meningitis‡	0	0	0
Unknown§	3 (0.6)	2 (0.8)	1 (0.4)
Modified MRC disease-severity grade — no. (%)¶			
I	196 (37.7)	99 (37.6)	97 (37.7)
II	251 (48.3)	125 (47.5)	126 (49.0)
III	73 (14.0)	39 (14.8)	34 (13.2)
Median score on the Glasgow Coma Scale (IQR)‖	14 (12–15)	14 (12–15)	14 (12–15)
CSF microbiologic tests — no./total no. (%)			
Positive Ziehl–Neelsen stain	100/504 (19.8)	52/255 (20.4)	48/249 (19.3)
Positive Xpert MTB/RIF test	107/401 (26.7)	53/204 (26.0)	54/197 (27.4)
Positive Xpert MTB/RIF Ultra test**	46/113 (40.7)	22/56 (39.3)	24/57 (42.1)
Positive mycobacterial culture	148/508 (29.1)	77/256 (30.1)	71/252 (28.2)
ART status at enrollment — no. (%)			
No previous ART	255 (49.0)	133 (50.6)	122 (47.5)
ART for >3 mo	104 (20.0)	46 (17.5)	58 (22.6)
ART of undetermined duration††	106 (20.4)	58 (22.1)	48 (18.7)
Unknown status or missing data	55 (10.6)	26 (9.9)	29 (11.3)
CD4 cell count at enrollment — no./total no. (%)			
≤50 per cubic millimeter	251/484 (51.9)	126/244 (51.6)	125/240 (52.1)
51 to 100 per cubic millimeter	89/484 (18.4)	45/244 (18.4)	44/240 (18.3)
101 to 200 per cubic millimeter	71/484 (14.7)	36/244 (14.8)	35/240 (14.6)
>200 per cubic millimeter	73/484 (15.1)	37/244 (15.2)	36/240 (15.0)

* Percentages may not total 100 because of rounding. ART denotes antiretroviral therapy, CSF cerebrospinal fluid, IQR interquartile range, and MRC Medical Research Council.

† Definite tuberculous meningitis was defined as a positive CSF Ziehl–Neelsen stain for acid-fast bacilli, a positive CSF Xpert MTB/RIF or MTB/RIF Ultra test, or a positive CSF mycobacterial culture. Probable or possible tuberculous meningitis was defined according to the uniform case definition.[16]

‡ No participants had another brain infection that was microbiologically confirmed by means of a positive CSF India ink stain, a positive test for CSF or blood cryptococcal antigen, a positive CSF bacterial gram stain, a positive CSF bacterial culture, or a positive CSF viral or helminth polymerase-chain-reaction test.

§ For three participants with an unknown diagnostic category (two in the dexamethasone group and one in the placebo group), clinical criteria for a diagnosis of tuberculous meningitis were met[16]; however, the total diagnostic score was less than 6 (i.e., below the threshold for "possible" tuberculous meningitis).

¶ Participants with grade I disease had a score on the Glasgow Coma Scale of 15 (range, 3 to 15, with higher scores indicating better status) with no focal neurologic signs; those with grade II disease had either a score of 11 to 14 or a score of 15 with focal neurologic signs; and those with grade III disease had a score of 10 or less.

‖ Data were available for 515 participants: 259 in the dexamethasone group and 256 in the placebo group.

** The availability of data for the Xpert MTB/RIF Ultra test varied among sites and over time, and data became more widely available only during the last 12 months of the trial.

†† Whether these participants had received ART for 3 months or less or for more than 3 months was unclear.

IRIS events occurred during administration of dexamethasone or placebo in 8 participants; overall, such events occurred during the first 6 months after randomization in 11 of 263 participants (4.2%) who received dexamethasone and in 9 of 257 participants (3.5%) who received placebo (hazard ratio, 1.11; 95% CI, 0.46 to 2.69). Open-label glucocorticoids were prescribed to 70 of 263 participants (26.6%) in the dexamethasone group and 68 of 257 participants (26.5%) in the placebo group; reasons for and time until use of open-label glucocorticoids are provided in Table S10. The time to initiation of treatment with open-label glucocorticoids for any reason was similar in the two trial groups (hazard ratio, 0.97; 95% CI, 0.69 to 1.35). No HIV-associated cancers occurred by 12 months, and only 1 participant (in the dexamethasone group) underwent ventriculoperitoneal shunt insertion.

