



STUDY PROTOCOL

REVISED **A statistical analysis plan for the Adjunctive Corticosteroids for Tuberculous meningitis in HIV-positive adults (ACT HIV) clinical trial [version 2; peer review: 3 approved]**

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Abstract

TBM is the most severe form of tuberculosis. Clinical trial data are required to provide an evidence base for adjunctive dexamethasone in HIV-positive individuals with TBM, and to guide clinical practice. This document details the planned analyses at 12 months post randomisation for the ACT HIV clinical trial (NCT03092817); 'a randomised double-blind placebo-controlled trial of adjunctive dexamethasone for the treatment of HIV co-infected adults with tuberculous meningitis (TBM)'. The primary endpoint of the ACT HIV trial is death (from any cause) over the first 12 months after randomisation. This statistical analysis plan expands upon and updates the analysis plan outlined in the published study protocol.

Keywords

Tuberculous meningitis, human immunodeficiency virus, corticosteroids, clinical trial, analysis plan



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REVISED Amendments from Version 1

The update clarifies that the per protocol population will not include individuals subsequently found to have not met all inclusion criteria, or to have met any exclusion criteria, at the time of enrolment. This had not been stated in the previous version.

Any further responses from the reviewers can be found at the end of the article

Scope of document

This document details the planned analyses at 12 months post randomisation for the ACT HIV clinical trial (NCT03092817); ‘a randomised double-blind placebo-controlled trial of adjunctive dexamethasone for the treatment of HIV co-infected adults with tuberculous meningitis (TBM)’. A further analysis will follow at 24 months post randomisation. This statistical analysis plan expands upon and updates the analysis plan outlined in the published study protocol¹.

Background and rationale for study

The ACT HIV clinical trial is a randomised double-blind placebo-controlled trial of adjunctive dexamethasone for the treatment of tuberculous meningitis (TBM) in HIV-positive adults. TBM is the most severe form of tuberculosis, with mortality approaching 50% in people living with HIV^{2–5} despite the best available appropriate anti-TB chemotherapy.

TBM develops when *Mycobacterium tuberculosis*, initially acquired via the respiratory route, disseminates via the blood to form a secondary focus in the brain. Rupture of this secondary focus into the subarachnoid space results in TBM, with the consequent host inflammatory response being important for bacterial killing, but also responsible for the pathological complications and often-fatal consequences of the infection.

Adjunctive anti-inflammatory corticosteroid therapy, which may control excessive host inflammation, has long been considered to have a role in TBM treatment⁶. In 2004, a landmark clinical trial in Vietnam demonstrated that a 6–8 week (duration dependent on Modified Research Council [MRC] TBM severity grade) tapering course of dexamethasone reduced mortality in adults and adolescents with TBM⁴. In this study, only 98/545 (18.0%) individuals were HIV positive, which was too small to determine if dexamethasone benefited this important sub-group of patients. No other trials have been published since 2004 that examine whether corticosteroids improve outcomes from TBM in HIV-positive adults.

How dexamethasone might confer its clinical benefit on those with TBM remains uncertain. A recent study of cerebrospinal fluid (CSF) cytokines in TBM suggested that HIV-positive individuals have higher cytokine concentrations than HIV-negative individuals⁷. Whether adjunctive dexamethasone is more or less likely to be beneficial in HIV-positive individuals with TBM is not known. There are an estimated 100,000 cases of TBM globally each year⁸, many associated with HIV.

Clinical trial data are required to provide an evidence base for adjunctive dexamethasone in HIV-positive individuals with TBM, and to guide clinical practice.

Structure and status of trial

The ACT HIV trial commenced recruitment on 25th May 2017. By April 29th 2021, the predefined sample size of 520 adults with TBM and HIV co-infection had been enrolled from four hospitals in Vietnam and Indonesia: the Hospital for Tropical Diseases (HTD) and Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease (PNT) in Ho Chi Minh City, Vietnam, and Cipto Mangunkusumo Hospital and Persahabatan Hospital in Jakarta, Indonesia. Detailed enrolment criteria for ACT HIV, including consent and ethical approvals, are described in the published trial protocol¹.

Once enrolled, study participants were randomised to dexamethasone or placebo (a double-blinded allocation), with this intervention termed ‘study drug’. Randomisation was stratified by TBM MRC severity score and by hospital. Participants with MRC grade 1 TBM received a 6-week tapering course of study drug, whereas participants with MRC grades 2 or 3 received an 8-week tapering course of study drug. Study drug regimens are shown in Table 1. Participants then underwent clinical assessments at baseline, at days 3, 7, 10, 14, 21, and 30, monthly until month 12, and then 3-monthly until 24 months. Baseline assessment included blood tests, chest X-ray, lumbar puncture, and brain imaging.

