Cryptococcal meningitis management
in South Africa

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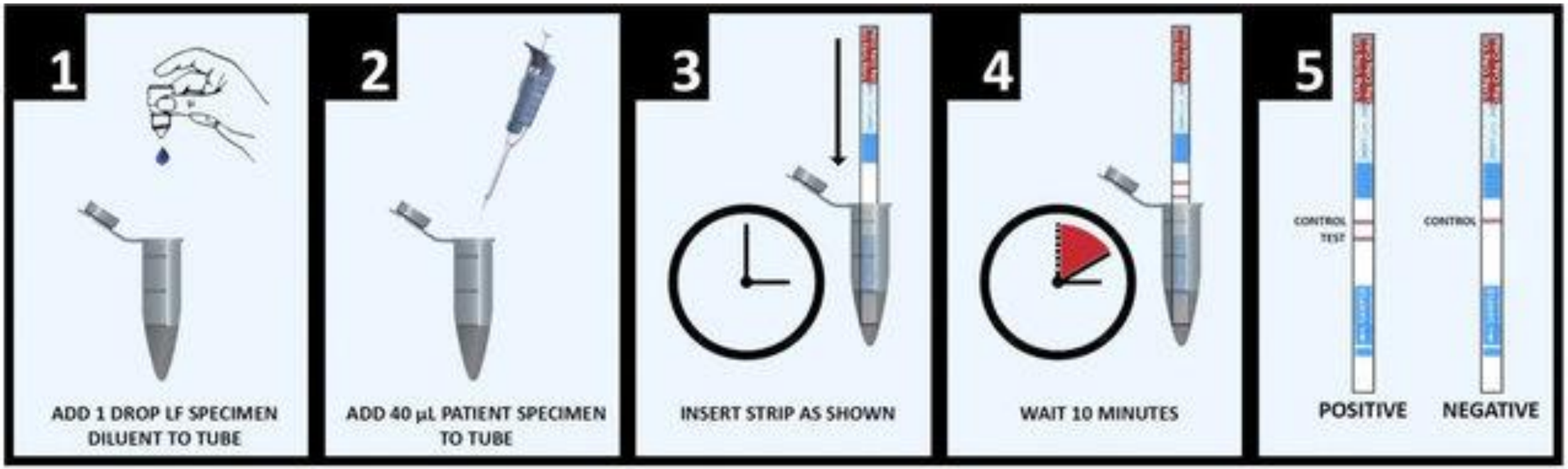
Burden of Cryptococcal Meningitis (CM)

- Globally, CM responsible for 15% of AIDS-related deaths
- Annual global deaths estimated at 181 100
- 135 900 deaths in sub-Saharan Africa.
- 6,636 cases of se detected by NICD in 2017 in SA
- (60%) of those were on ART at Diagnosis or at some time in past

Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis*. 2017;17(8):873–881. doi:10.1016/S1473-3099(17)30243-8

Diagnosis

- Diagnosis is **easy** – if you think about it at least.
- NHLS currently does **reflex cryptococcal antigen (CrAg) testing on all CD4 counts <100-200** (differs by province at the moment).


1
ADD 1 DROP LF SPECIMEN DILUENT TO TUBE
2
ADD 40 µL PATIENT SPECIMEN TO TUBE
3
INSERT STRIP AS SHOWN
4
WAIT 10 MINUTES
5
CONTROL
TEST
CONTROL
POSITIVE
NEGATIVE

Interpreting the result

Positive	Current cryptococcal disease Previous cryptococcal disease
Negative	No cryptococcal disease False negatives (VERY rare)

What should you do if the patient's serum CrAg is positive?

- **EVERYONE with a positive CrAg should have a lumbar puncture** – even if they don't have symptoms.

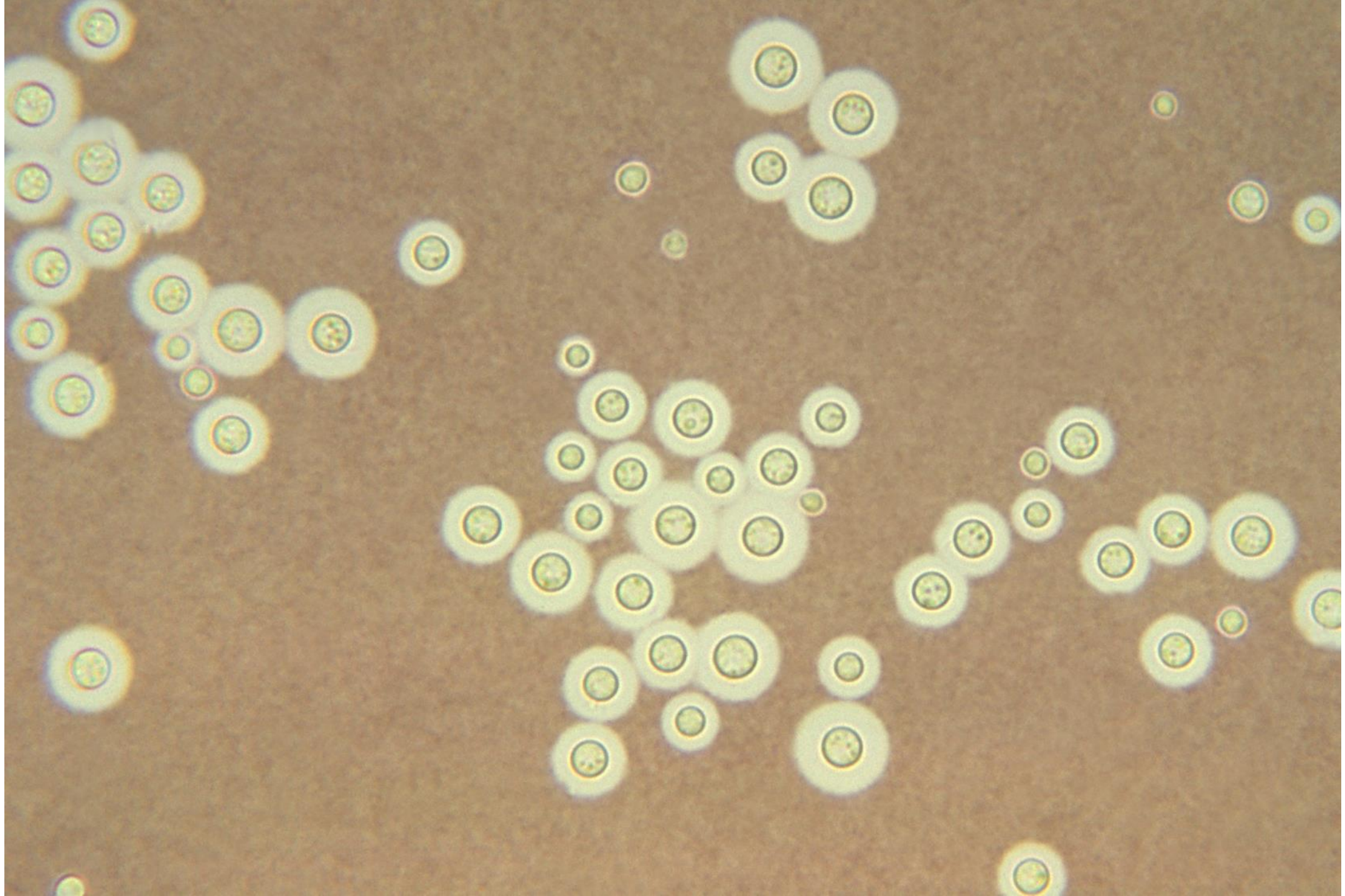
- Data suggests that up to 1/3 serum CrAg-positive patients who are asymptomatic will have cryptococcal meningitis on lumbar puncture.
  - Might be less than this in reality but still…

