Treatment of Cryptococcal Meningitis

Graeme Meintjes
University of Cape Town
GF Jooste Hospital
Imperial College London

Imperial College London

CIDRI
CLINICAL INFECTIOUS DISEASES RESEARCH INITIATIVE

IIDMM
INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

Cryptococcal meningitis

- Predominantly in HIV infected patients with CD4 < 200
  - Studies in Cape Town median CD4 = 27 - 49
- Sub-acute meningo-encephalitis
  - Symptom onset over 1 - 2 weeks
- Clinical presentation
  - Headaches
  - Vomiting
  - Visual disturbance / diplopia
  - Confusion
  - Focal neurology

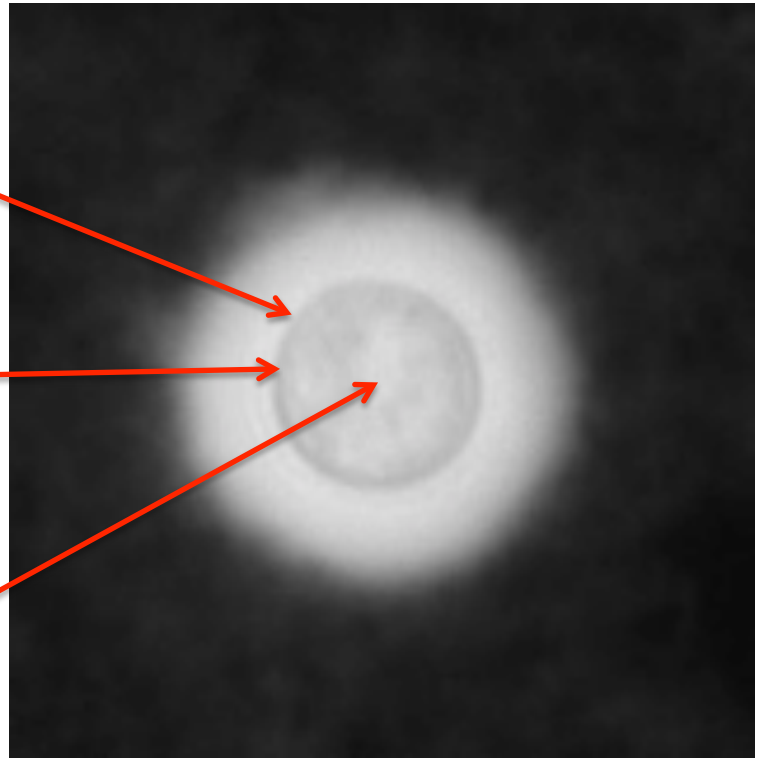
Bicanic, Clin Infect Dis 2007
Bicanic, Clin Infect Dis 2008
Jarvis, Clin Infect Dis 2012

Cryptococcal meningitis treatments

Amphotericin B (IVI)
Forms transmembrane channels

Fluconazole (PO/IVI)
Inhibits membrane ergosterol synthesis

Flucytosine (PO/IVI)
Interferes with RNA and DNA synthesis



WHO Guidelines 2011*

INDUCTION PHASE	2 WEEKS	Amphotericin B + Flucytosine (or Amphotericin B + Fluconazole 800mg/d)
CONSOLIDATION PHASE	8 WEEKS	Fluconazole 400-800mg/d
MAINTENANCE PHASE (SECONDARY PROPHYLAXIS)	UNTIL CD4 > 200 ON ART FOR 6 MONTHS	Fluconazole 200mg/d

*For settings where Amphotericin B and adequate toxicity monitoring is available

Problems with treatment

- Amphotericin B side effects
  - Phlebitis
  - Renal impairment
  - Hypokalaemia and hypomagnesaemia
  - Anaemia
  - Febrile reactions
- Amphotericin B and Flucytosine unavailable in many African countries
- Alternatives
  - High dose Fluconazole (1200mg/d) + Flucystosine
  - High dose Fluconazole (1200mg/d)

