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TB meningitis

AWACC 2023

Richard Lessells

Case presentation

- 39-year-old HIV positive male - diagnosed 2017, interrupted ART 2020 (CD4 not yet known)
- Prior pulmonary TB 2017
- Presented with 2 week history of headache and neck stiffness, associated with intermittent confusion
- No seizures

- Clinical examination – GCS 14 (E-4 V-4 M-6), neck stiffness, no focal neurological signs, no papilloedema

Contraindications to lumbar puncture

Neurological contraindications

- Coma or markedly ↓ level of consciousness (GCS<10)
- Papilloedema
- Unexplained new focal neurological deficit, e.g. hemiparesis
- New seizures
- Presence of a ventriculoperitoneal shunt

Non-neurological contraindications

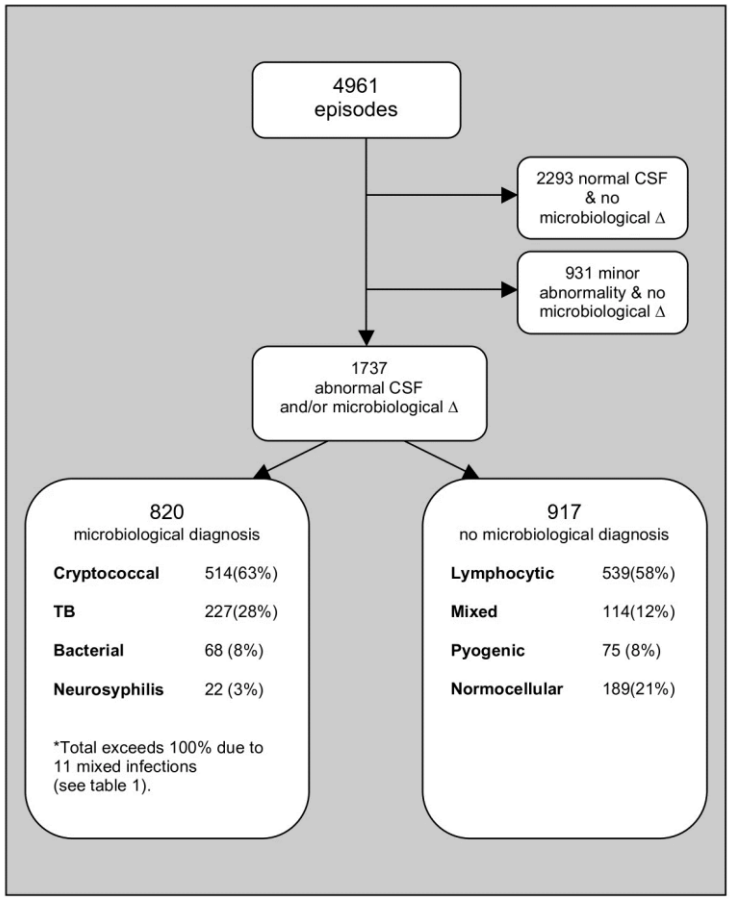
- Severe cardiorespiratory compromise
- Severe coagulopathy
- Local sepsis at the LP site

SAHCS Adult advanced HIV disease guidelines

Differential diagnosis in HIV-positive adult presenting with subacute meningitis

- Cryptococcal meningitis
- TB meningitis
- Others - bacterial meningitis, neurosyphilis, herpesviruses (HSV, VZV, CMV), and other less common causes

