



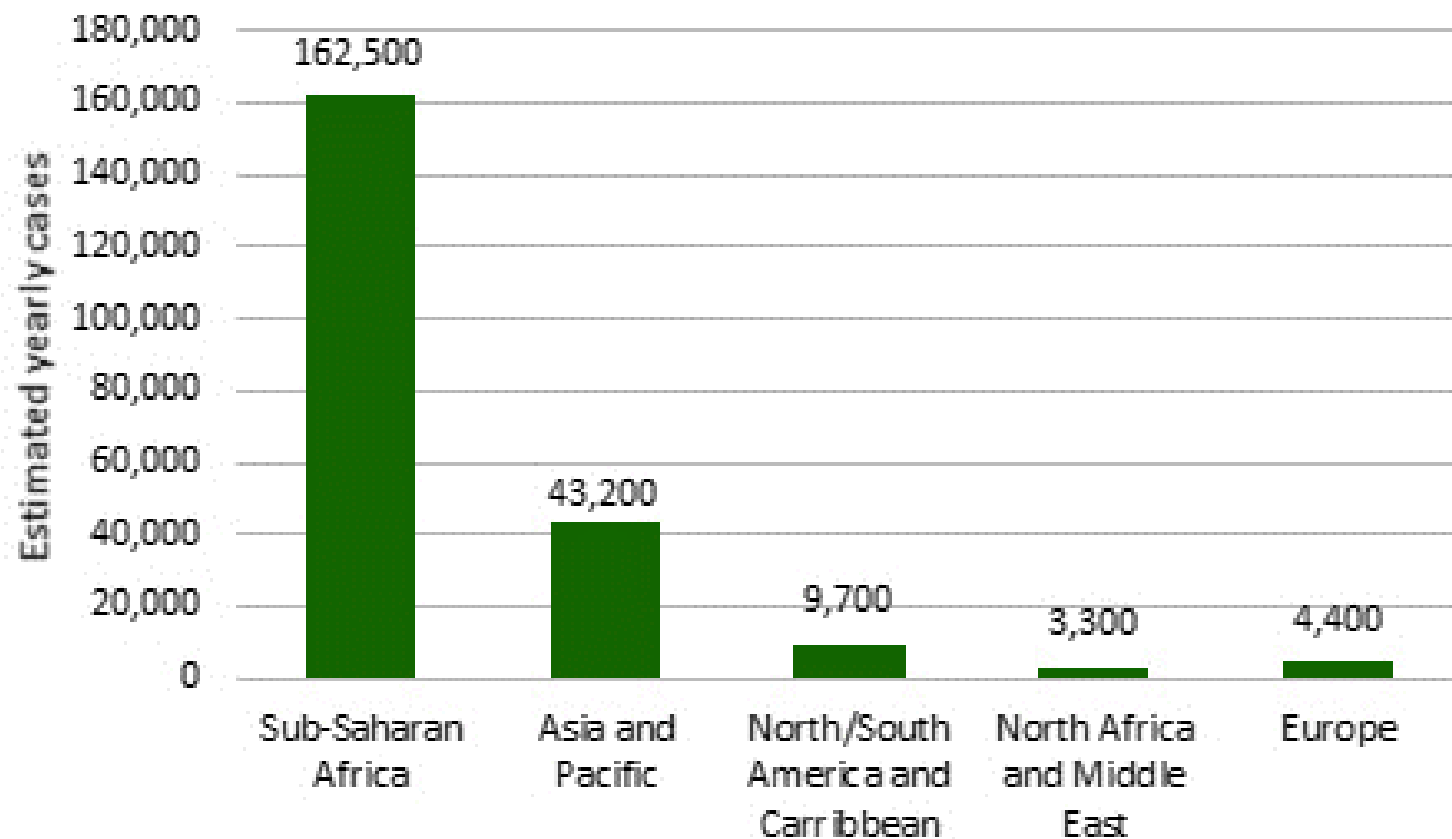
The latest management in
cryptococcal meningitis.
Time to rethink

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Department of Infectious Diseases

