Cryptococcal Meningitis Treatment: What's on the horizon?

Tom Harrison

Professor of Infectious Diseases, St Georges University of London

21st July 2020

ICAP Columbia University Mailman School of Public Health

HIV LEARNING NETWORK
The CQUIN Project for Differentiated Service Delivery

Current recommendations

- Symptomatic meningitis: WHO (2018), SA HIV Clinicians Soc. (2019)

Preferred: A short course (1 week) induction with AmB + 5FC

Alternative: 2 weeks fluconazole 1200 mg/d + 5FC

both followed by fluconazole consolidation and maintenance and ART at 4-6 wks

- Early infection - Asymptomatic CrAg-positive cases identified during screening:

Recommend LP; if LP declined (majority of cases), or CSF CrAg negative: fluconazole 1200 mg/d 2 weeks, followed by fluconazole consolidation/maintenance and ART at 2 wks

AmB = amphotericin B deoxycholate; 5FC = flucytosine. ART antiretroviral treatment, CrAg = cryptococcal antigen, CSF = cerebrospinal fluid.

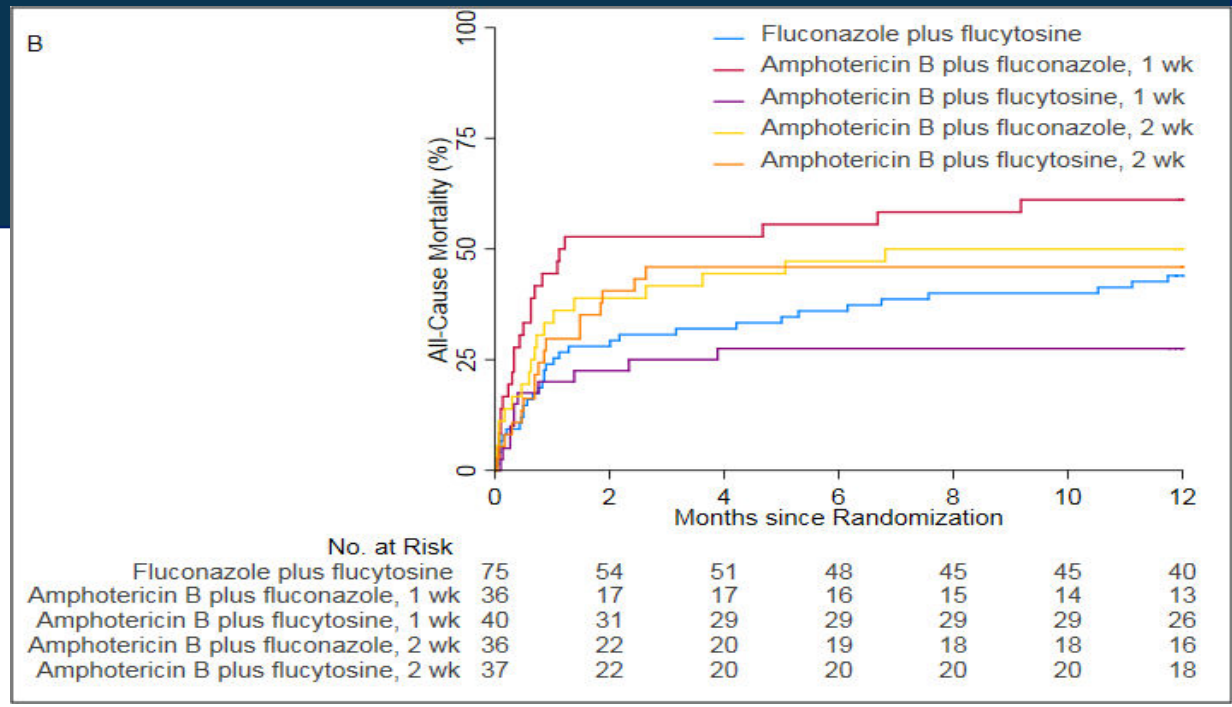
Current recommendations

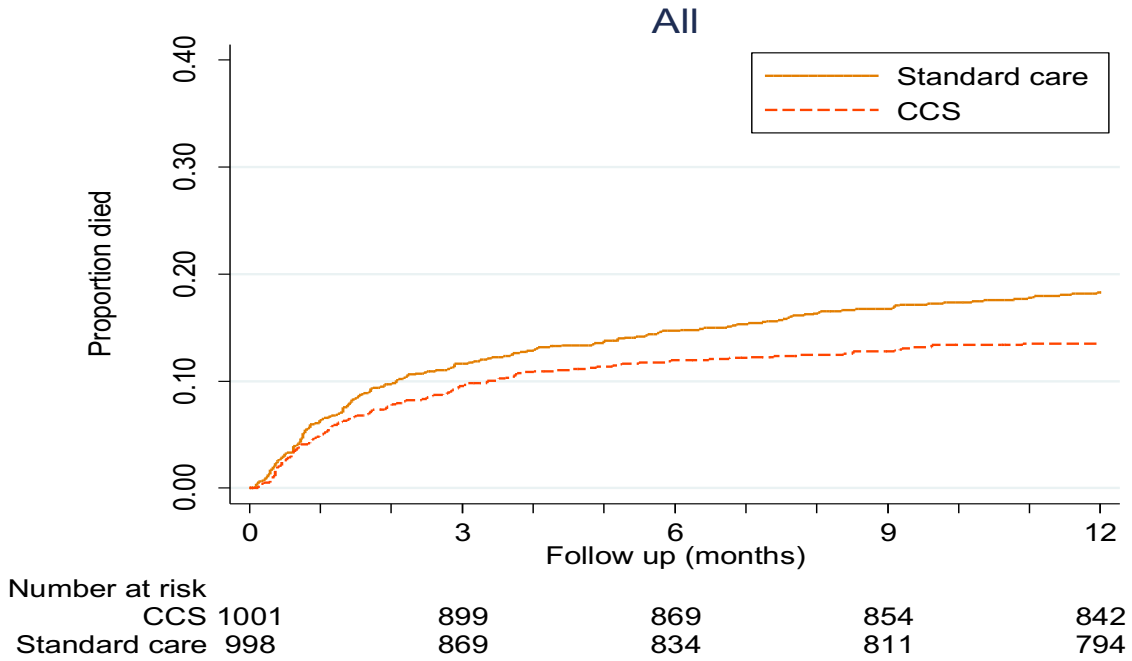
Both based RCT mortality benefit data:

Symptomatic meningitis - ACTA

Molloy et al. NEJM 2018 378:1004

long term follow-up data CID 2020;70:521 ➔





Screening – REMSTART

Mfinanga, et al. *Lancet* 2015 385:2173-82

➔

Approx half mortality benefit due screening

The future? Optimising use of Liposomal Amphotericin B: The AMBITION-CM trial

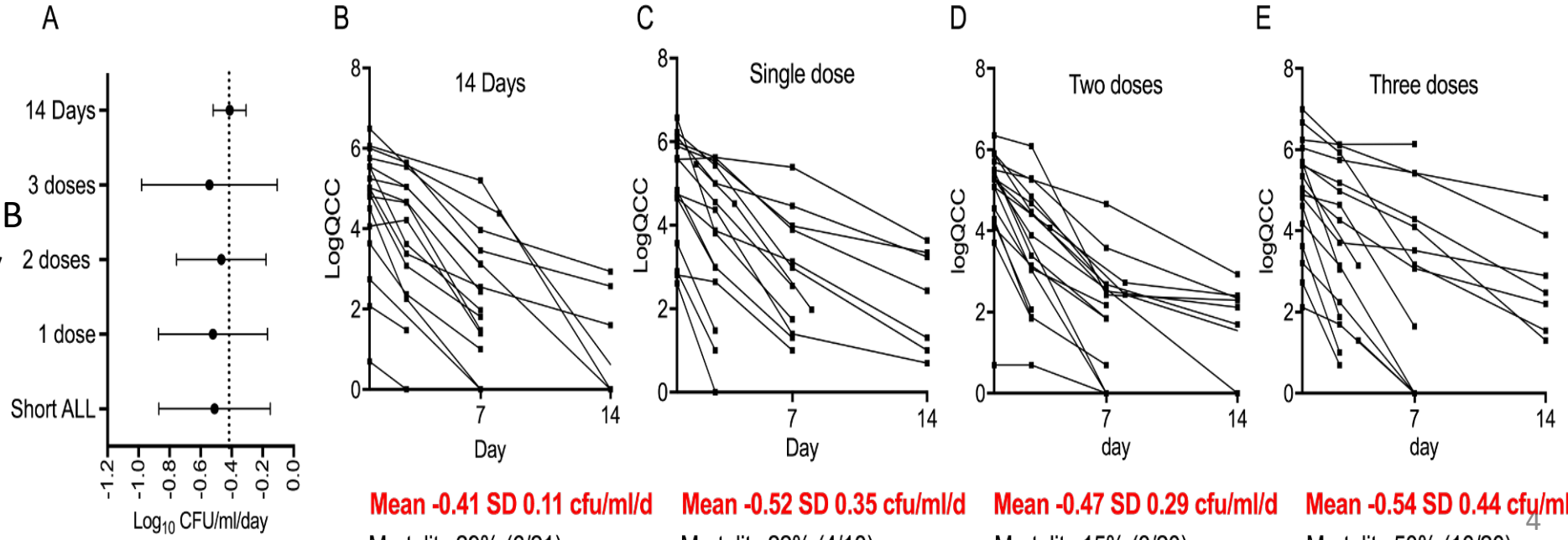
Liposomal amphotericin (L-AmB, Ambisome) – in prior trials, no more effective but less toxic (renal impairment, anaemia) than conventional amphotericin B deoxycholate; even longer half life; excellent brain levels