ACT HIV has numerous sub-studies, as described in the protocol¹. Key follow up outcomes include survival, disability, and severe adverse events; especially neurological events, events requiring corticosteroids, HIV-associated complications (malignancies, immune reconstitution inflammatory syndrome [IRIS]), and adverse events considered related to dexamethasone.

Table 1. Study drug treatment regimen following randomisation.

	MRC Grade I Daily dexamethasone dose/route	MRC Grades II and III Daily dexamethasone dose/route
Week 1	0.3 mg/kg/24 hrs IV	0.4 mg/kg/24 hrs IV
Week 2	0.2 mg/kg/24 hrs IV	0.3 mg/kg/24 hrs IV
Week 3	0.1 mg/kg/24 hrs IV	0.2 mg/kg/24 hrs IV
Week 4	3mg/24 hrs oral	0.1 mg/kg/24 hrs IV
Week 5	2mg/24 hrs oral	4 mg/24 hrs oral
Week 6	1 mg/24 hrs oral	3 mg/24 hrs oral
Week 7	Stop	2 mg/24 hrs oral
Week 8		1 mg/24 hrs oral

IV=intravenous. MRC=Modified Research Council.

Trial endpoints

Primary endpoint

The primary endpoint of the ACT HIV trial is death (from any cause) over the first 12 months after randomisation.

Secondary endpoints

The secondary endpoints of the ACT HIV trial are as follows:

1. Neurological disability at 12 months from randomisation
2. First new neurological event or death over the first 12 months after randomisation
3. Neurological IRIS events over the first 6 months after randomisation
4. New AIDS-defining event or death over the first 12 months after randomisation
5. HIV-associated malignancy by 12 months from randomisation
6. Use of open-label corticosteroid treatment for any reason over the first 12 months after randomisation
7. Requirement for shunt surgery by 12 months
8. Any serious adverse events reported by 12 months from randomisation

Individuals included in analysis

Primary analysis

The primary analysis includes all randomised participants. As such, an intention-to-treat (ITT) analysis will be performed for the primary and secondary endpoints. Participants will remain included in this analysis even if no study drug was received after randomisation.

Per protocol analysis

The per protocol (PP) analysis includes all randomised patients with the exception of those subsequently found to have not met all inclusion criteria, or to have met any exclusion criteria, at the time of enrolment, those with a final diagnosis other than TBM (confirmed by microbiology, serology, or histopathology), and those who received less than 7 days of administration of the randomised study drug for reasons other than death, or less than 30 days of anti-tuberculosis drugs for any reason other than death. Trial inclusion and exclusion criteria are listed in the trial protocol¹. A per protocol analysis will be performed for all primary and secondary endpoints.

Statistical software

Data will be analysed using the program R⁹, using the most up to date version available at the time of final analysis.

Baseline characteristics

Definition: The following baseline characteristics will be summarised by treatment arm for ITT and PP analyses: age, sex, country, site, diagnostic category (definite, probable,

possible, or not TBM by Marais criteria¹⁰), history of previous tuberculosis treatment, chest X-ray findings (no TB/miliary TB/pulmonary TB), enrolment MRC TBM grade, enrolment Glasgow coma score (GCS), weight (kg), duration of symptoms, cranial nerve palsy, hemiplegia, para/tetraplegia, urinary retention, history of diabetes, HbA1c, history of intravenous drug use, hepatitis B sAg positivity, hepatitis C Ab positivity, alanine aminotransferase (ALT), bilirubin, full blood count (haemoglobin, white cell count, platelets), plasma sodium, *leukotriene A4 hydrolase (LTA4H)* genotype (CC/CT/TT), routine CSF parameters (opening pressure, total leucocytes, total neutrophils, total lymphocytes, protein, blood:CSF glucose ratio, Ziehl-Neelsen stain, Gene Xpert MTB/RIF, Gene Xpert MTB/RIF Ultra, mycobacterial culture), duration of anti-tuberculosis chemotherapy (days) before enrolment, enrolment anti-TB regimen, anti-TB drug susceptibility results in culture-confirmed sub-group (multi-drug resistant [MDR] TB or rifampicin mono-resistant TB, isoniazid resistant non-MDR, pre-extensively drug resistant [XDR] TB, XDR TB, no or other resistance), HIV infection (new or known diagnosis), anti-retroviral therapy (ART) treatment at enrolment (ART naïve, ≤3 months of ART, >3 months of ART) and time to starting ART (if ART naïve), enrolment CD4 count (median values and categories [<50, 51–100, 101–200, >200]), HIV viral load. These will be described in a baseline variable table (Table 2).