No beneficial effect of dexamethasone was identified in the planned subgroup analysis of selected secondary outcomes (Tables S11 and S12 and Figs. S11 through S20). The possible exception was among the 52 participants with possible tuberculous meningitis in the intention-to-treat population, with those in the dexamethasone group having a lower incidence of new neurologic events or death than those in the placebo group.

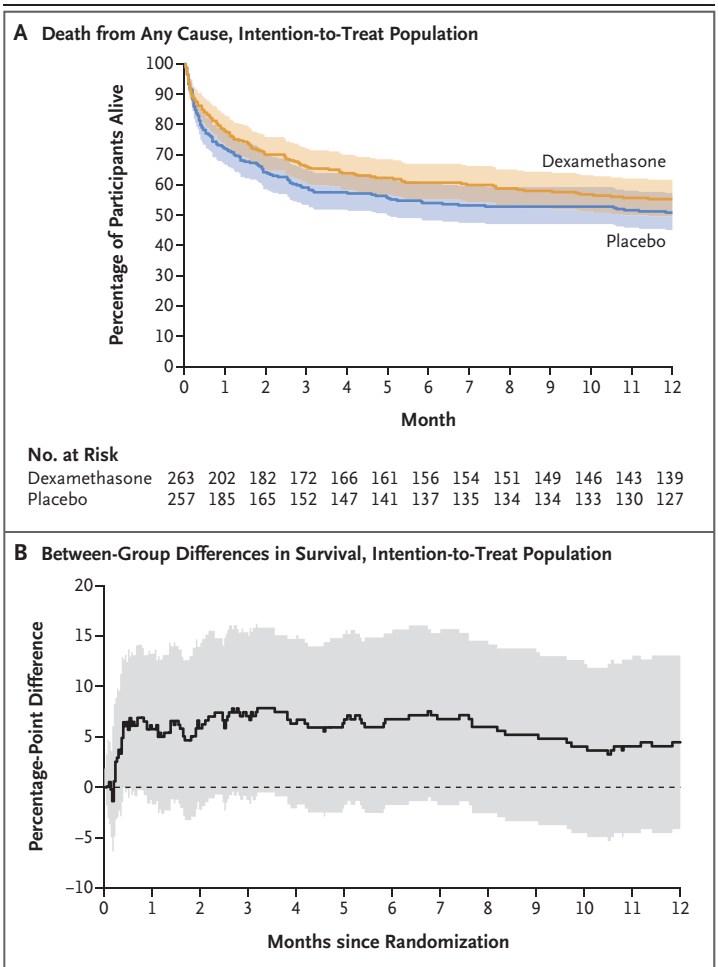

Figure 2. Death from Any Cause during 12 Months after Randomization.
Panel A shows death from any cause during the first 12 months after randomization in the intention-to-treat population. Panel B shows between-group differences in survival (the value in the dexamethasone group minus the value in the placebo group) in the intention-to-treat population. In both panels, the shading represents 95% confidence intervals.

SERIOUS ADVERSE EVENTS

The numbers of participants with at least one serious adverse event were similar in the dexamethasone group (192 of 263 [73.0%]) and the placebo group (194 of 257 [75.5%]) (P=0.52) (Table 3 and Tables S13 and S14). Fewer participants had serious neurologic adverse events in the dexamethasone group (95 of 263 [36.1%]) than in the placebo group (115 of 257 [44.7%]). These serious neurologic adverse events (275 events in 210 participants) were predominantly depressed consciousness (149 events) and new focal neurologic signs (45 events). Gastrointestinal bleeding events and other adverse events that were possibly, probably, or definitely related to glucocorticoids occurred with a similar incidence in the two trial groups (Table S15). Similarly, the incidence of clinical grade 3 or 4 adverse events (Table S16), adverse events leading to interruptions in antituberculosis chemotherapy or ART (Table S17), and grade 3 or 4 laboratory abnormalities (Table S18) was similar in the two groups, with the exception of episodes of high ALT levels, which were more likely in the dexamethasone group (36 of 263 participants [13.7%]) than in the placebo group (20 of 257 participants [7.8%]).