18 March 2019

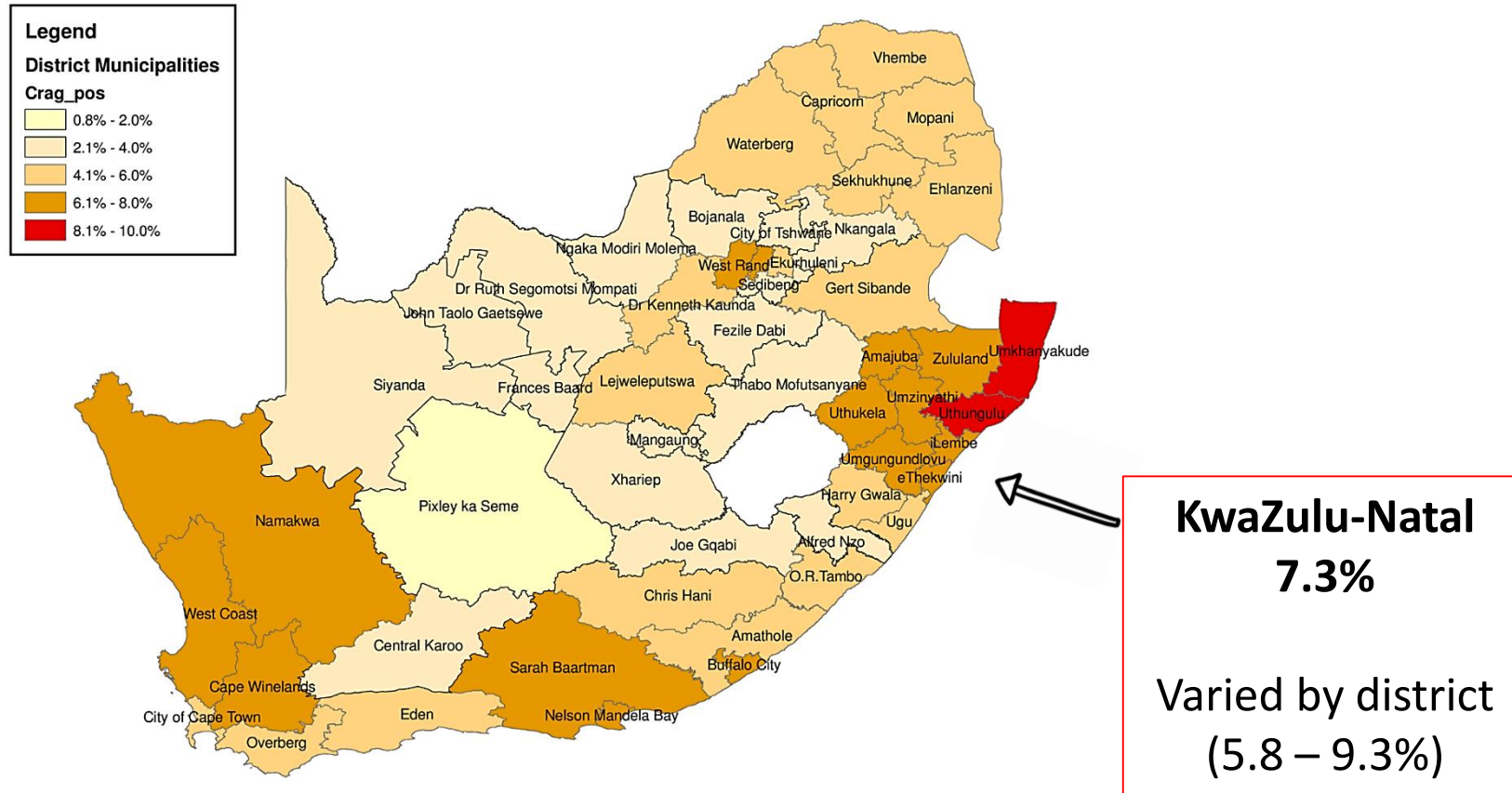
Global burden of HIV-related cryptococcal meningitis