Analysis: Baseline characteristics will be summarised as median (lower and upper quartiles) for continuous data and frequency (percentage) for categorical data. The amount of missing data for each baseline characteristic will also be displayed. We will perform multiple imputation of a variable in case of >5% missing values, and it is assumed that data are missing at random. Otherwise, a complete case analysis will be performed.

Use of the uniform case definition diagnostic score

The published TBM diagnostic score¹⁰ will be used and subjects will be categorised as ‘definite’, ‘probable’, ‘possible’, or ‘not TBM’. Participants will only be categorised as ‘not TBM’ if they have a confirmed alternative diagnosis (alternative to TBM) or they recovered without TB drugs.

Primary endpoint

The primary endpoint of this trial is death over the first 12 months after randomisation. The primary analysis is a Cox proportional hazards regression model with treatment as the only covariate. Since TBM MRC severity grade at enrolment (I, II, or III) is an important risk factor for mortality and was used as stratification variable in the randomisation, we will additionally perform a secondary analysis with MRC grade added as stratum variable. The proportional hazards assumption will be formally tested based on scaled Schoenfeld residuals and visually assessed by a plot of the scaled Schoenfeld residuals versus transformed time. Deaths, by study drug arm, and the results of the analyses will be shown as per Table 3 and Table 4.

Survivors known to be alive at 12 months will be censored at that time-point and subjects who withdrew or were lost to

Table 2. Baseline characteristics template table.

Characteristic	Dexamethasone (N=XX)		Placebo (N=XX)	
	N	Summary statistic	N	Summary statistic
Age (years)	XX	XX (XX,XX)	XX	XX (XX,XX)
Sex - male	XX	XX (XX%)	XX	XX (XX%)
Country	XX	XX (XX%)	XX	XX (XX%)
Site				
- HTD	XX	XX (XX%)	XX	XX (XX%)
- PNT	XX	XX (XX%)	XX	XX (XX%)
- Cipto Mangunkusumo	XX	XX (XX%)	XX	XX (XX%)
- Persahabatan	XX	XX (XX%)	XX	XX (XX%)
Diagnostic category				
- Definite TBM	XX	XX (XX%)	XX	XX (XX%)
- Probable TBM	XX	XX (XX%)	XX	XX (XX%)
- Possible TBM	XX	XX (XX%)	XX	XX (XX%)
- Not TBM	XX	XX (XX%)	XX	XX (XX%)
Previous tuberculosis treatment	XX	XX (XX%)	XX	XX (XX%)
Chest X-ray findings				
- No tuberculosis	XX	XX (XX%)	XX	XX (XX%)
- Miliary tuberculosis	XX	XX (XX%)	XX	XX (XX%)
- Pulmonary tuberculosis	XX	XX (XX%)	XX	XX (XX%)
Modified MRC grade				
- Grade I	XX	XX (XX%)	XX	XX (XX%)
- Grade II	XX	XX (XX%)	XX	XX (XX%)
- Grade III	XX	XX (XX%)	XX	XX (XX%)
Glasgow coma score	XX	XX (XX,XX)	XX	XX (XX,XX)
Weight (kg)	XX	XX (XX,XX)	XX	XX (XX,XX)
Duration of symptoms (days)	XX	XX (XX,XX)	XX	XX (XX,XX)
Neurological signs				
- Cranial nerve palsy	XX	XX (XX%)	XX	XX (XX%)
- Hemiplegia	XX	XX (XX%)	XX	XX (XX%)
- Paraplegia/tetraplegia	XX	XX (XX%)	XX	XX (XX%)
- Urinary retention	XX	XX (XX%)	XX	XX (XX%)
History of diabetes	XX	XX (XX%)	XX	XX (XX%)
HbA1c (%)	XX	XX (XX,XX)	XX	XX (XX,XX)
History of intravenous drug use	XX	XX (XX%)	XX	XX (XX%)
Hepatitis B sAg positivity,	XX	XX (XX%)	XX	XX (XX%)
Hepatitis C Ab positivity	XX	XX (XX%)	XX	XX (XX%)
Alanine aminotransferase (ALT) (IU/L)	XX	XX (XX,XX)	XX	XX (XX,XX)
Bilirubin (µmol/L)	XX	XX (XX,XX)	XX	XX (XX,XX)