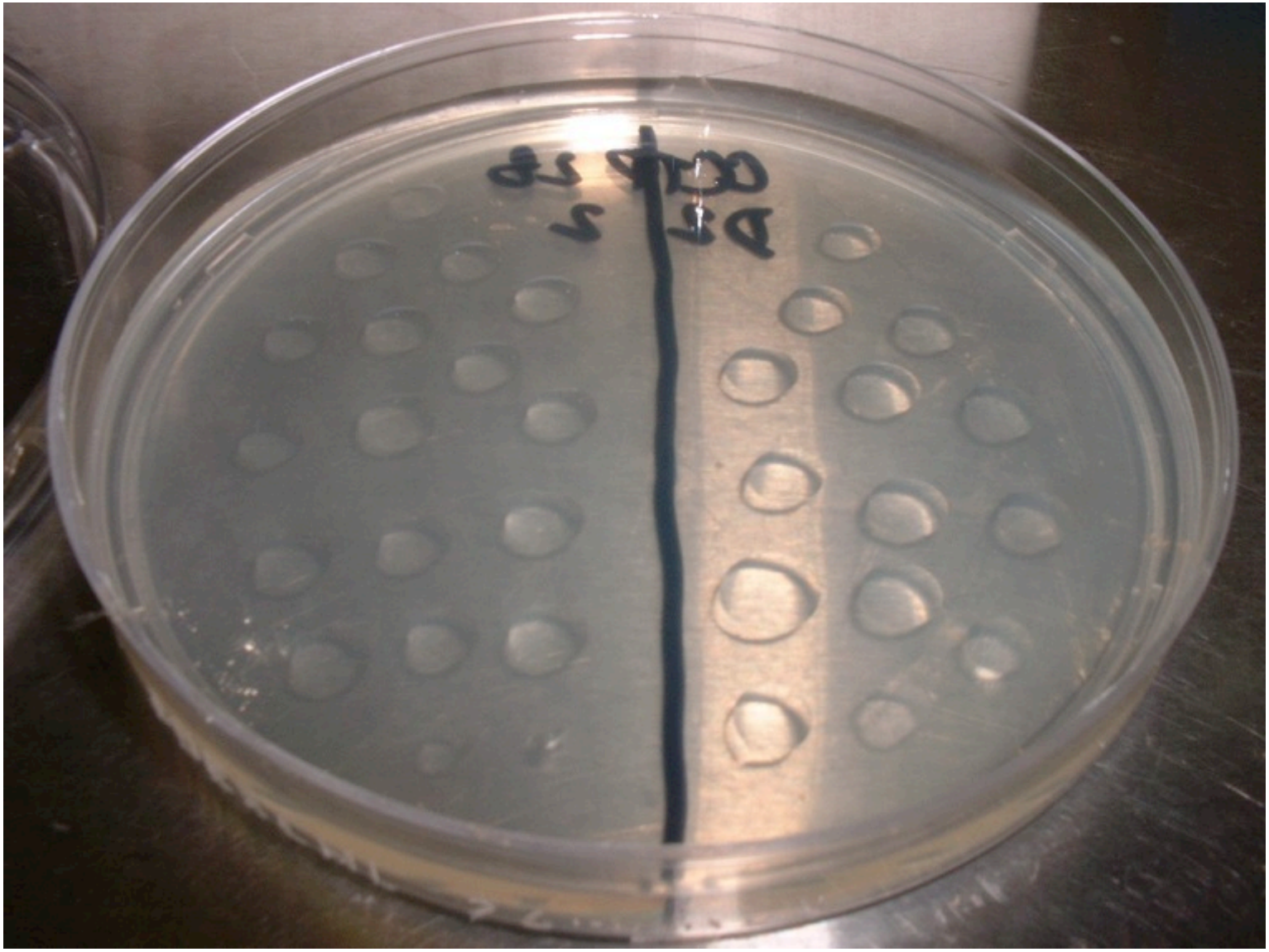
Early fungicidal activity (EFA)

- Serial CSF quantitative cultures
  - 1, 3, 7 and 14 days
- Slope of linear regression of log CFU against time calculated for each patient
- EFA: mean rate of fall in CSF log CFU counts per day for each treatment group
- Accurate with increased power to detect differences between drug regimens in Phase 2 studies