Clin Infect Dis. 2018 Feb 10;66(5):686-692. doi: 10.1093/cid/cix872.

CRYPTOCOCCAL DIAGNOSTICS' sensitivity

Using **fungal culture** as the gold standard:

Test	Sensitivity
India Ink	70%
Cryptococcal antigen (CrAg)	> 95%



CSF Culture?

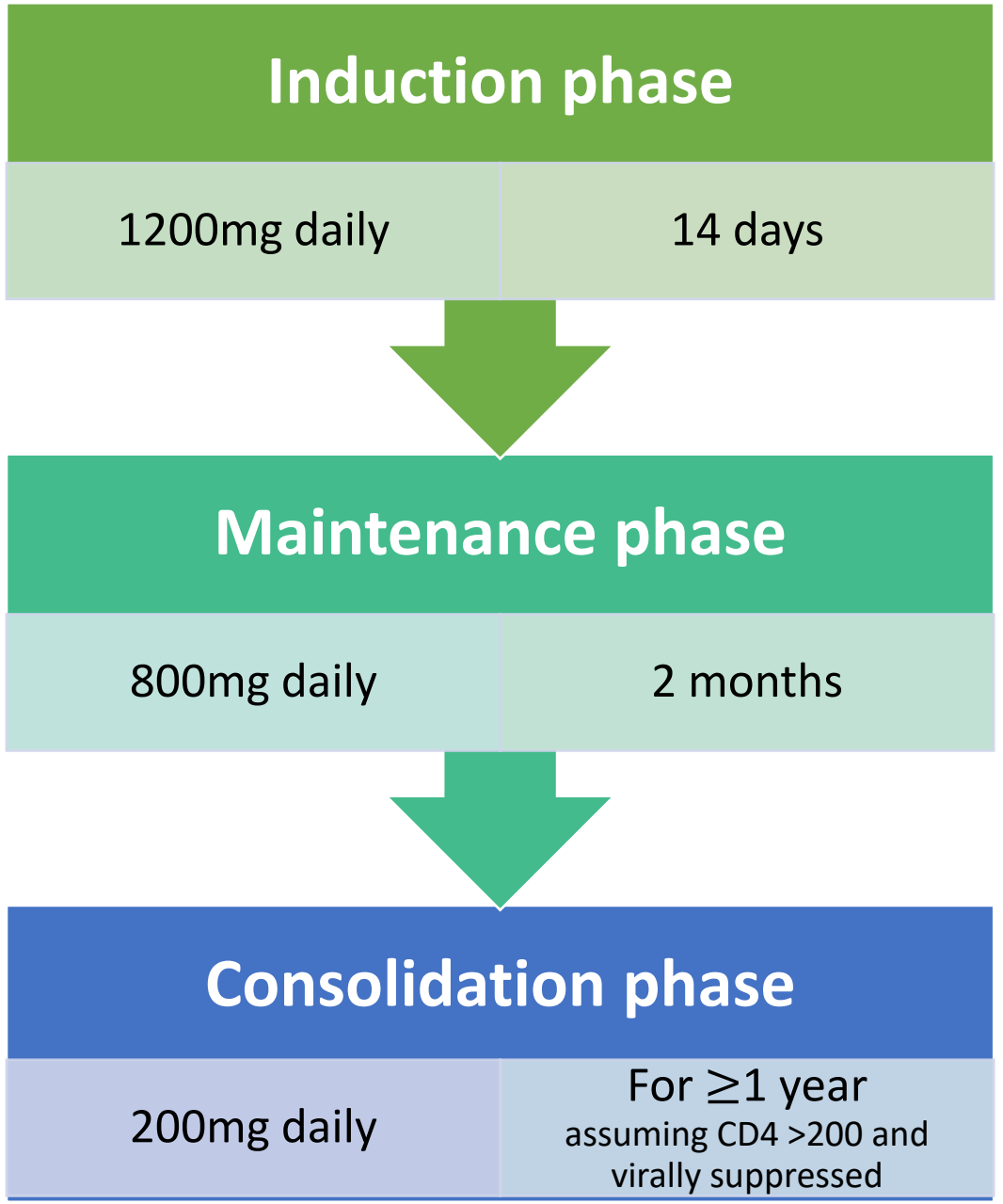
Sensitive test, but can take up to 14 days.

Not useful for urgent diagnosis (use CrAg).

BUT – can help for ?relapse cases – culture will be positive in a relapse but not generally in an IRIS.

What if cryptococcal meningitis excluded?

- Patients need **fluconazole**
- ART can be started **immediately**.



Careful with these patients though…

- Mortality still very high despite giving them fluconazole.
  - 2-3x higher than controls without positive serum CrAg at 6 months.

- **Advanced HIV patients** – so check:
  - **Bactrim** prophylaxis
  - **Exclude TB**, and if no active TB, give **TPT**
  - **ART** asap if no reasons to delay

Clin Infect Dis. 2023 Feb 15; 76(4): 764–770

What to do if cryptococcal meningitis confirmed?