Characteristic	Dexamethasone (N=XX)		Placebo (N=XX)	
	N	Summary statistic	N	Summary statistic
Full blood count				
- Haemoglobin (g/dL)	XX	XX (XX,XX)	XX	XX (XX,XX)
- White cell count ($\times 10^3/\mu\text{L}$)	XX	XX (XX,XX)	XX	XX (XX,XX)
- Platelets ($\times 10^3/\mu\text{L}$)	XX	XX (XX,XX)	XX	XX (XX,XX)
Plasma sodium (mmol/L)				
<i>Leukotriene A4 hydrolase</i>				
- TT	XX	XX (XX%)	XX	XX (XX%)
- CT	XX	XX (XX%)	XX	XX (XX%)
- CC	XX	XX (XX%)	XX	XX (XX%)
CSF parameters				
- Opening pressure (cmH_2O)	XX	XX (XX,XX)	XX	XX (XX,XX)
- Total leucocytes (cells/mm^3)	XX	XX (XX,XX)	XX	XX (XX,XX)
- Total neutrophils (cells/mm^3)	XX	XX (XX,XX)	XX	XX (XX,XX)
- Total lymphocytes (cells/mm^3)	XX	XX (XX,XX)	XX	XX (XX,XX)
- Protein (g/L)	XX	XX (XX,XX)	XX	XX (XX,XX)
- Blood:CSF glucose	XX	XX (XX,XX)	XX	XX (XX,XX)
CSF microbiological tests				
- Positive ZN stain	XX	XX (XX%)	XX	XX (XX%)
- Positive GeneXpert MTB/RIF	XX	XX (XX%)	XX	XX (XX%)
- Positive GeneXpert MTB/RIF Ultra	XX	XX (XX%)	XX	XX (XX%)
- Positive mycobacterial culture	XX	XX (XX%)	XX	XX (XX%)
Duration of anti-tuberculosis chemotherapy before enrolment (days)	XX	XX (XX,XX)	XX	XX (XX,XX)
Enrolment anti-tuberculosis chemotherapy regimen				
- Rifampicin	XX	XX (XX%)	XX	XX (XX%)
- Isoniazid	XX	XX (XX%)	XX	XX (XX%)
- Pyrazinamide	XX	XX (XX%)	XX	XX (XX%)
- Ethambutol	XX	XX (XX%)	XX	XX (XX%)
- Streptomycin	XX	XX (XX%)	XX	XX (XX%)
Anti-tuberculosis drug resistance*				
- Multi-drug resistant or rifampicin mono-resistant	XX	XX (XX%)	XX	XX (XX%)
- Isoniazid resistant non-MDR	XX	XX (XX%)	XX	XX (XX%)
- Pre-XDR	XX	XX (XX%)	XX	XX (XX%)
- XDR	XX	XX (XX%)	XX	XX (XX%)
- No or other resistance	XX	XX (XX%)	XX	XX (XX%)
HIV infection: new diagnosis or known positive status	XX	XX (XX%)	XX	XX (XX%)
ART status at enrolment				
- ART naïve	XX	XX (XX%)	XX	XX (XX%)
- ≤ 3 months of ART	XX	XX (XX%)	XX	XX (XX%)
- > 3 months of ART	XX	XX (XX%)	XX	XX (XX%)
- Unknown	XX	XX (XX%)	XX	XX (XX%)
- Undetermined	XX	XX (XX%)	XX	XX (XX%)
Time to starting ART [#]	XX	XX (XX,XX)	XX	XX (XX,XX)
Enrolment CD4 count (per mm^3)	XX	XX (XX,XX)	XX	XX (XX,XX)

Characteristic	Dexamethasone (N=XX)		Placebo (N=XX)	
	N	Summary statistic	N	Summary statistic
Enrolment CD4 count (per mm ³)				
- <50	XX	XX (XX%)	XX	XX (XX%)
- 51–100	XX	XX (XX%)	XX	XX (XX%)
- 101–200	XX	XX (XX%)	XX	XX (XX%)
- >200	XX	XX (XX%)	XX	XX (XX%)
HIV viral load (copies/mL)	XX	XX (XX,XX)	XX	XX (XX,XX)

*Results given for sub-group with positive mycobacterial culture on baseline CSF. Pre-XDR and XDR are defined following World Health Organisation definitions¹¹. #Results given for sub-group naïve to ART at enrolment.

N = number of patients included in that statistic. Summary statistic = the median (1st and 3rd quartile) value for continuous data, and the number and frequency (%) of patients with the characteristic for categorical data.

Definite TBM = positive acid fast bacilli (AFB) on CSF Ziehl Neelsen stain, or positive CSF TB GeneXpert test, OR positive CSF TB culture. Probable or possible TBM defined following uniform case definition¹⁰. Confirmed non-TBM = microbiologically confirmed other brain infection. Confirmed additional brain infection includes positive CSF India Ink stain, OR CSF cryptococcal antigen, OR positive blood cryptococcal antigen, OR positive CSF bacterial Gram stain, OR positive CSF bacterial culture, OR positive CSF viral or helminth PCR test.