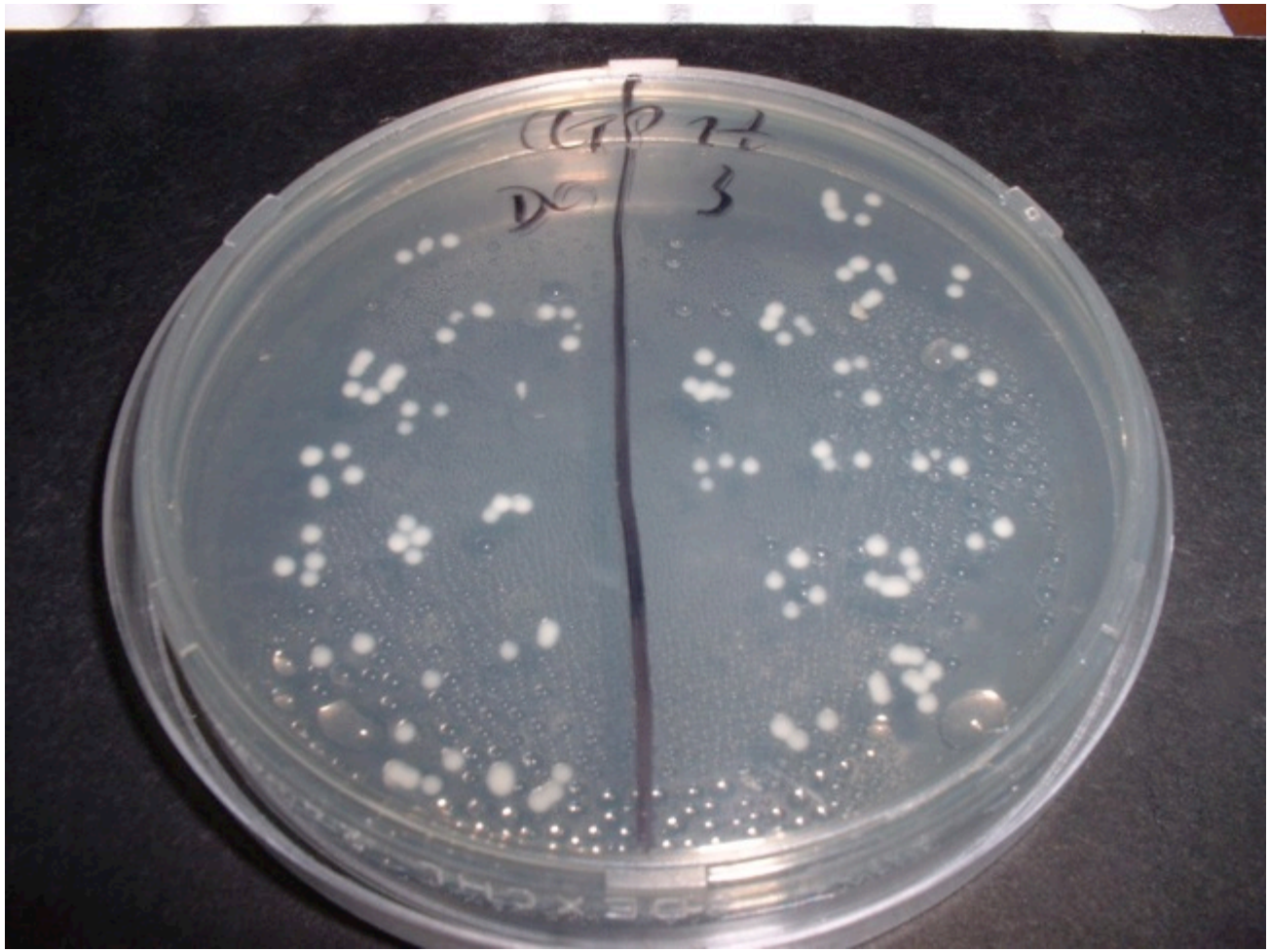
Tom Harrison

CSF 10-fold dilutions: neat to 1:10,000

100 µl of each CSF dilution spotted out on ½ SAB plate



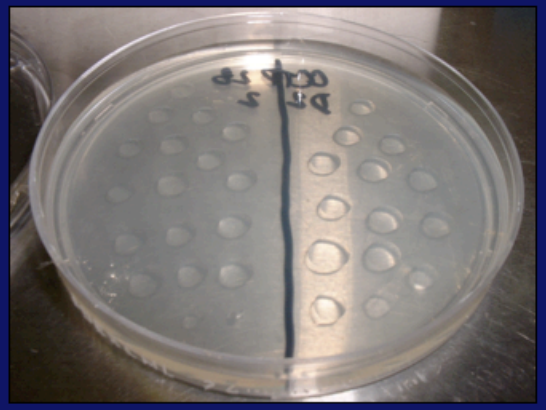
Lowest dilution with distinct colonies: count

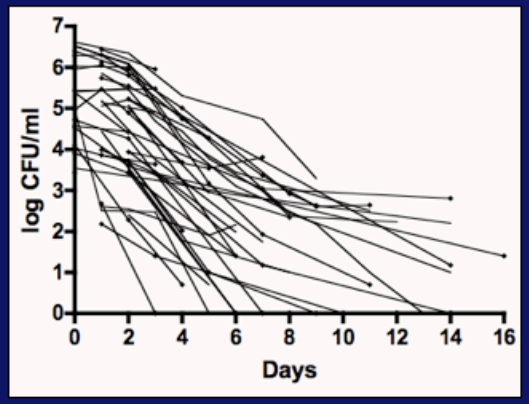


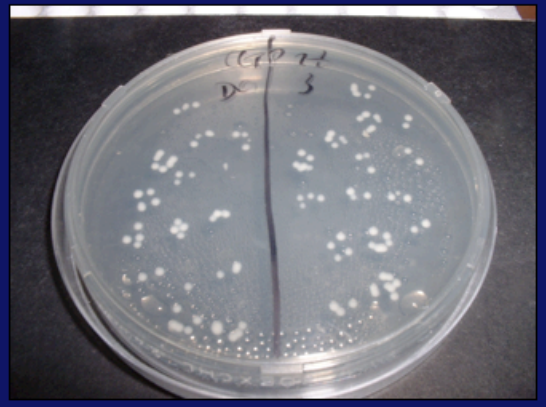
1:1000 dilution

L=85; R=90. QC= 87.5 x 1000 X 10 = 875,000 CFU/ml CSF

St George's
University of London







BRIEF REPORT

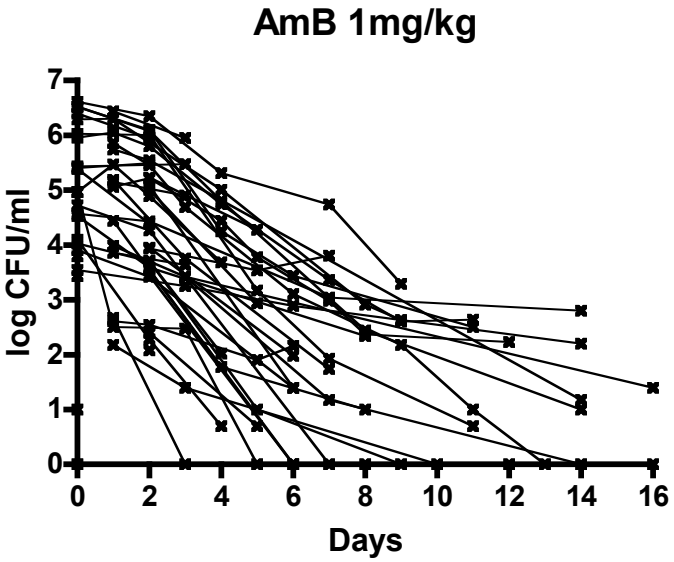
Fungal Burden, Early Fungicidal Activity, and Outcome in Cryptococcal Meningitis in Antiretroviral-Naive or Antiretroviral-Experienced Patients Treated with Amphotericin B or Fluconazole