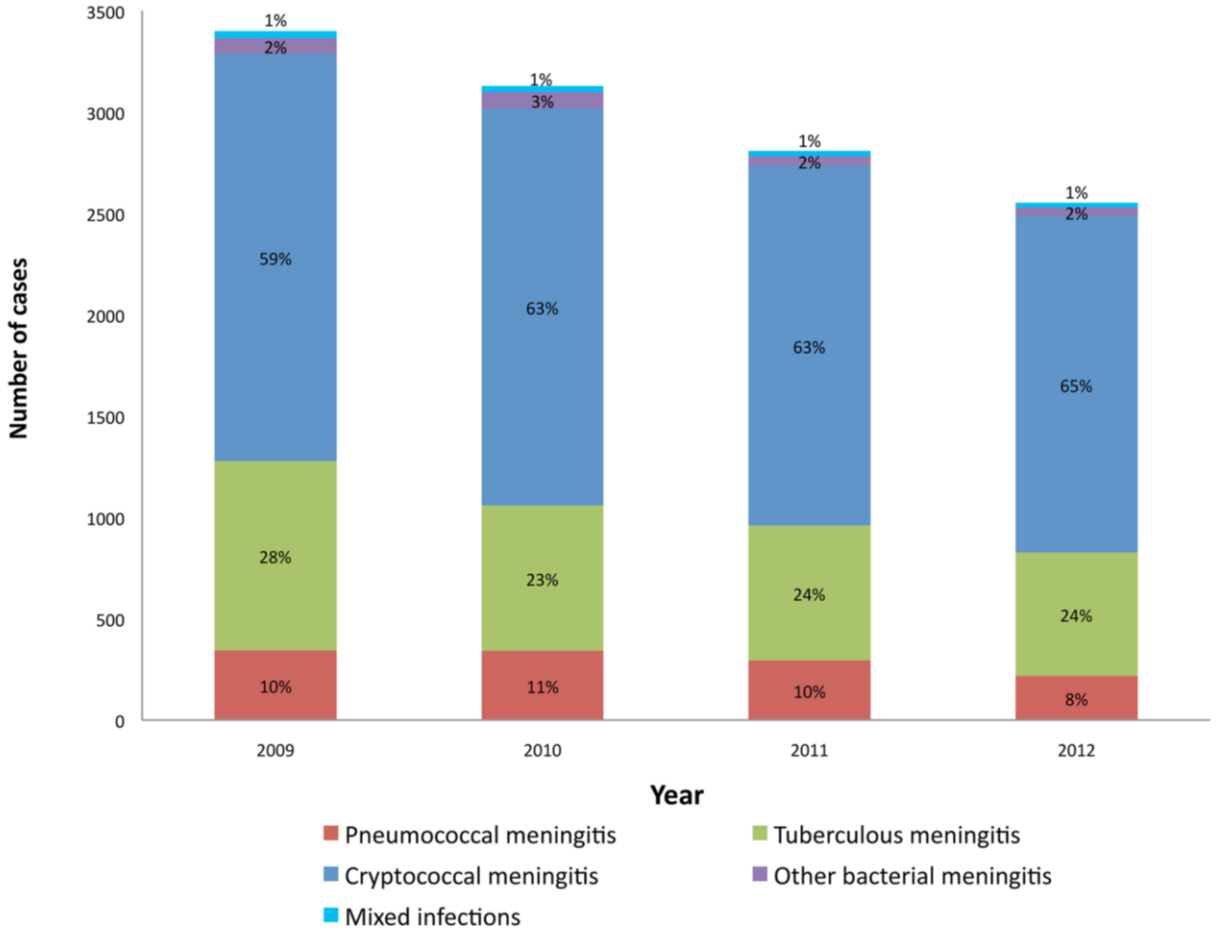
Causes of meningitis



- Adults undergoing lumbar punctures between 1 Jan 2006 and 31 Dec 2008 at a public sector referral hospital in Western Cape
- In those with microbiological diagnosis, cryptococcal (63%) > TB (28%) > bacterial (8%) > neurosyphilis (3%)

Jarvis BMC ID 2010

Causes of meningitis



- Retrospective study of CSF laboratory data for adults from Gauteng public sector laboratories between 2009 and 2012
- 11,891 microbiologically confirmed cases (10.7% of all CSF specimens)

Britz PLoS One 2016

CSF results

Glucose	1.9
Protein	2.16
Lymphocytes	56
Polymorphs	4
Erythrocytes	110
CrAg	Negative
Gram stain	No Bacteria

Other initial investigations

CD4+ count 96 cells/µL

Serum CrAg negative

CSF results

TB-NAAT: GeneXpert MTB/Rif Ultra

PCR result — Mycobacterium tuberculosis complex NOT detected

The negative GeneXpert MTB/RIF Ultra assay does not conclusively rule out TB. Please manage according to national guidelines. If the patient is HIV infected, please submit a second specimen for TB culture and susceptibility testing.