Even better suited than conventional AmB to short course high dose induction treatment (as used in ACTA) – aimed at loading brain compartment

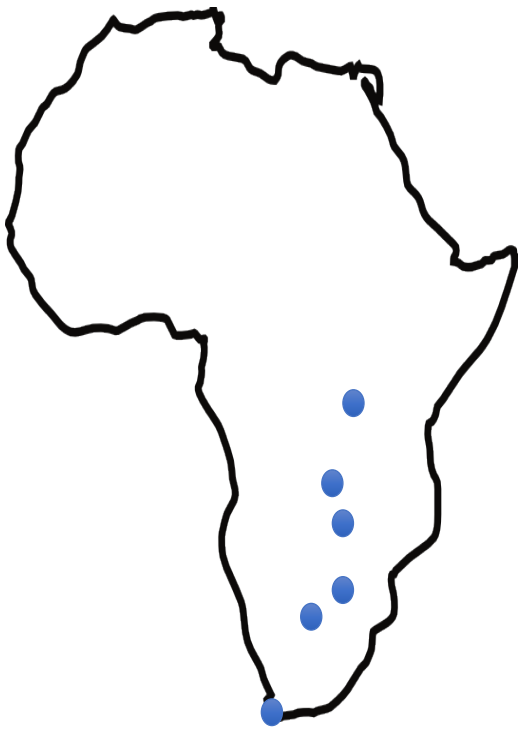
IF one / few doses effective, could be cost effective due shorter admission, less monitoring; and feasible to implement

Phase II RCT
Single 10 mg/kg/d dose:
Safe, safer than Deoxy AmB
As rapid clearance as daily dosing for 2 weeks

Jarvis et al Clin Infect Dis. 2019 Jan 18;68:393



The AMBITION-CM trial: Phase-III study – clinical endpoint non-inferiority trial



- **Liposomal-AmB 10 mg/kg day 1 (single dose) plus 5FC plus fluconazole (for initial 2 weeks) vs**
- Amphotericin B deoxycholate 1.0 mg/kg/d 7 days plus 5FC (*"control arm" new WHO standard – from ACTA*)
- All patients fluconazole 800 mg/d to 10 weeks, 200 mg/d thereafter. ART initiated 4-6 weeks
- Endpoints: *Primary:* All-cause mortality within 10 weeks
- *Secondary:* Early Fungicidal Activity (EFA); 2-week mortality; tolerability and adverse events; cost-effectiveness

EDCTP
European & Developing Countries Clinical Trials Partnership

UKaid
from the British people

MRC Medical Research Council

wellcome

>650 of target of 850 participants already enrolled

Results expected early 2021

Wide access to Flucytosine, and Modified-Release Flucytosine

- Access to 5FC is increasing and costs of 5FC are coming down:

UNITAID AHD programme (launched Jan 2019)

South African access programme, 5FC in routine use from May 2019:

> 24% in-hospital mortality first 335 patients, with 1 week AmB+5FC regimen, compared with 35% from long term surveillance data in South Africa. *Govender N et al ICASA Dec2019*

- Major (Mylan) and multiple manufacturers committed

- Funding secured for development of easier to use modified release formulation that could be given twice rather than 4 x daily (EDCTP – DNDi and partners)
- In fact, progress since release of ACTA results showing that 5FC is an essential part of best treatment has been rapid

The future? More effective antifungal treatment for those testing CrAg-positive during screening