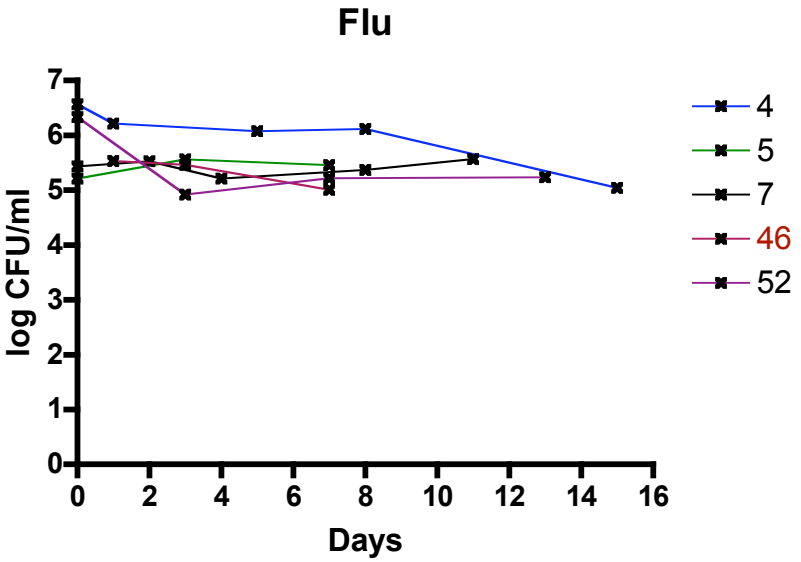
Tihana Bicanic,[1,4] Graeme Meintjes,[2,3] Robin Wood,[1] Madeleine Hayes,[4] Kevin Rebe,[2,3] Linda-Gail Bekker,[1] and Thomas Harrison[1,4]

[1]Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, and [2]Department of Medicine, University of Cape Town, and [3]HIV Service, GF Jooste Hospital, Cape Town, South Africa; and [4]Division of Infectious Diseases, Department of Cellular and Molecular Medicine, St. George's University of London, London, United Kingdom

Clin Infect Dis 2007

EFA: Amphotericin B vs Fluconazole treated patients (n = 54)