Other investigations

Urine LAM negative

CXR normal

No sputum specimen obtained

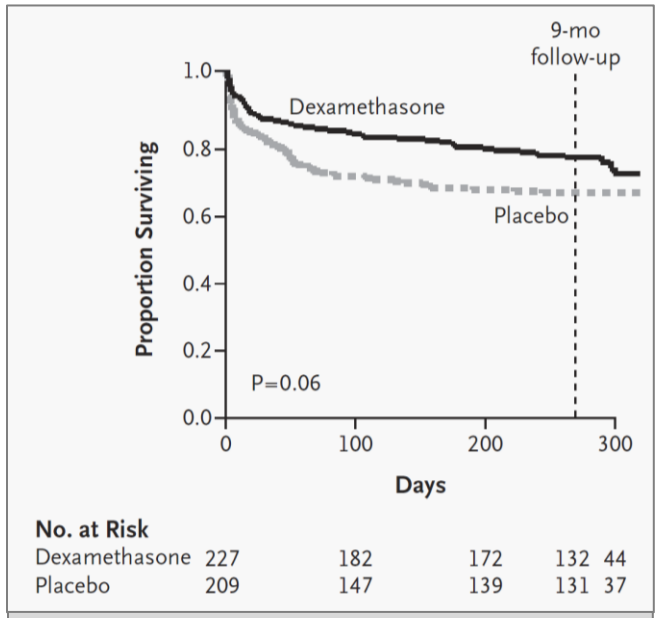
Common pitfalls in TBM investigation

- Delay in performing lumbar puncture
- Not sending sufficient CSF for TB investigations (ideally >6mL CSF)
- Not recognizing that some people with TBM will have acellular CSF (especially people with advanced HIV disease)
- Not recognizing that although TBM usually gives lymphocyte pleocytosis, can sometimes see polymorph predominance
- Interpreting negative Xpert MTB/RIF Ultra as excluding TBM
- Not performing other TB investigations that may be helpful (i.e. uLAM, CXR, sputum Xpert MTB/RIF Ultra)

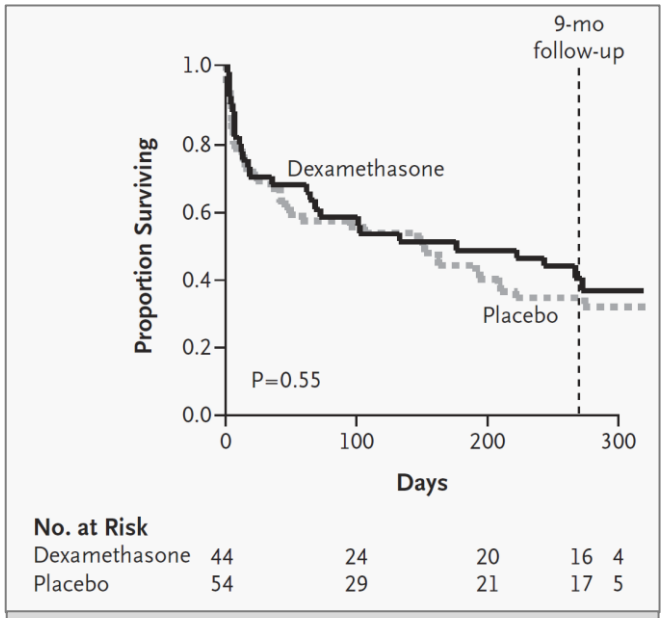
Steroids in TB meningitis

- SA TB Guidelines (2014) recommend high-dose steroids - IV dexamethasone 12mg bd then prednisolone 120mg od for one week, then taper over 6 weeks
- Standard Treatment Guidelines (2019) recommend steroids for HIV-negative individuals with grade II-III disease (state uncertainty whether beneficial in HIV-positive adults)
- Evidence for steroids in adult TB meningitis essentially based on a single RCT 20 years ago showing reduction in mortality in Vietnam
- Results recently reported from a large RCT (ACT HIV) specifically in adults with HIV in Vietnam and Indonesia

Steroids in TB meningitis



HIV negative (n=436)



HIV positive (n=98)