- Those testing CrAg positive have continued high mortality, despite fluconazole
- And a significant proportion 30-40% CrAg positives have subclinical CM (defined by +ve CSF CrAg) if they agree to LP
- A high CrAg titre predicts subclinical CM; and a high titre and subclinical CM are both associated with higher mortality

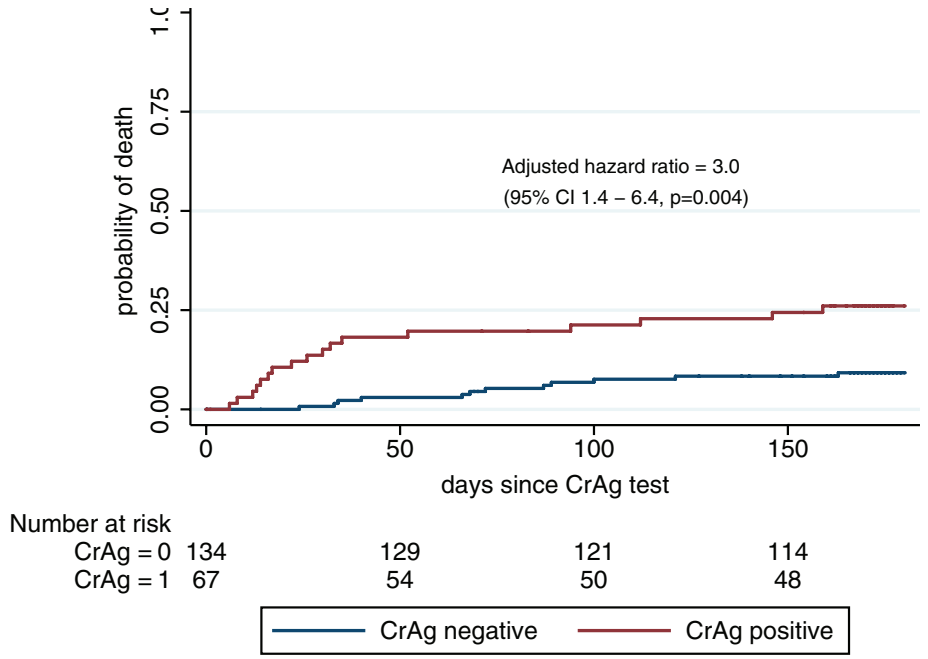
We need to study more effective antifungal therapy for those who are CrAg+ve, in the context of a bundle of diagnostics and ART adherence support for all

Clinical Infectious Diseases

MAJOR ARTICLE

Cryptococcal-related Mortality Despite Fluconazole Preemptive Treatment in a Cryptococcal Antigen Screen-and-Treat Program

Rachel M. Wake,[1,2] Nelesh P. Govender,[1,3,4] Tanvier Omar,[5,6] Carolina Nel,[5,6] Ahmad Haeri Mazanderani,[7,8] Aaron S. Karat,[9] Nazir A. Ismail,[10] Caroline T. Tiemessen,[7,11] Joseph N. Jarvis,[12,13,14] and Thomas S. Harrison[2]



More effective antifungal treatment for those testing CrAg-positive: EFFECT and ACACIA trials

- EFFECT trial – funded MRC WT DFID Global Health Trials
  - From ACTA we know Fluconazole plus flucytosine (2 wks) is safe and effective and could be sustainable, cost-effective oral option for CrAg +ve, that may preclude need for LP and i/v Rx
  - South Africa, Tanzania, pragmatic trial, within screening programmes
  - 600 asymptomatic CrAg positive randomised to:
  - Fluconazole vs Fluconazole + flucytosine (first 2 wks)
  - All participants: ART adherence support, TB diagnostics

- ACACIA trial - Single Dose iv Liposomal Amphotericin for Asymptomatic Cryptococcal Antigenemia (ACACIA)
  Uganda, enrolling 2019 - 2023

Stratified management for those testing CrAg-positive according to CrAg titre

Semi-quantitative tests are in development:
IMMY CrAgSQ (negative, 1+ to 4+)
Jarvis et al J. Clin. Microbiol. Online 27 May 2020 ➔

But may not be as easy to use in routine care as standard CrAg LFA - Depends relative intensity different test bands

Biosynex Crypto PS (negative, 1+, 2+)
Simple to use *But* sensitivity and specificity sub-optimal compared IMMY LFA. Tenforde et al, unpublished

Nevertheless prospect is that more aggressive antifungal treatment could be directed at those with higher blood titre, at greatest risk of poor outcome.
EFFECT and ACACIA can be analyzed by titre in retrospect in order to guide management pathways