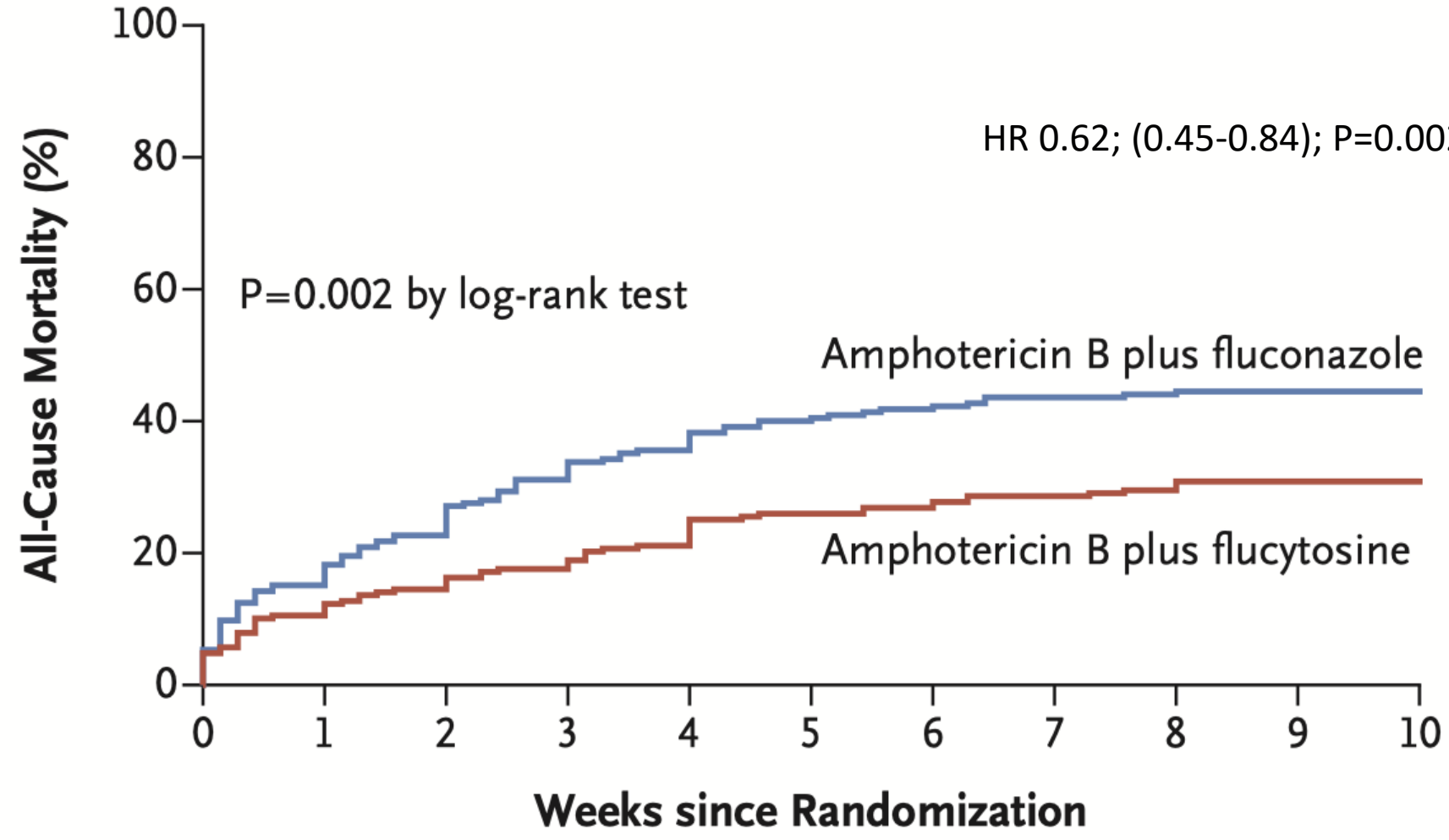
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa

S.F. Molloy, C. Kanyama, R.S. Heyderman, A. Loyse, C. Kouanfack, D. Chanda, S. Mfinanga, E. Temfack, S. Lakhi, S. Lesikari, A.K. Chan, N. Stone, N. Kalata, N. Karunaharan, K. Gaskell, M. Peirse, J. Ellis, C. Chawinga, S. Lontsi, J.-G. Ndong, P. Bright, D. Lupiya, T. Chen, J. Bradley, J. Adams, C. van der Horst, J.J. van Oosterhout, V. Sini, Y.N. Mapoure, P. Mwaba, T. Bicanic, D.G. Lalloo, D. Wang, M.C. Hosseinipour, O. Lortholary, S. Jaffar, and T.S. Harrison, for the ACTA Trial Study Team*

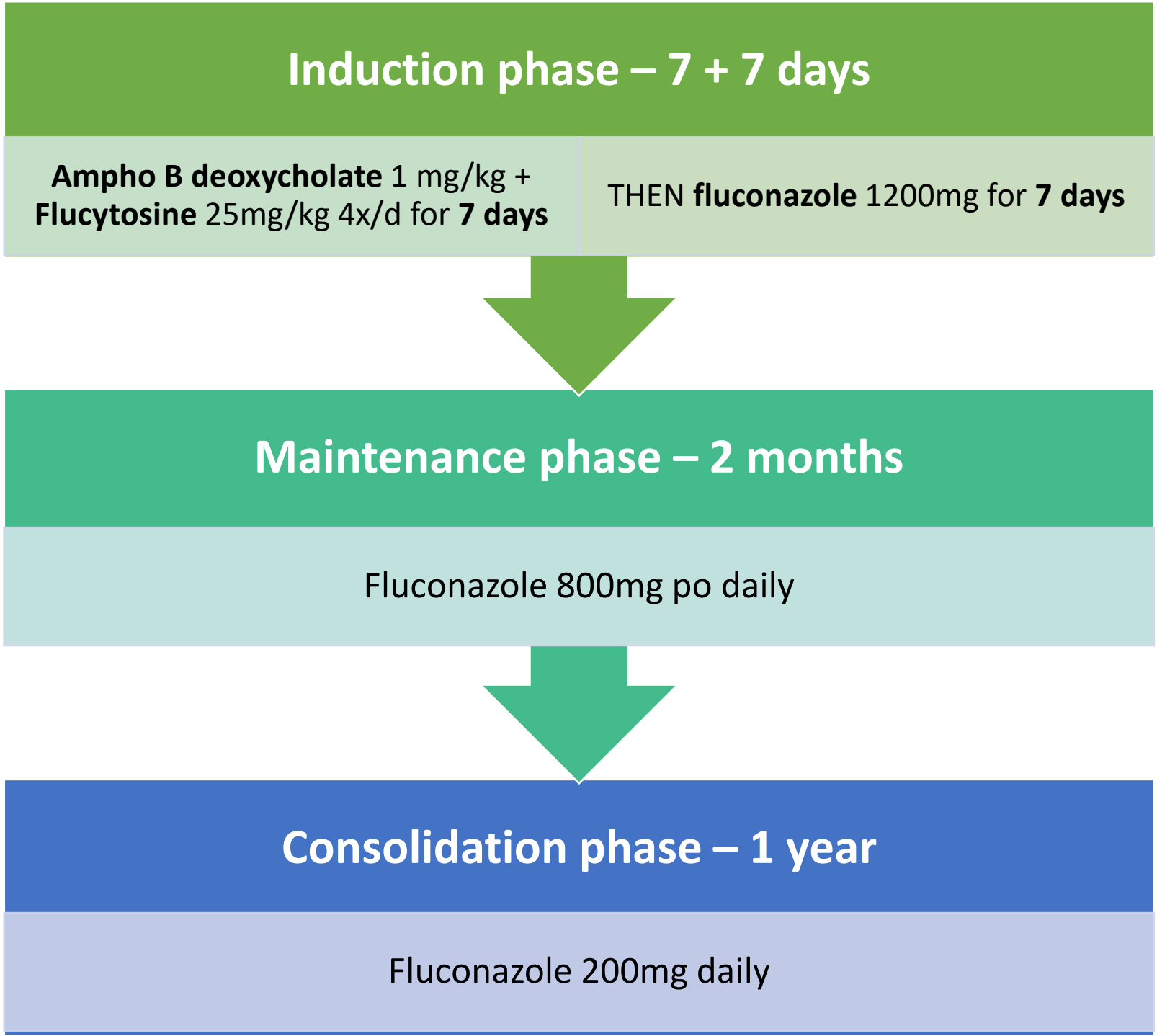
N Engl J Med 2018;378:1004-17.
DOI: 10.1056/NEJMoa1710922