DISCUSSION

We were unable to confirm a benefit of adjunctive dexamethasone in HIV-positive adults with tuberculous meningitis with respect to survival or any prespecified secondary end point. Planned

Table 2. Death from Any Cause in Prespecified Subgroups in the Intention-to-Treat Population.*

Subgroup	Dexamethasone (N=263)	Placebo (N=257)	Hazard Ratio (95% CI)
	no. of deaths/no. of participants		
Overall	116/263	126/257	0.85 (0.66–1.10)†
Modified MRC disease-severity grade			
I	22/99	28/97	0.72 (0.41–1.25)
II	60/125	68/126	0.82 (0.58–1.16)
III	34/39	30/34	1.03 (0.63–1.69)
Diagnostic category			
Definite tuberculous meningitis	48/108	49/104	0.90 (0.61–1.35)
Probable tuberculous meningitis	61/129	61/124	0.91 (0.64–1.30)
Possible tuberculous meningitis	5/24	15/28	0.34 (0.12–0.94)
LTA4H genotype‡			
TT	12/25	11/26	1.06 (0.47–2.41)
CT	49/117	59/114	0.72 (0.49–1.05)
CC	38/84	36/80	1.04 (0.66–1.63)
Antituberculosis-drug resistance§			
MDR or rifampin monoresistance	7/10	5/6	0.66 (0.21–2.11)
Isoniazid resistance without MDR	6/14	13/20	0.56 (0.21–1.49)
No or other resistance	22/52	13/45	1.58 (0.79–3.13)
ART status at enrollment			
No previous ART	64/133	64/122	0.85 (0.60–1.21)
>3 Mo of ART	20/46	26/58	0.96 (0.54–1.72)
ART of undetermined duration	19/58	19/48	0.80 (0.42–1.51)
CD4 cell count at enrollment			
≤50 per cubic millimeter	67/126	67/125	0.96 (0.69–1.35)
51–100 per cubic millimeter	12/45	19/44	0.52 (0.25–1.06)
101–200 per cubic millimeter	14/36	13/35	1.04 (0.49–2.22)
>200 per cubic millimeter	11/37	15/36	0.70 (0.32–1.52)

* The primary end point was death from any cause during the first 12 months after randomization (i.e., the time from randomization to death during the first 12 months of follow-up). This table shows the results from the Cox proportional-hazards regression model. The primary effect measure was the resulting hazard ratio comparing dexamethasone and placebo with a corresponding two-sided 95% confidence interval. In the intention-to-treat population, trial group was the only covariate. We also report the hazard ratio with the modified MRC disease-severity grade included as a stratum variable. In subgroup analyses, a separate Cox model was fitted for each value of the subgroup. The proportional-hazards assumption was tested for each model and was not violated. MDR denotes multidrug resistance.
† P=0.22.
‡ The rationale for the *LTA4H* genotype subgroup is provided in Text S6 in the Supplementary Appendix.
§ Results are given for a subgroup of participants with a positive CSF mycobacterial culture at baseline.

subgroup analyses did not identify a subpopulation that clearly benefited from dexamethasone. The incidence of serious adverse events was similar in the two trial groups.

In dexamethasone-treated HIV-negative adults with tuberculous meningitis, survival has been associated previously with elevated CSF concentrations of inflammatory cytokines,[5] which suggests that dexamethasone benefits patients with excessive intracerebral inflammation. Among persons with tuberculous meningitis, CSF concentrations of inflammatory cytokines are higher in HIV-positive persons than in HIV-negative persons,[21] yet our trial findings indicate little

Table 3. Serious Adverse Events.*

Event	Dexamethasone (N=263)		Placebo (N=257)	
	no. of participants (%)	*no. of events*	*no. of participants (%)*	*no. of events*
Any selected serious adverse event	192 (73.0)	486	194 (75.5)	442
Nervous system disorder	95 (36.1)	128	115 (44.7)	147
Infection or infestation	60 (22.8)	79	50 (19.5)	63
Metabolism or nutrition disorder	51 (19.4)	66	59 (23.0)	68
Respiratory, thoracic, or mediastinal disorder	39 (14.8)	40	37 (14.4)	39
Hepatobiliary disorder	38 (14.4)	44	29 (11.3)	29
Gastrointestinal disorder	32 (12.2)	33	21 (8.2)	25
Blood or lymphatic system disorder	20 (7.6)	23	17 (6.6)	17
Investigation†	14 (5.3)	14	9 (3.5)	9
General disorder or administration-site condition	14 (5.3)	15	7 (2.7)	7
Vascular disorder	10 (3.8)	10	11 (4.3)	11
Skin or subcutaneous-tissue disorder	12 (4.6)	13	5 (1.9)	6
Cardiac disorder	7 (2.7)	7	4 (1.6)	4
Renal or urinary disorder	4 (1.5)	4	6 (2.3)	6
Musculoskeletal or connective-tissue disorder	4 (1.5)	4	2 (0.8)	2
Psychiatric disorder	3 (1.1)	3	1 (0.4)	1
Eye disorder	0	0	3 (1.2)	3
Endocrine disorder	1 (0.4)	1	2 (0.8)	2
Ear or labyrinth disorder	1 (0.4)	1	1 (0.4)	1
Injury, poisoning, or procedural complication	1 (0.4)	1	1 (0.4)	1
Immune system disorder	0	0	1 (0.4)	1