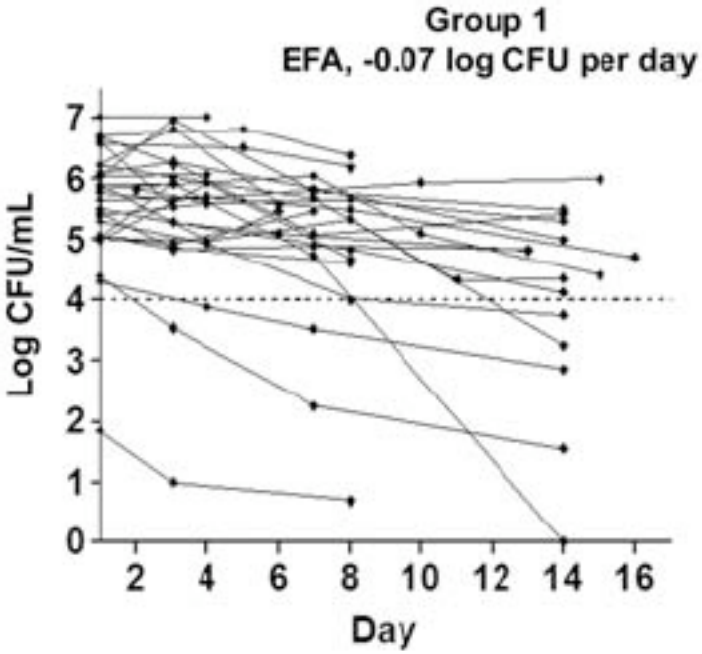


n=47, EFA=-0.44 log CFU/ml/d

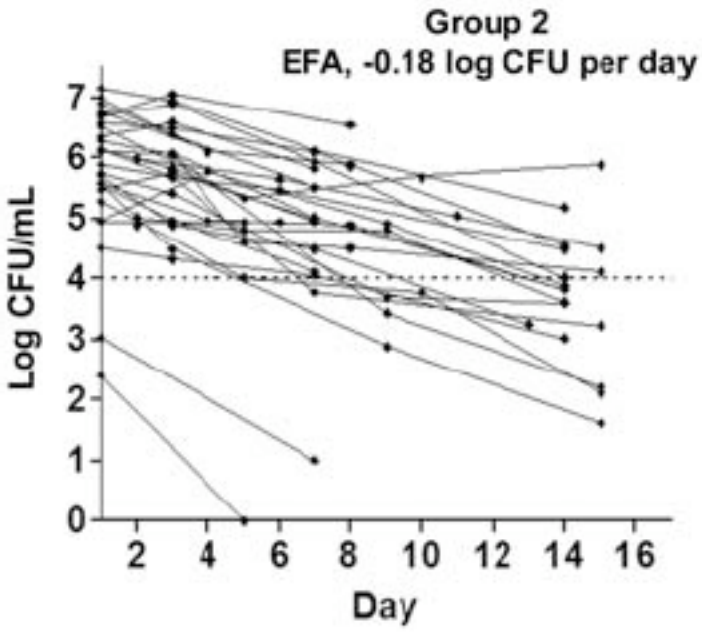
n=5, EFA=-0.02 log CFU/ml/d

p=0.001 for comparison

EFA: Higher doses of Fluconazole



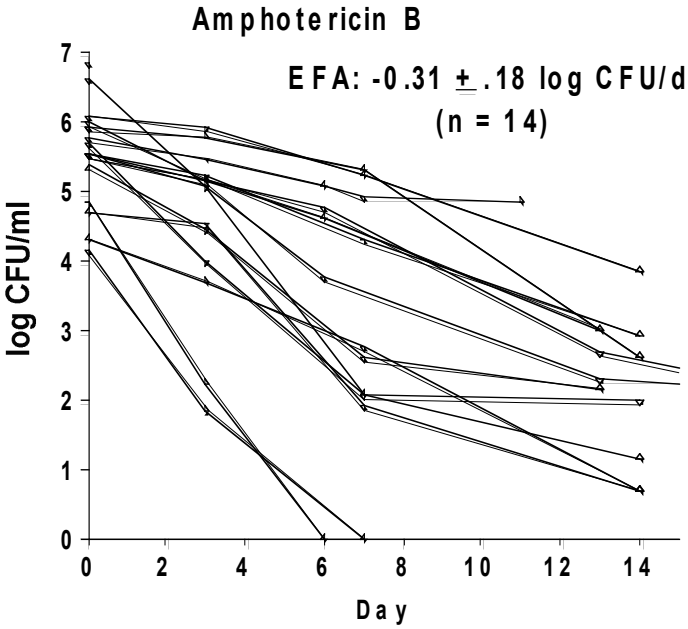
Fluconazole 800mg/day

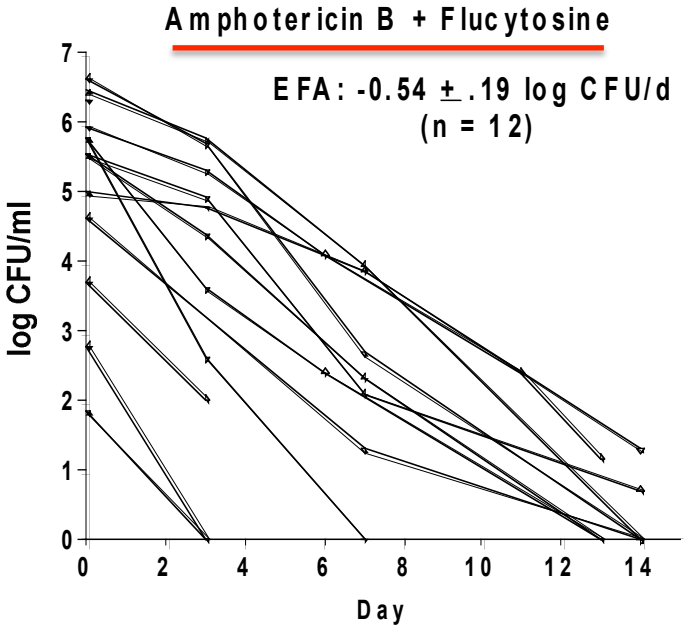


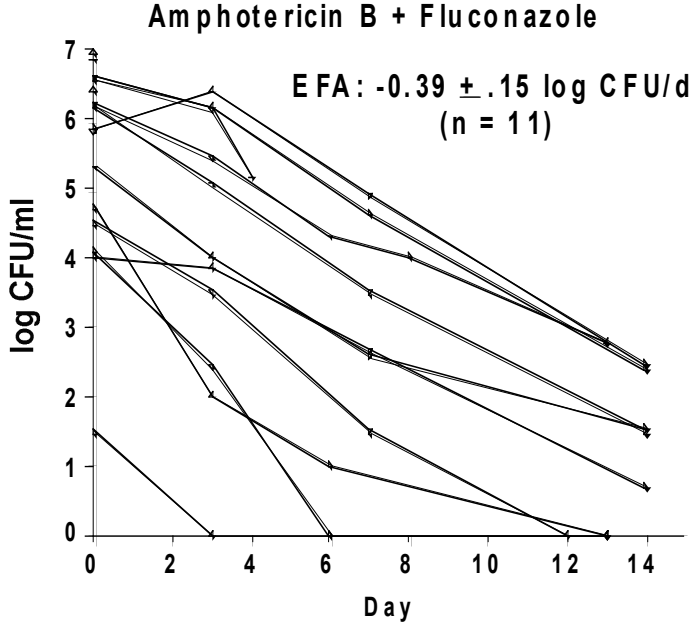
Fluconazole 1200mg/day

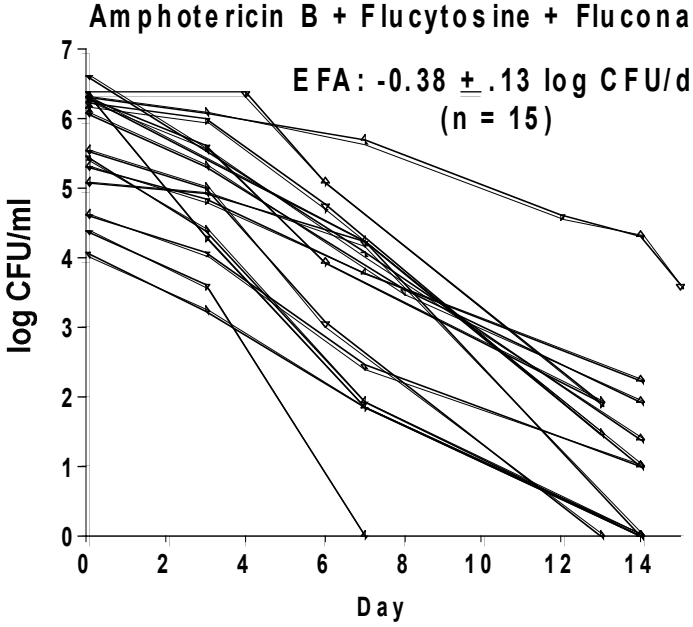
p=0.007 for comparison of two groups

Longley, Clin Infect Dis 2008;47:1556









Brouwer, Rajanuwong, Chierakul, Griffin, Larsen, White, Harrison. Lancet. 2004 *363:1764*