HR 0.62; (0.45-0.84); P=0.002

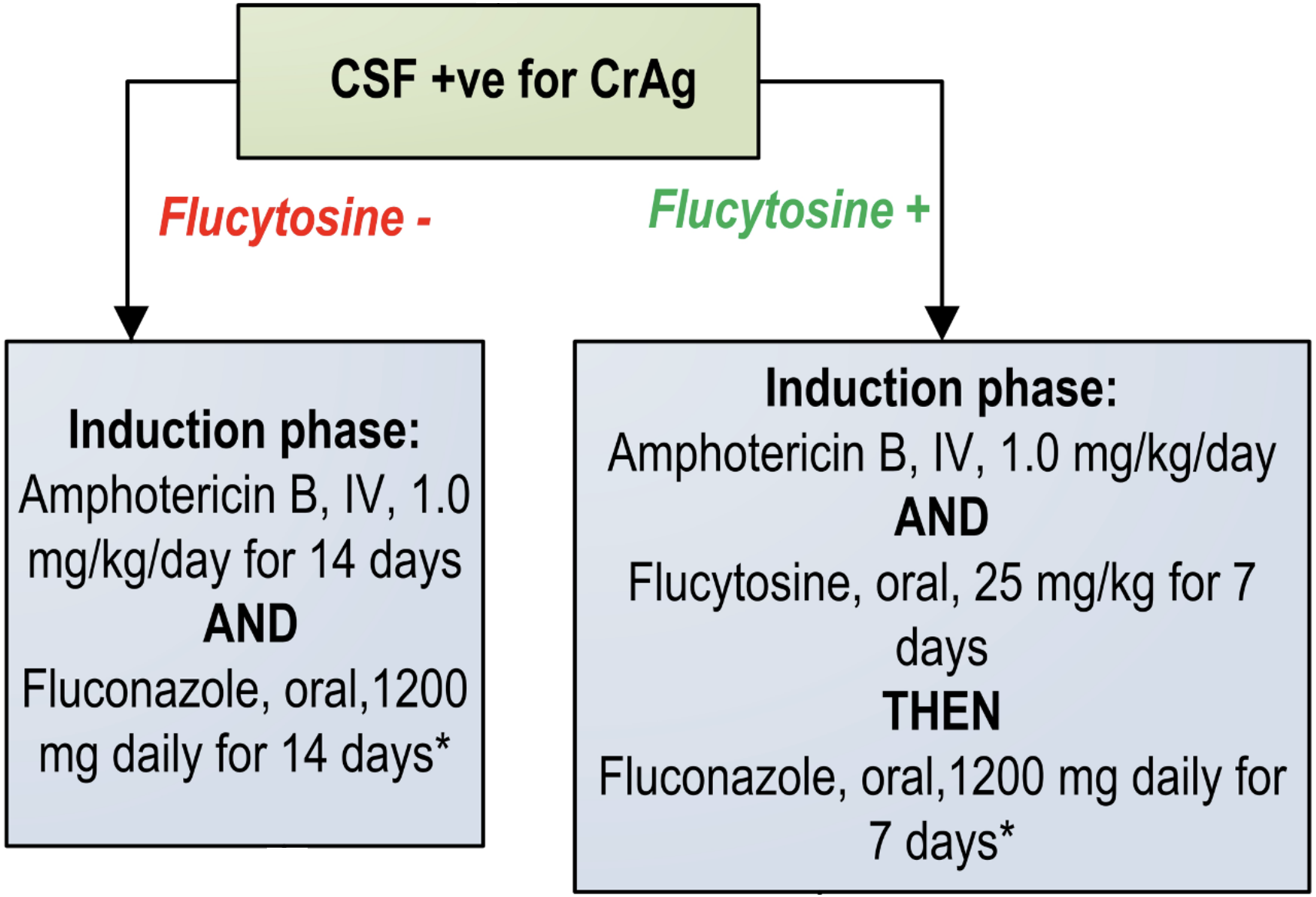
No. at Risk

Amphotericin B plus fluconazole	225	191	174	155	145	135	130	126	125	124	122
Amphotericin B plus flucytosine	228	203	194	187	179	167	165	161	159	156	153