RCT in Vietnam 2001-2003

Dexamethasone vs. placebo

Dexamethasone associated with reduced mortality

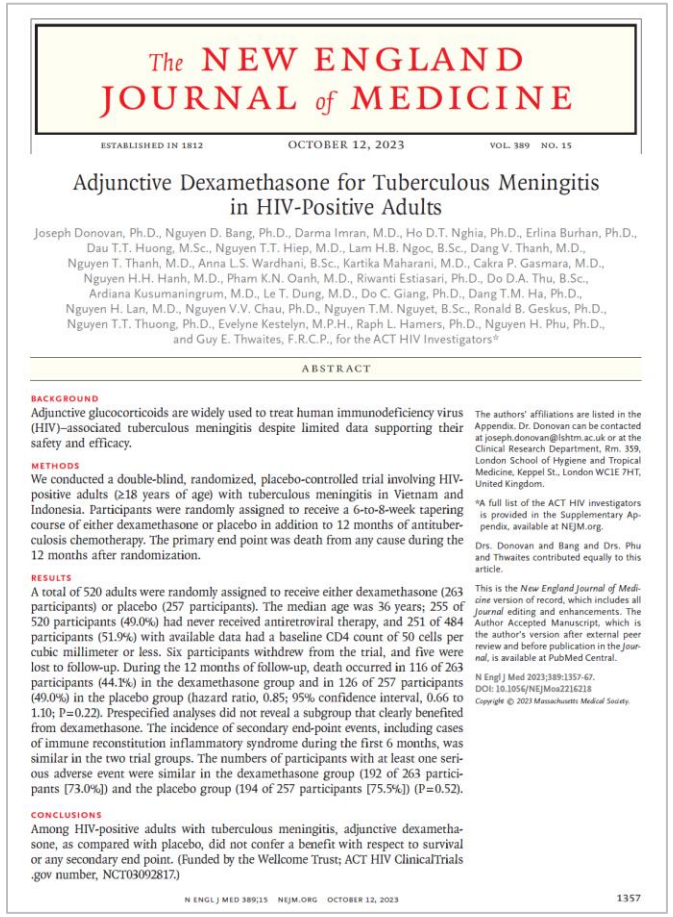
- 32% vs. 41%
- RR 0.69, 95% CI 0.52-0.92

Benefit in terms of reduced mortality more obvious for HIV-negative participants

- HIV negative: mortality 25% vs. 32% (RR 0.72, 95% CI 0.51-1.02)
- HIV positive: mortality 61% vs. 69% (RR 0.86, 95% CI 0.52-1.41)

Thwaites NEJM 2004

Steroids in TB meningitis



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Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults

Joseph Donovan, Ph.D., Nguyen D. Bang, Ph.D., Darma Imran, M.D., Ho D.T. Nghia, Ph.D., Erlina Burhan, Ph.D., Dau T.T. Huong, M.Sc., Nguyen T.T. Hiep, M.D., Lam H.B. Ngoc, B.Sc., Dang V. Thanh, M.D., Nguyen T. Thanh, M.D., Anna L.S. Wardhani, B.Sc., Kartika Maharani, M.D., Cakra P. Gasmara, M.D., Nguyen H.H. Hanh, M.D., Pham K.N. Oanh, M.D., Riwanti Estiasari, Ph.D., Do D.A. Thu, B.Sc., Ardiana Kusumaningrum, M.D., Le T. Dung, M.D., Do C. Giang, Ph.D., Dang T.M. Ha, Ph.D., Nguyen H. Lan, M.D., Nguyen V.V. Chau, Ph.D., Nguyen T.M. Nguyet, B.Sc., Ronald B. Geskus, Ph.D., Nguyen T.T. Thuong, Ph.D., Evelyne Kestelyn, M.P.H., Raph L. Hamers, Ph.D., Nguyen H. Phu, Ph.D., and Guy E. Thwaites, F.R.C.P., for the ACT HIV Investigators*

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.)

The authors' affiliations are listed in the Appendix. Dr. Donovan can be contacted at joseph.donovan@lshtm.ac.uk or at the Clinical Research Department, Rm. 359, London School of Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, United Kingdom.

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

Drs. Donovan and Bang and Drs. Phu and Thwaites contributed equally to this article.

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ACT HIV trial – RCT in Vietnam and Indonesia

HIV-positive adults randomly assigned to receive dexamethasone vs. placebo (6-8 week course) in addition to 12 months of anti-TB therapy