Open label RCT in Vietnam (n = 299)

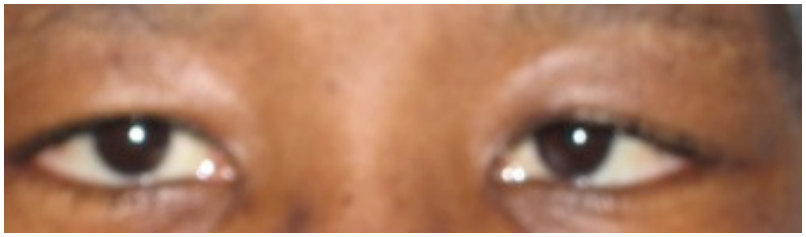
- Induction:
  - Arm 1: AmB x 4 weeks
  - Arm 2: AmB plus flucytosine x 2 weeks
  - Arm 3: AmB plus fluconazole 400mg bd x 2 weeks
- Fluconazole consolidation/maintenance
- 6 month survival:
  - **AmB/flucytosine vs AmB: HR = 0.56 (p=0.01)**
  - AmB/fluconazole vs AmB: HR = 0.78 (p=0.23)
- **Conclusion: AmB/flucytosine resulted in 44% reduction in mortality vs AmB alone**

Day, ICAAC 2011

Raised Intracranial Pressure

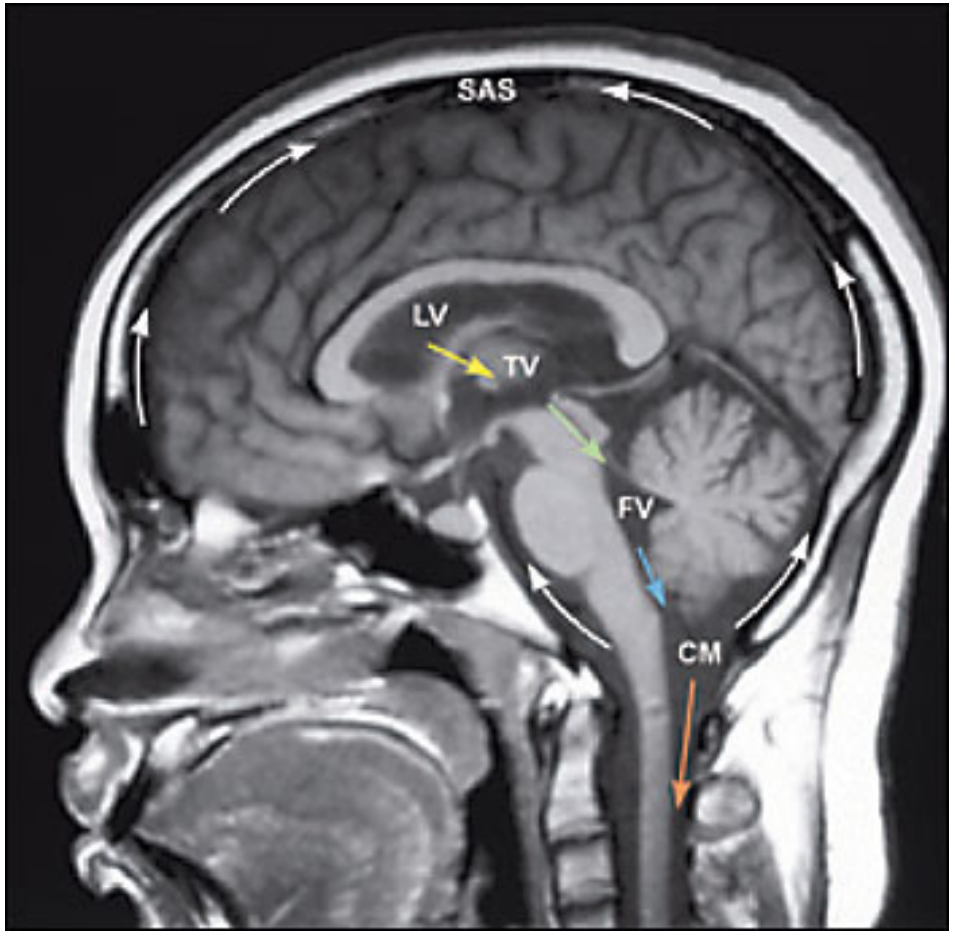
- Common in CM:

  60-80% > 20cmH_2O[1,2]
- Patients with OP > 25 have poorer short-term survival
- Pathophysiology: CSF outflow obstruction by organism or polysaccharide capsule at arachnoid villi

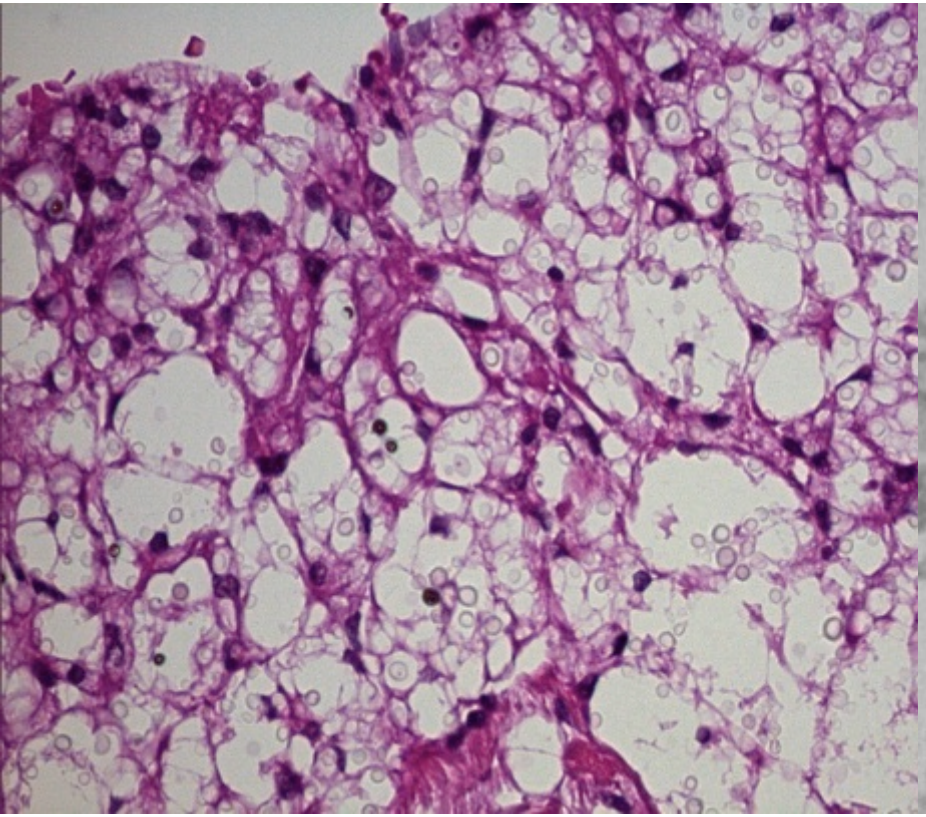


1. Graybill et al. CID 2000; 30: 47-54
2. Kambugu et al. CID 2008: 46: 1694-1701

Normal CSF drainage

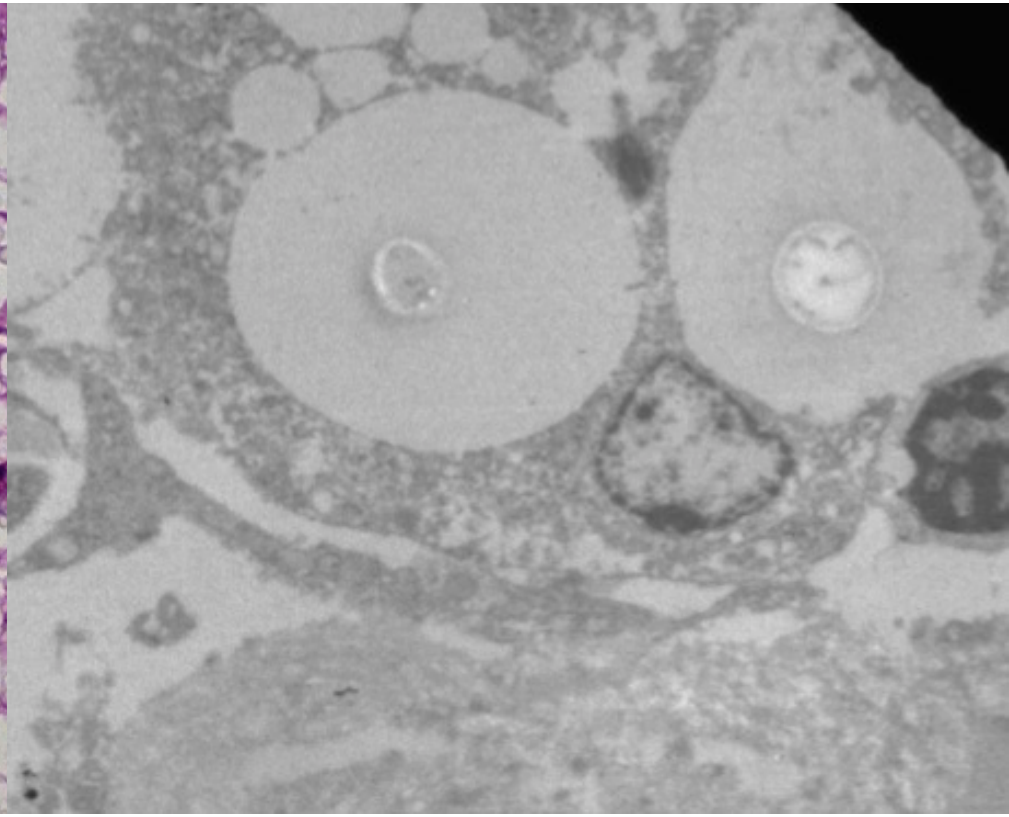


Histopathology of arachnoid villi



x100 Arachnoid granulation showing large numbers of cryptococcal cells and little inflammation (Mucicarmine)