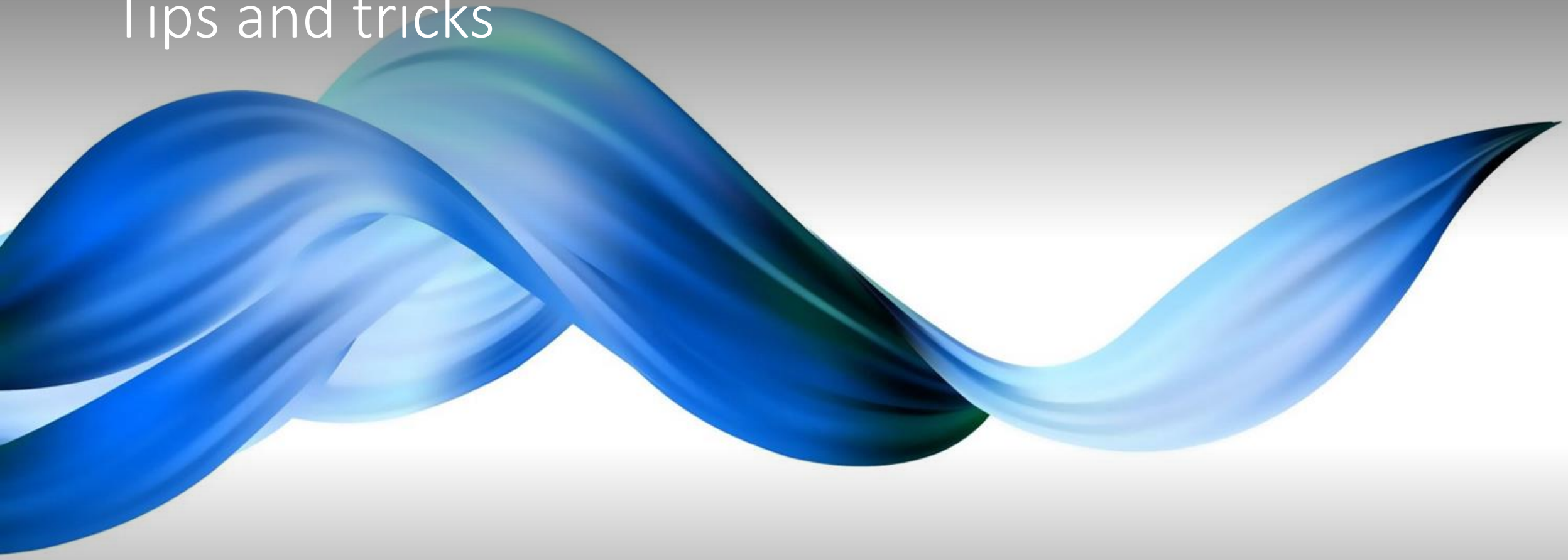


New as of 2023

Same as before

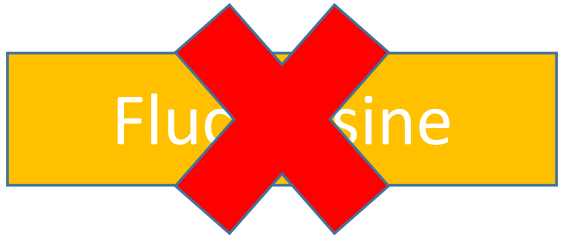

CSF +ve for CrAg
Flucytosine -
Flucytosine +
Induction phase:
Amphotericin B, IV, 1.0 mg/kg/day for 14 days
AND
Fluconazole, oral,1200 mg daily for 14 days*
Induction phase:
Amphotericin B, IV, 1.0 mg/kg/day
AND
Flucytosine, oral, 25 mg/kg for 7 days
THEN
Fluconazole, oral,1200 mg daily for 7 days*

Tips and tricks

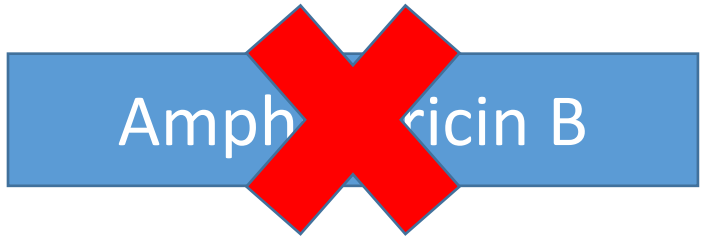


Which of the following are **nephrotoxic**?

Amphotericin B



Which of the following **need dose adjustment** in patients with impaired renal function?



Fluconazole

Flucytosine

Adjusting the doses…

Fluconazole

- halve the dose if eGFR <50 ml/min

e.g. change induction dose from 1200mg daily to 600mg daily.

Flucytosine

- still 25mg/kg per dose, but:
  - Switch to twice daily if eGFR 10-50 ml/min, and
  - Switch to daily dosing if eGFR <10 ml/min.

And amphotericin B in renal failure?

- If creatinine increases by >2-fold from baseline, either omit an amphotericin B dose, or increase pre-hydration to 1 litre 8 hourly.
  - Once improved, restart at 0.7 mg/kg daily and consider alternate day amphotericin B.

↳ … then continue with consolidation and maintenance phases as usual

- Avoid nephrotoxic drugs such as NSAIDs including ibuprofen and aminoglycosides

5-FC dose adjustment for renal impairment

- 5-FC may accumulate in patients with renal impairment owing to poor excretion
- The hal- life of 5-FC is prolonged in patients with renal insufficiency; the average half-life is 85 hours (versus 2.4-4.8 hours in patients with normal renal function)
- If creatinine clearance reduces to <50 ml/min, give same initial dose but reduce subsequent doses by 50%
- Intermittent haemodialysis: **25 mg/kg every 58-72hrs (administer after dialysis)**

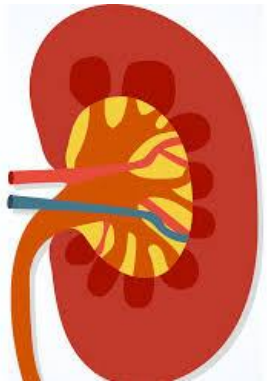
Creatinine Clearance ml/min	**Individual dose (mg/kg)**	**Dose Interval**
>40	25	6 hourly
20-40	25	12 hourly
10-19	25	24
<10	25	48 hourly

Est. creatinine clearance =
(140 – age) * (weight in kg) / (72 * Cr in mg/dL)
[Multiply result by **0.85** for women]

Safe administration of Amphotericin B

Administer over 2-6 hrs to avoid arrhythmias

Inject AmB dose into 1000ml bag of 5% **dextrose** or 10% Dextrose (never normal saline as drug will precipitate).

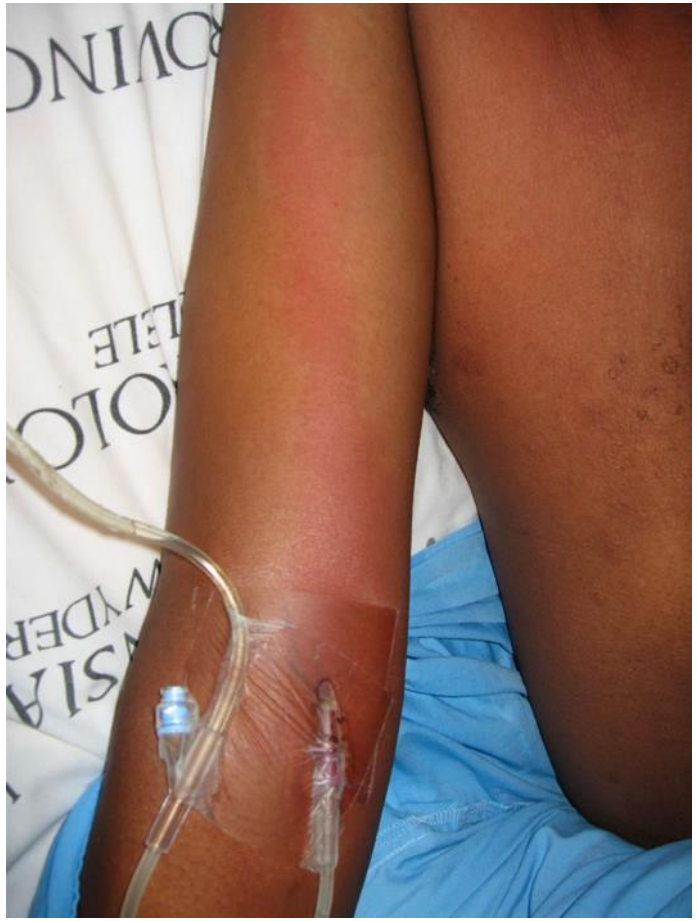


Renal toxicity more likely in 2nd week of Tx. (if using 2 week regimen). Monitor fluid input and output carefully