ART status of a patient will be unknown if i) they are on ART treatment and the start ART date is missing completely; or ii) their ART status is unknown. ART status of a patient will be undetermined if start ART date is present but distinction between ≤3 months of ART, and >3 months of ART, cannot be made due to limited date information.

ART=antiretroviral therapy. HTD=Hospital for Tropical Diseases. MRC=Modified Research Council. PNT=Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease. TBM=tuberculous meningitis. XDR=Extensively drug resistant. Xpert=Gene Xpert MTB/RIF. ZN=Ziehl Neelsen.

Table 3. Hazard ratio for death (from any cause) over the first 12 months after randomisation.

	No. of deaths		Hazard ratio (95% CI); p value	Test for proportional hazards
	Dexamethasone	Placebo		
All patients	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX
Corrected for modified MRC grade			X.XX (X.XX, X.XX)	X.XX

The primary endpoint will be overall survival, i.e., time from randomisation to death, over the first 12 months of follow-up. This table reports the results from the Cox proportional hazards regression model. The primary effect measure will be the resulting hazard ratio comparing dexamethasone vs. placebo with a corresponding two-sided 95% confidence interval. In "All patients", treatment will be the only covariate. We will additionally report the hazard ratio if the modified MRC grade is included as stratum variable. The test for proportional hazards will use the Kaplan-Meier as time transformation.

MRC=Modified Research Council.

follow-up before 12 months will be censored at the date they were last known to be alive. Subjects who withdrew or were lost to follow-up before 12 months are estimated to be less than 5% of enrolled participants.

The homogeneity of the treatment effect on overall survival across subgroups will be assessed by formal tests of interaction between treatment and the following pre-defined grouping variables: TBM MRC severity grade at enrolment (I, II, or III), diagnostic category (definite, probable, possible), *LTA4H*

genotype (CC/CT/TT), drug resistance pattern (MDR TB or rifampicin mono-resistant TB, isoniazid resistant non-MDR, no or other resistance), ART status at enrolment (ART naïve, ≤3 months of ART, >3 months of ART), and CD4 cell count at enrolment (<50, 51–100, 101–200, >200). We will estimate and report the treatment effect by fitting a separate Cox model per subgroup. We will additionally fit a Cox model that includes CD4 count at enrollment as a continuous variable via a restricted cubic spline with four knots and an interaction term with treatment arm.

Table 4. Hazard ratios for death (from any cause) by sub-group over the first 12 months after randomisation.

	No. of deaths		Hazard ratio (95% CI); p value	Test for proportional hazards	p-value for heterogeneity*
	Dexamethasone	Placebo			
Modified MRC grade:					
- Grade I	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	X.XX
- Grade II	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
- Grade III	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
Diagnostic category					
- Definite TBM	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	X.XX
- Probable TBM	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
- Possible TBM	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
- Not TBM	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
<i>Leukotriene A4 hydrolase</i>					
- TT	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	X.XX
- CT	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
- CC	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
Anti-tuberculosis drug resistance*					
- Multi-drug resistant or rifampicin mono-resistant	XX	XX (XX%)	XX	X.XX	X.XX
- Isoniazid resistant non-MDR	XX	XX (XX%)	XX	X.XX	
- Pre-XDR	XX	XX (XX%)	XX	X.XX	
- XDR	XX	XX (XX%)	XX	X.XX	
- No or other resistance	XX	XX (XX%)	XX	X.XX	
ART status at enrolment					
- ART naïve	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	X.XX
- ≤3 months of ART	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
- >3 months of ART	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
Enrolment CD4 count (per mm ³)					
- <50	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	X.XX
- 51–100	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
- 101–200	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	
- >200	XX/XX	XX/XX	X.XX (X.XX, X.XX)	X.XX	

*Heterogeneity will be tested with a Cox regression model that includes an interaction between treatment effect and subgroup. #Results will be given for sub-group with positive mycobacterial culture on baseline CSF. Pre-XDR and XDR are defined following World Health Organisation definitions¹¹.

The primary endpoint will be overall survival, i.e., time from randomisation to death, over the first 12 months of follow-up. This table reports the results from the Cox proportional hazards regression model. The primary effect measure will be the resulting hazard ratio comparing dexamethasone vs. placebo with a corresponding two-sided 95% confidence interval.

In these subgroup analyses, a separate Cox model will be fitted for each value of the subgroup. The “Test for heterogeneity” will be based on the likelihood ratio test that includes subgroup as covariate and compares the models with subgroup as main effect only and with subgroup as treatment effect modifier, with TBM MRC severity grade at enrolment (I, II, or III) as covariates.