CSF OP 80 cm H_2O, light perception only before death. Died despite lumbar drain.



EM of arachnoid cell containing 2 cryptococcal cells with large capsules (mean 20/hpf). Vacuoles within the cell contain material of the same electron density as the cryptococcal capsule

Loyse A et al AIDS 2010 Jan 28;24(3):405-10

Daily therapeutic lumbar punctures
to reduce raised intracranial pressure
(Remove ~ 20 ml CSF)

Cryptococcal Meningitis IRIS

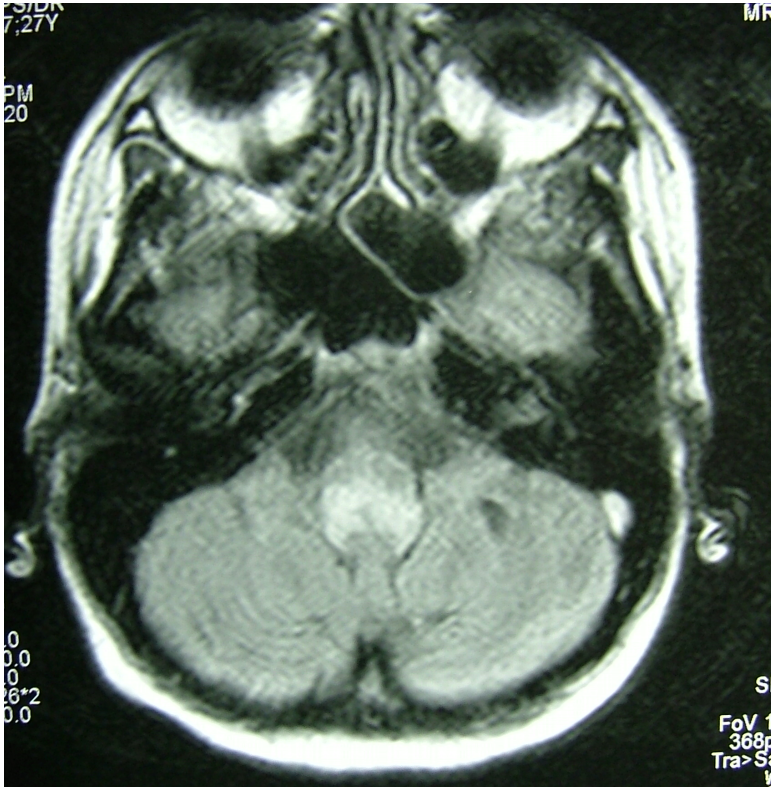
IRIS = Immune Reconstitution Inflammatory Syndrome

Patient diagnosed with CM
Started on treatment and improves

Starts ART

Days to months later (median 28 days)

Develops meningitis symptoms again
Typically fungal culture negative



CRYPTOCOCCAL IRIS CASE:

MRI demonstrating hydrocephalus and marked periventricular, brainstem and meningeal enhancement

Cryptococcal Optimal ART Timing **(COAT)** Trial

- Phase IV randomised strategy trial
- 3 sites in Uganda and South Africa
- Enrollment target = 500

- ART started at **1-2 weeks** vs **5-6 weeks**
- Induction: Amphotericin B + Fluconazole 800mg/d

- Stopped by DSMB (177 enrolled) due to substantially higher mortality in those who started early
  - 42.5% (early) versus 27.6% (deferred) mortality (HR = 1.7)
  - Difference in mortality more evident in those with GCS < 15 and between 8-30 days on ART

NIAID, September 21, 2012

Mortality: South Africa

- Cape Town (Bicanic, Clin Infect Dis 2007 & 2008)
  - 24 - 37% 10 week mortality
- Johannesburg (Govender, unpublished)
  - 67% died or lost to follow-up by 3 months
- Rural Kwazulu-Natal (Lessells, SAMJ 2011)
  - 41% in-hospital mortality
  - 11% alive in ART care at 2 years

Management: Key points

- Amphotericin-B based combination therapy for induction
- Therapeutic lumbar punctures
- ART at 4-6 weeks
- Counselling and support (“treatment buddy”)

Study team and collaborators

GF JOOSTE HOSPITAL
Charlotte Schutz
Brian Memela
Monica Magwayi

ST GEORGE'S HOSPITAL
Tom Harrison
Tihana Bicanic
Joe Jarvis
Angela Loyse
Nicky Longley

UNIVERSITY OF MINNESOTA
David Boulware
Paul Bohjanen

MAKERERE UNIVERSITY
David Meya

MBARARA UNIVERSITY
Conrad Muzoora

NICD
Nelesh Govender