Tips and tricks

- **Amphotericin B** = toxicities. Major ones:
  - **Hypokalaemia, hypomagnesaemia**: monitor at baseline and twice weekly
  - **Anaemia** – usually after 7 days: monitor at baseline and weekly
  - **Renal failure** – ensure adequate hydration. Dose adjust meds if needed.
- **Fluconazole**
  - Generally safe. Occasionally hepatitis picture
  - Dose adjust in renal failure
- **Flucytosine**
  - Bone marrow toxicity – mainly platelets and neutrophils
  - Dose adjust in renal failure

Safe Amphotericin B (deoxycholate) administration: avoiding and managing infection at IV site



Chemical phlebitis is often complicated by infection at IV insertion site - can cause bacteraemia - Monitor daily for thrombophlebitis.

Flush IV lines with normal saline immediately after amphotericin B infusion is complete.

The empty bag should not be left attached to the intravenous line.

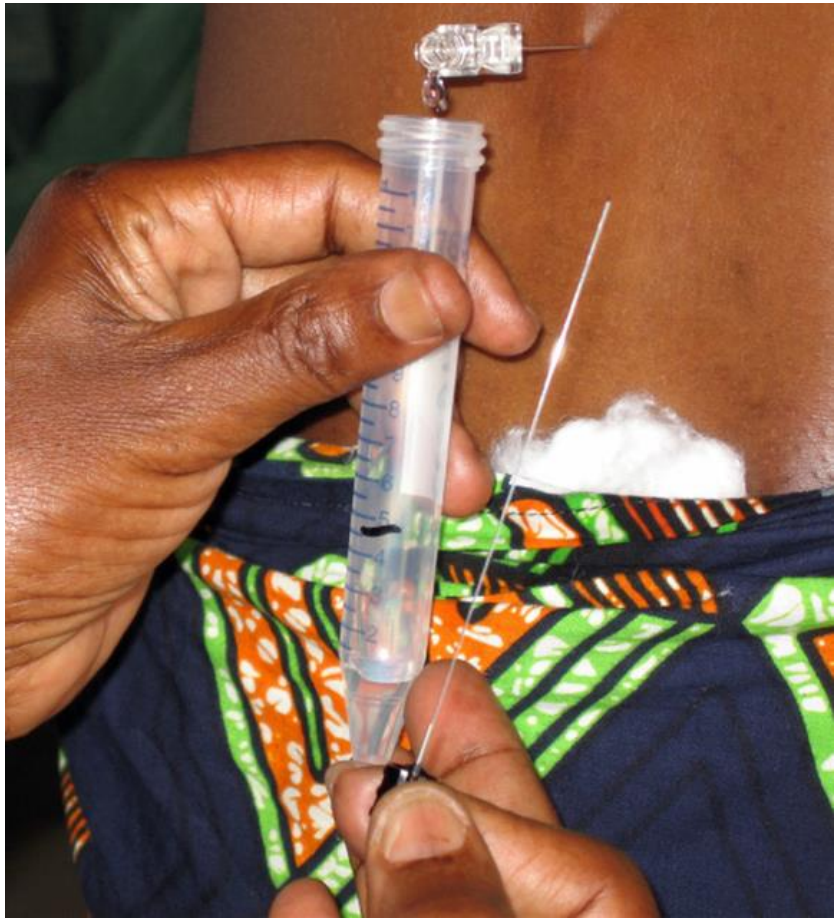
Remove IV if the patient develops a fever after the infusion or at the first sign of redness or discomfort at the insertion site

If amphotericin B-induced rigors occur, the infusion length can be increased and/or acetaminophen / paracetamol (650-1000mg) PO/PR administered 30 minutes prior to AmB.

febrile patients with a suspected insertion site infection should be appropriately investigated and managed.

Intracranial pressure measurement and therapeutic LP

- The pressure should be measured using a manometer with the patient lying down and without excessive spinal flexion.
- ~15% of patients with initially normal intracranial pressure (IPC) will develop raised ICP during treatment.
- All patients should be monitored daily for headache or signs of raised intracranial pressure that should prompt an LP.



When to measure the ICP?

- At the time of the initial LP.
- Repeat LP and measurement of ICP: persistent symptoms during induction therapy, especially if severe or worsening: especially if the baseline ICP was elevated.
- If recurrent symptoms after initial improvement (suspect treatment failure)

Therapeutic LP

- If the opening pressure is raised **(>20 cm H_2O)**, then remove sufficient CSF (maximum 30 mL) to lower pressure to 50% of the opening pressure but not less than 20 cm H_2O.
  - If no pressure taken on 1st LP, repeat to take a “baseline” pressure
- Thereafter need dictated by recurrence of symptoms of raised ICP intracranial pressure
  - daily LPs until the patient is asymptomatic and the CSF pressure : normal and/or stable
- Therapeutic LP typically relieves symptoms if they were due to increased ICP

When should ARVs be started?