ART=antiretroviral therapy. MRC=Modified Research Council. TBM=tuberculous meningitis. XDR=extensively drug resistant.

Kaplan-Meier plots and explicit survival estimates at 3, 6, and 12 months of follow-up will be calculated for the full sample and in the subgroups defined above. We will compare the treatment arms via the absolute risk of death at 12 months (using a Wald-type test based on Kaplan-Meier estimates at 12 months and associated standard errors using Greenwood’s formula) and the restricted mean survival until 12 months (using the survRM2¹² package in R).

Secondary endpoints

Secondary outcomes 2 to 7 below are time-to-event outcomes. For each, we will compute and plot the Kaplan-Meier estimates (outcomes 2, 4) or the competing risks Aalen-Johansen estimates (outcomes 3, 5, 6 and 7) and report the values of the estimates at 3, 6 and 12 months. We will also fit a Cox proportional hazards model (results are interpreted as relative cause-specific hazards in the presence of competing risks). Analyses will

be performed for the full samples (ITT and PP). Subgroup analyses are specified below per secondary endpoint. For the subgroup analyses, we follow the same procedure as for the primary outcome: we fit separate models per subgroup and we fit a model in which we test for interaction by subgroup.

1. Neurological disability at 12 months from randomisation

Neurological disability will be assessed by the modified Rankin score at months 1, 2, 3, 6, 9, and 12 from randomisation (Table 5). The main secondary endpoint is the 12-month assessment and subjects who died before 12 months will be treated as having a score of 6 ('dead'). Rankin score assessments will be included from clinical assessments performed monthly (+/- 7 days), with the exception of the 12-month clinical assessment for which an acceptable range of -10 days/+1 month will be applied. All clinical assessment timings are based on days from randomisation (i.e., 'day 0' is labeled as the first day study drug is received, with study drug received immediately after randomisation).

Neurological disability (as assessed by the ordinal modified Rankin scale) at 12 months will be compared between the two arms with a proportional odds logistic regression model with the treatment assignment as the main covariate and adjustment for TBM MRC severity grade. The result will be summarised as a cumulative odds ratio with corresponding 95% confidence interval and p-value. Individuals who withdrew or were lost to follow-up before 12 months are excluded.

2. First new neurological event or death over the first 12 months after randomisation

A new neurological event is defined as a fall in GCS by ≥ 2 points for ≥ 2 days from the highest previously recorded GCS (including baseline) or the onset of any of the following clinical adverse events: cerebellar symptoms, focal neurological signs, or onset of seizures. A description of all the events will be given, summarising how they met the criteria.

Analyses will additionally be performed in the subgroups defined by TBM MRC severity grade, diagnostic category, ART status at enrolment, time from randomisation to start of ART, and baseline CD4 count.

3. First IRIS event over the first 6 months after randomisation

The criteria for neurological IRIS diagnosis is defined in the study protocol¹. The neurological IRIS rate will be defined as the number of IRIS events divided by the observed person-time of follow-up in each treatment group. A description of all the IRIS events will be given, describing how they met the IRIS diagnostic criteria.

The number of IRIS events in each group will be summarised. Death will be interpreted as a competing risk. Analyses will additionally be performed in the subgroups defined by TBM MRC grade, diagnostic category, ART status at enrolment, time from randomisation to start of ART, and baseline CD4 count.

4. AIDS-defining event or death over the first 12 months after randomisation

Acquired immunodeficiency syndrome (AIDS)-defining illnesses will be defined as per the World Health Organisation (WHO) classification. WHO define AIDS as a clinical diagnosis (presumptive or definitive) of any stage 4 HIV condition¹³.

5. HIV-associated malignancy over the first 12 months after randomisation

HIV-associated malignancy is defined as new diagnosis of one or more of the three major HIV-associated malignancies; Kaposi sarcoma, high grade B-cell non-Hodgkin lymphoma or invasive cervical cancer.

The number of HIV-associated malignancy events in each group will be summarised. Death will be interpreted as a competing risk. Analyses will additionally be performed in the subgroups defined by ART status at enrolment.

6. Use of open-label corticosteroid treatment for any reason, and at any time, after randomisation

The number of open-label corticosteroid treatment events in each group will be summarised. The reasons for corticosteroid treatment will be listed. Death will be interpreted as a competing risk.

7. Requirement for shunt surgery by 12 months

The number of shunts performed in each group will be summarised. Death will be interpreted as a competing risk.

Adverse events until 12 months

Serious adverse events (SAE) are defined in the study protocol¹. SAE will be sub-grouped into categories. SAE will be grouped and graded as per Common Terminology Criteria for Adverse Events (CTCAE)¹⁴.