* Events were summarized according to the system organ class of the *Medical Dictionary for Regulatory Activities* hierarchy. The number of participants with any adverse events and specific events were summarized and compared between the two trial groups on the basis of chi-square tests or (if the expected number in one of the table cells was <1) Fisher's exact test.

† Abnormal results of investigations were reported.

benefit of adjunctive dexamethasone on survival among HIV-positive persons with tuberculous meningitis. These observations suggest that intracerebral inflammation in HIV-associated tuberculous meningitis may be qualitatively different from that in tuberculous meningitis not associated with HIV or that the mechanisms leading to death are different in HIV-positive persons and HIV-negative persons.

Our trial population was profoundly immunosuppressed: 51.9% presented with a CD4 count of 50 cells per cubic millimeter or less, and 49.0% had not previously received ART. These persons are at risk for other opportunistic infections, which might alter the effect of dexamethasone on outcome and increase the risk of adverse events. In addition, many participants were at risk for IRIS after starting ART, the neurologic inflammatory complications of which can be fatal or disabling.[22] Glucocorticoids were previously shown to prevent IRIS in persons with nonneurologic tuberculosis,[23] but we found that dexamethasone did not reduce the incidence of IRIS or the timing or use of open-label glucocorticoid treatment after randomization. However, dexamethasone doses were usually low by the time that ART was initiated (median, 33 days after randomization), which may have reduced the ability of dexamethasone to prevent IRIS.

Our trial has several limitations. First, we cannot exclude the possibility that a larger trial may have shown a smaller mortality reduction

than we hypothesized. The effect size that was observed (hazard ratio, 0.85; 95% CI, 0.66 to 1.10) was less than anticipated (hazard ratio, 0.69), although it was similar to that in the HIV-positive population in our previous trial (relative risk, 0.86; 95% CI, 0.52 to 1.41).[3] Second, 138 participants (26.5%) were given open-label glucocorticoids at some time during treatment, and although the incidence and timing of their use were similar in the two trial groups and the trial-group assignments remained masked, the additional glucocorticoids may have obscured outcome differences between the two groups. Third, the findings may not be generalizable to better-resourced settings, with patients with less advanced HIV and wider access to ventriculoperitoneal shunting for hydrocephalus, a common life-threatening complication of tuberculous meningitis.[24]

A strength of our trial is that it examines adjunctive glucocorticoids exclusively in HIV-positive adults with tuberculous meningitis, which increases the available data from this important population by more than five times. The trial was pragmatic, enrolling all those with suspected tuberculous meningitis warranting antituberculosis drugs and therefore generating findings of real-world relevance; in non-trial settings, a high proportion of patients are treated for tuberculous meningitis without bacteriologic confirmation. Finally, the trial had high retention, with only five participants lost to follow-up.

Given the high mortality among persons with HIV-associated tuberculous meningitis and the high incidence of inflammatory intracerebral complications, there is an ongoing need to explore alternative antiinflammatory strategies. These might include more targeted immunosuppression (e.g., against tumor necrosis factor α or interleukin-1) that may be superior to glucocorticoids for the prevention or treatment of inflammatory complications. Case reports and small case series have shown a potential role for infliximab,[25] thalidomide,[26] and anakinra[27] in some patients with tuberculous meningitis. Evaluation of these agents in clinical trials is needed.

In this trial, we did not find a benefit of adjunctive dexamethasone in HIV-positive adults with tuberculous meningitis with respect to survival or any secondary end point over a period of 12 months. The mortality associated with tuberculous meningitis among HIV-positive persons remains unacceptably high, which emphasizes the global importance of enhanced detection and early treatment of HIV and tuberculosis.

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APPENDIX

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