The NEW ENGLAND JOURNAL of MEDICINE

COAT Trial

ORIGINAL ARTICLE

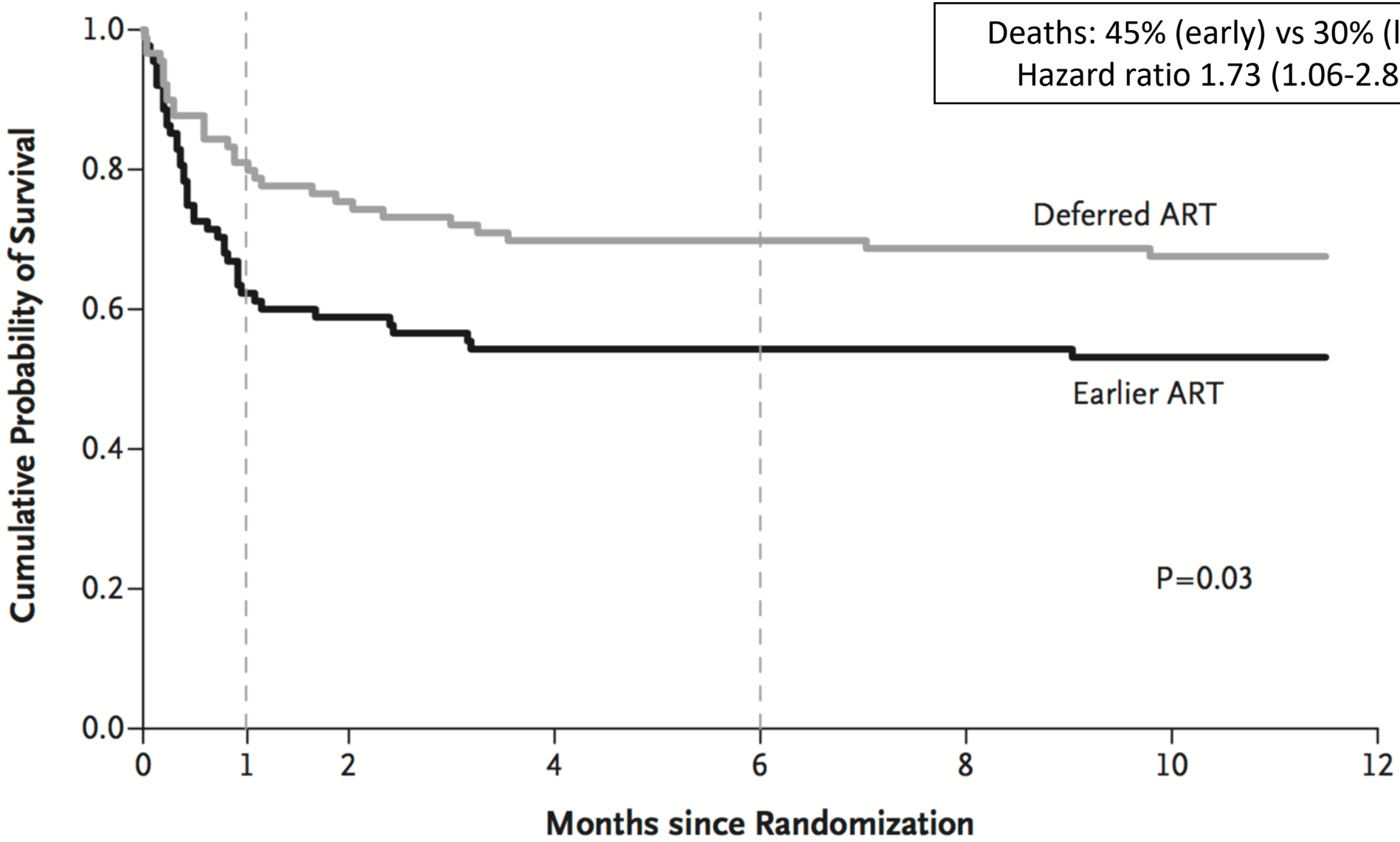
Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis

N ENGL J MED 370;26 NEJM.ORG JUNE 26, 2014

METHODS

We assessed survival at 26 weeks among 177 human immunodeficiency virus–infected adults in Uganda and South Africa who had cryptococcal meningitis and had not previously received ART. We randomly assigned study participants to undergo either earlier ART initiation (1 to 2 weeks after diagnosis) or deferred ART initiation (5 weeks after diagnosis). Participants received amphotericin B (0.7 to 1.0 mg per kilogram of body weight per day) and fluconazole (800 mg per day) for 14 days, followed by consolidation therapy with fluconazole.

Deaths: 45% (early) vs 30% (late)
Hazard ratio 1.73 (1.06-2.82)

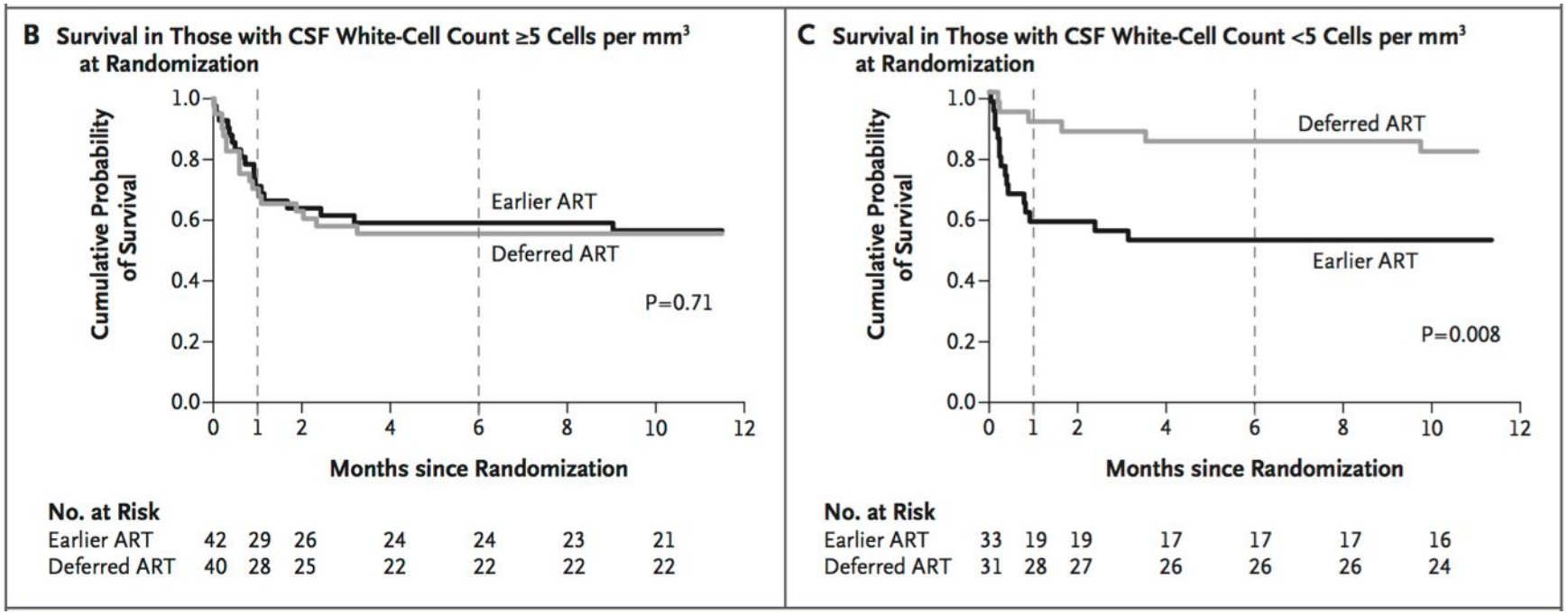


No. at Risk

Earlier ART	88	54	51	47	47	46	42
Deferred ART	89	72	67	62	62	61	59

Cause of excess death

- Seemed to be related to **cryptococcal IRIS** within the CNS.
- The excess death rate was essentially only seen in those with low CSF white cell count (< 5) – reflects poor initial immunity and highest propensity for severe IRIS.