The number of patients with any serious adverse event will be summarised and compared between the two treatment arms based on the chi-squared test, or Fisher's exact test in case the expected count under the null hypothesis in at least one of the cells is smaller than one¹⁵. Specific adverse events will be summarised, but not formally compared. The total number of serious adverse event episodes per patient will also be summarised and informally compared based on a quasi-Poisson regression model with treatment as the only covariate.

The following subgroups of adverse events will also be separately summarised: clinical grade 3&4 adverse events; serious adverse events possibly, probably, or definitely related to the study drug; adverse events leading to TB treatment or ARV interruptions. Grade 3&4 laboratory abnormalities will be summarised in the same way as clinical adverse events. Adverse events will be shown as per Table 6–Table 10.

Explanatory analysis via multivariate model

A multivariate model of variables independently associated with death will include: age, enrolment GCS, TBM diagnostic category (definite, probable, possible), study drug allocation

Table 5. The Modified Rankin Scale.

Score	Description
0	No symptoms
1	Minor symptoms not interfering with lifestyle
2	Symptoms that lead to some restriction in lifestyle, but do not interfere with the patients ability to look after themselves
3	Symptoms that restrict lifestyle and prevent totally independent living
4	Symptoms that clearly prevent independent living, although the patient does not need constant care and attention.
5	Totally dependent, requiring constant help day and night.
6	Death

Table 6a. Summary of serious adverse events.

Characteristic	Dexamethasone (N=XX)		Placebo (N=XX)		Comparison (p-value)
	N.pt	N.ae	N.pt	N.ae	
Any selected serious adverse event	XX (XX%)	XX	XX (XX%)	XX	X.XX
Serious adverse events of all types	XX (XX%)	XX	XX (XX%)	XX	X.XX

N.pt = the number of patients with at least one serious adverse event (% of all patients receiving the same intervention)

N.ae = the total number of episodes of that particular serious adverse event

Table 6b. Summary of serious adverse events, shown by reasons for which they were considered serious, not shown by study arm.

	Causes death (N=XX)	Life threatening event* (N=XX)	Hospitalisation or prolongation of hospitalisation (N=XX)	Persistent or significant disability/incapacity** (N=XX)	Congenital anomaly/birth defect (N=XX)	Important medical event which may jeopardise the patient and/or require intervention (N=XX)
	n Summary statistic	n Summary statistic	n Summary statistic	n Summary statistic	n Summary statistic	n Summary statistic
Name of event	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)

* Subjects were at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

** A substantial disruption of a person's ability to conduct normal life functions

N is the number of all patients, n is the number of patients with a non-missing value

Summary statistic is absolute count (%) for categorical variable(s).

Table 7. Summary of serious adverse events possibly, probably, or definitely related to the study drug.

Characteristic	Dexamethasone (N=XX)		Placebo (N=XX)		Comparison (p-value)
	N.pt	N.ae	N.pt	N.ae	
Any selected serious adverse event possibly, probably, or definitely related to the study drug	XX (XX%)	XX	XX (XX%)	XX	X.XX
Serious adverse events of all types possibly, probably, or definitely related to the study drug	XX (XX%)	XX	XX (XX%)	XX	X.XX

N.pt = the number of patients with at least one serious adverse event (% of all patients receiving the same intervention)

N.ae = the total number of episodes of that particular serious adverse event

Table 8. Summary of clinical grade 3&4 adverse events.

Characteristic	Dexamethasone (N=XX)		Placebo (N=XX)		Comparison (p-value)
	N.pt	N.ae	N.pt	N.ae	
Any selected clinical grade 3&4 adverse event	XX (XX%)	XX	XX (XX%)	XX	X.XX
Clinical grade 3 adverse events of all types	XX (XX%)	XX	XX (XX%)	XX	X.XX
Clinical grade 4 adverse events of all types	XX (XX%)	XX	XX (XX%)	XX	X.XX
Clinical grade 3&4 adverse events of all types	XX (XX%)	XX	XX (XX%)	XX	X.XX

N.pt = the number of patients with at least one adverse event (% of all patients receiving the same intervention)

N.ae = the total number of episodes of that particular adverse event

The 'clinical grade 3&4 adverse events of all types' grouping will include only the group of adverse events that cannot be separated into grades 3 or 4 (recorded as 'grade 3 or 4' at the beginning of the trial). These events will not also be represented in the above 'grade 3' and 'grade 4' rows.

Table 9. Summary of adverse events leading to TB treatment or antiretroviral (ARV) interruptions.