Primary end point – death from any cause within 12 months

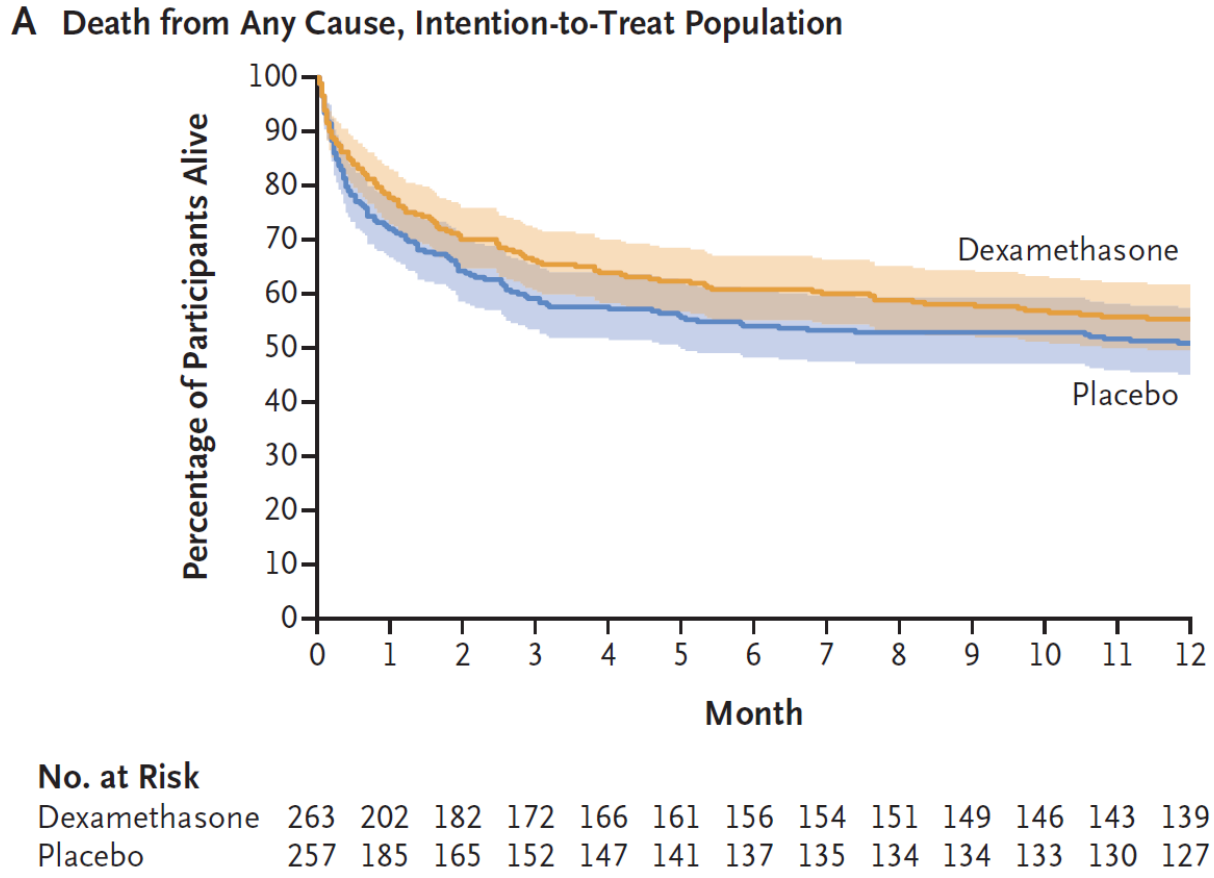
Donovan NEJM 2023

ACT HIV trial

Characteristic	Total	Dexamethasone	Placebo
Median age (IQR)	36 (30-41)	36 (29-41)	36 (30-42)
Male sex	396 (76.2)	208 (79.1)	188 (73.2)
ART naïve	255 (49.0)	133 (50.6)	122 (47.5)
CD4 ≤50 cells/mm^3	251/484 (51.9)	126/244 (51.6%)	125/240 (52.1)
Diagnostic category			
Definite TBM	212 (40.8)	108 (41.1)	104 (40.5)
Probable TBM	253 (48.7)	129 (49.0)	124 (48.2)
Possible TBM	52 (10.0)	24 (9.1)	28 (10.9)
MRC grade			
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)

Donovan NEJM 2023

ACT HIV trial



Death occurred in 116/263 (44.1%) in the dexamethasone arm vs. 126/257 (49.0%) in the placebo arm

Hazard ratio 0.85 (95% CI 0.66-1.10)

Donovan NEJM 2023

ACT HIV trial

- No evidence of a beneficial effect of dexamethasone in any prespecified subgroup (e.g. disease severity, diagnostic category, ART status, CD4+ count)
- Incidence of secondary endpoints similar in the two trial groups (e.g. neurologic disability, neurologic IRIS, AIDS-defining event or death)
- Serious adverse events similar in two groups – 192/264 (73.0%) dexamethasone vs. 194/257 (75.5%) placebo
- Fewer serious neurologic adverse events in dexamethasone group – 95/273 (36.1%) vs. 115/257 (44.7%) placebo

Avoiding pitfalls in TBM

- Don’t delay lumbar puncture for CT brain if no contraindication
- Send sufficient CSF for TB investigations (ideally >6mL CSF)
- Be aware that ‘atypical’ CSF findings can occur with TBM, e.g. acellular CSF, neutrophil predominance
- Look for other evidence of TB (i.e. uLAM, CXR, sputum Xpert MTB/RIF Ultra)
- Recognise that a negative Xpert MTB/RIF Ultra does not rule out TBM
- Have a low threshold for empirical anti-TB treatment if clinical presentation compatible and non-specific CSF findings suggestive