WHEN SHOULD ARVs be started in patients with CCM?

- After 4-6 weeks (all things being equal).

Could we give steroids to try to prevent IRIS?

The NEW ENGLAND JOURNAL of MEDICINE

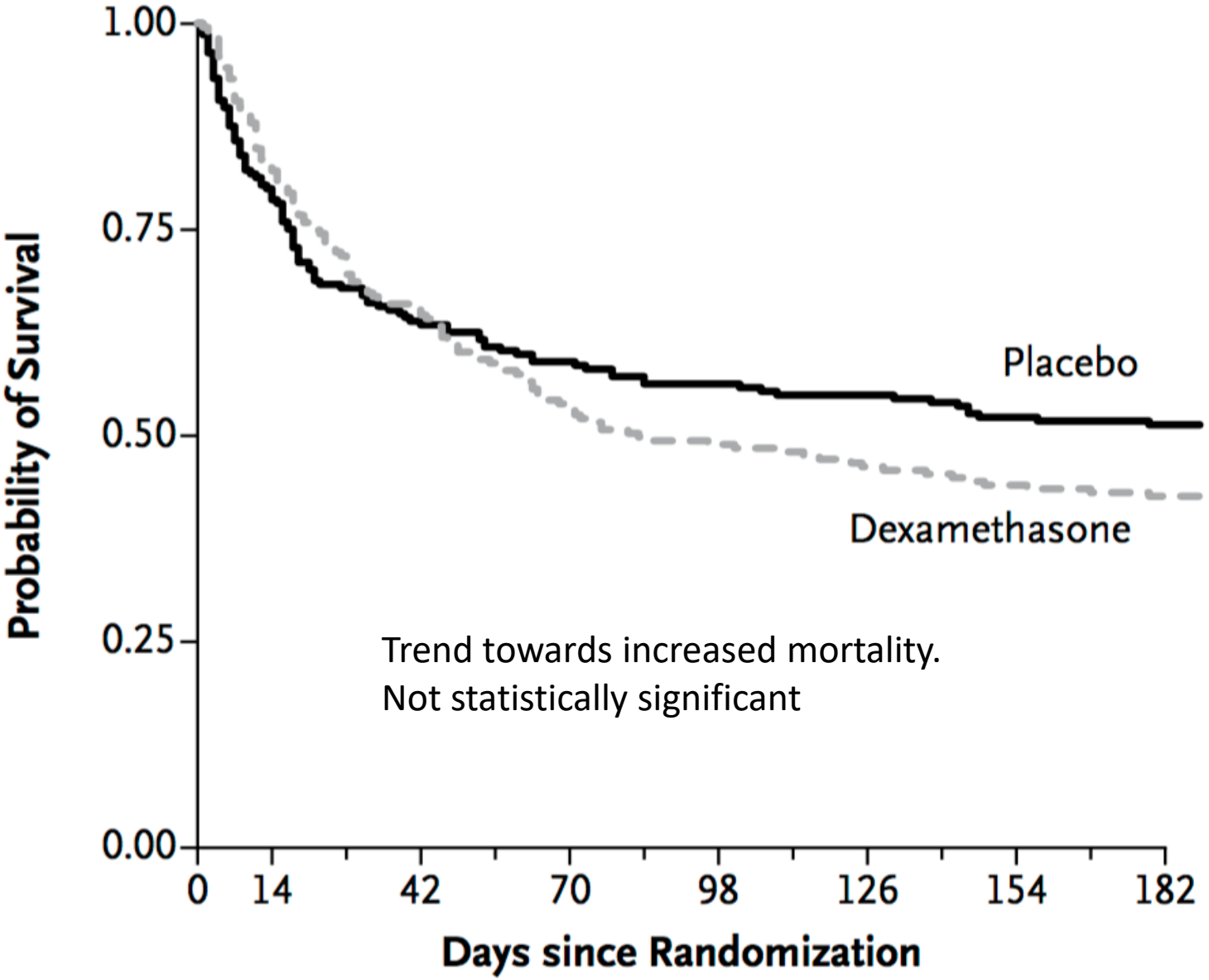
CyptoDex study

ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

METHODS

In this double-blind, randomized, placebo-controlled trial, we recruited adult patients with HIV-associated cryptococcal meningitis in Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi. All the patients received either dexamethasone or placebo for 6 weeks, along with combination antifungal therapy with amphotericin B and fluconazole.



Statistically significant:

- Disability at 10 weeks (OR 0.42)
- Composite endpoint of death and disability at 10 weeks
- Clinical adverse effects (infections esp.)
- Decreased fungal clearance in CSF

Cryptococcal meningitis relapse

Nonadherence to fluconazole

Failure of ART

Paradoxical IRIS

Ongoing isolated raised ICP

Resistance to fluconazole

Other diagnosis (e.g. TB meningitis)

Managing CM relapse

- **Identify cause**: Do LP, check pressure + fungal culture. Adherence issues? Recent ART suggesting IRIS?
- **If due to non-adherence** treat as per first episode, try to establish underlying factors and try to support patient.
- **Paradoxical cryptococcal IRIS**:affects approximately 20% of patients with cryptococcal disease who start ART and mortality may be substantial.
- **If CSF culture positive and adherence seems ok**, consider fluconazole susceptibility testing (NICD offers it on discussion/request).

Summary

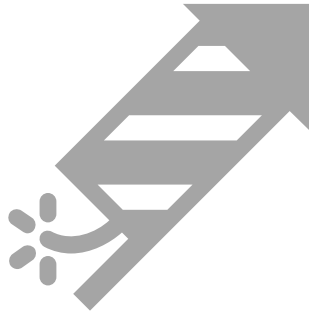
Diagnosis

Screen with serum CrAg (very good screening test!)

If positive, do a lumbar puncture, even if the patient is asymptomatic.

Treatment – CSF CrAg negative

Treat with fluconazole alone.



Initiate ARVs immediately.

Treatment – CSF CrAg positive

Induction therapy should now be ampho B deoxycholate PLUS flucytosine.

Management of raised intracranial pressure is **essential**.

Delay ART for 4-6 weeks.