Characteristic	Dexamethasone (N=XX)		Placebo (N=XX)		Comparison (p-value)
	N.pt	N.ae	N.pt	N.ae	
Any selected adverse event leading to TB treatment or antiretroviral interruptions	XX (XX%)	XX	XX (XX%)	XX	X.XX
Adverse events of all types leading to TB treatment or antiretroviral interruptions	XX (XX%)	XX	XX (XX%)	XX	X.XX

N.pt = the number of patients with at least one serious adverse event (% of all patients receiving the same intervention)

N.ae = the total number of episodes of that particular serious adverse event

Table 10. Summary of Grade 3&4 laboratory abnormalities.

Characteristic	Dexamethasone (N=XX)		Placebo (N=XX)		Comparison (p-value)
	N.pt	N.ae	N.pt	N.ae	
Any selected grade 3&4 laboratory abnormalities	XX (XX%)	XX	XX (XX%)	XX	X.XX
Grade 3&4 laboratory abnormalities of all types	XX (XX%)	XX	XX (XX%)	XX	X.XX

N.pt = the number of patients with at least one serious adverse event (% of all patients receiving the same intervention)

N.ae = the total number of episodes of that particular serious adverse event

(dexamethasone vs. placebo), CD4 count, CSF total leucocytes, CSF total neutrophils, CSF blood:glucose ratio, CSF lactate. Numeric variables will be analysed using restricted cubic splines. We will not include any interactions.

Data availability

No data is associated with this article.

Acknowledgments

The authors would like to acknowledge the ACT HIV investigators. A full list of ACT HIV investigators appears in [Box 1](#). Additionally the authors would like to acknowledge the ACT HIV steering committee (TSC); Dr Truong Huu Khanh

(Infectious Diseases Physician, Paediatric Hospital Number 1, Ho Chi Minh City, Vietnam), Professor Ben Marais (Senior Tuberculosis Researcher and Trialist, University of Sydney, Australia), Professor Nicholas Paton (Infectious Diseases Physician and Clinical Trialist, National University of Singapore, Singapore), and TSC Chair Professor Robert Wilkinson (Honorary Professor and Director Wellcome Centre for Infectious Diseases Research in Africa, University of Cape Town, South Africa), and the ACT HIV data monitoring committee (DMC); Professor Graeme Meintjes (Senior Infectious Diseases/HIV Physician, University of Cape Town, South Africa), Professor Nina Ruslami (Senior TBM Clinician and Researcher, Universitas Padjadjaran, Bandung, Indonesia), and DMC Chair Professor Sarah Walker (Senior Statistician and Clinical Trialist, MRC Clinical Trials Unit, University College London).

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Jeny	Dr Decy Subekti	

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Version 2

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Nico (Nicolaas) Nagelkerke 

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Change is just a useful clarification.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics and Infectious disease epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 10 November 2021

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Peter Mwaba

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Evidence from Clinical trials that have been done this far on disseminated tuberculosis and in Particular TBM have not been conclusive on the role of Corticosteroids in improving outcomes.

Corticosteroids have been tried in Tuberculous pericarditis, granulomatous diseases and Leprosy reactions with good outcomes. Their role in bacterial meningitis particularly Waterhouse-Friderichsen Syndrome has been shown to be positive.

Given the debate on BCG vaccine and its possible role in preventing Tuberculous meningitis it would be of value if there is a specific way of confirming the number of participants who have had the vaccine. Some of the Secondary end points may be drug related and it is therefore important to know the exact drug regimen used for both TBM and HIV. Otherwise an excellent piece of work

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 01 November 2021

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The issue of potential benefits of corticosteroids in HIV-associated TBM remains unaddressed so far. The authors have planned an almost flawless study to address the issue. The authors are trying the same corticosteroids regimen as had been used in earlier trials which included both

HIV-negative and HIV-positive TBM patients. A small paragraph detailing the anti-tuberculosis regimen (drugs and duration) and the ART regimen should be added for better clarity. How will the authors address the issue of "paradoxical reaction"? I find vision loss a major disability among TBM survivors, kindly give due attention to this as well.

Regarding analysis, I feel that the use of median should depend on the distribution instead of assuming an asymmetric distribution. We can, therefore, include 'mean' too and look for its statistical relevance.

In my opinion, the corticosteroids regimen that has been planned to use in this study is a bit complicated. With a simpler regimen compliance would be better.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: CNS tuberculosis and other CNS infections


We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 27 October 2021

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This is slick analysis plan by a clearly highly experienced team for a multi-centre randomized

clinical trial following highly standardized methodologies. The proposed analyses will lead to a correct, and generally accepted result, as well as guide the future standard of care guidelines for Tuberculous meningitis in HIV+ patients. As the drug on trial is cheap and easy to administer, guidelines will be applicable globally (including Africa where HIV prevalence is highest).

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics and Infectious disease epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