Epidemiology of cryptococcal disease

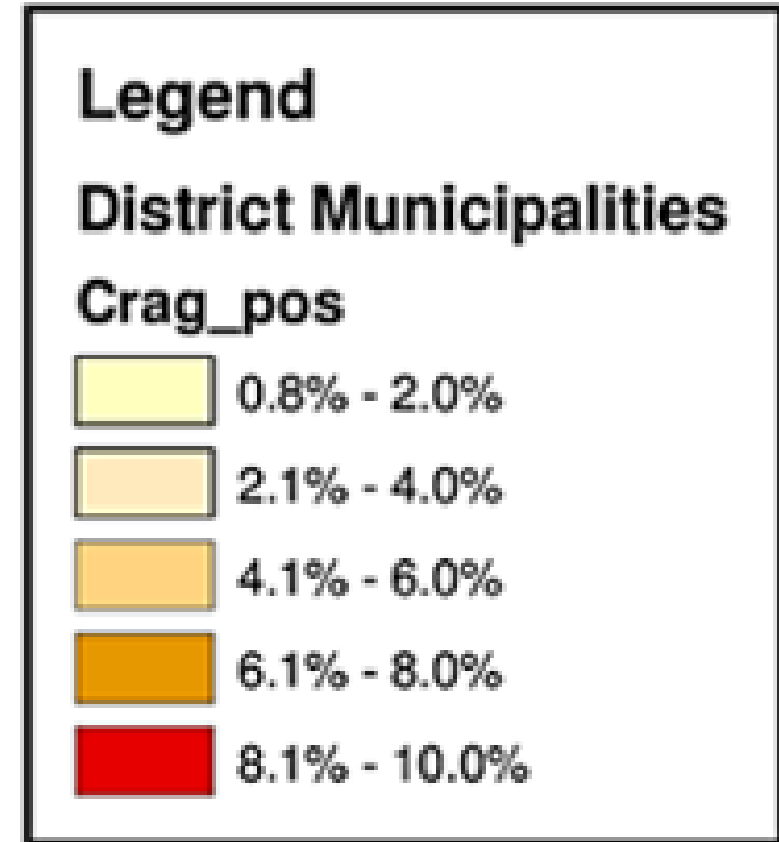
Proportion of samples with CD4+ count <100 cells/ μ L with positive CrAg

July 2016 - April 2017



~400 CrAg positive serum samples per month across KZN (Q1 2018)

Closer look at Kwazulu-Natal

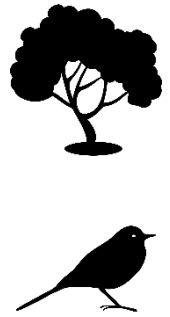


Case fatality rate

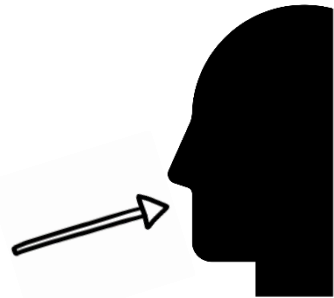
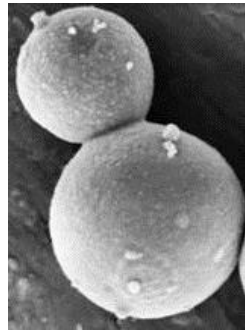
- Cape town (Bicanic, Clin Infect Dis 2007 & 2008)
 - 24-37% 10 week mortality
- Johannesburg (Govender, unpublished)
 - 67% died or lost to follow up by 3 months
- Rural KwaZulu-Natal (Lessels, SAMJ 2011)
 - 41% in-hospital mortality
 - 11% alive in ART care at two years

Cryptococcal disease

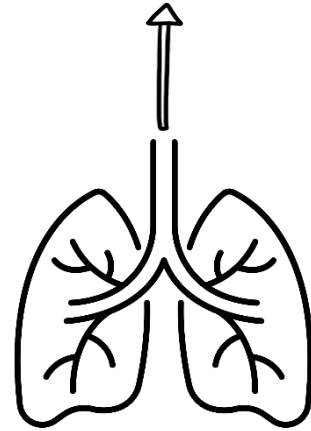
Natural history



Environmental niches for *Cryptococcus sp.*

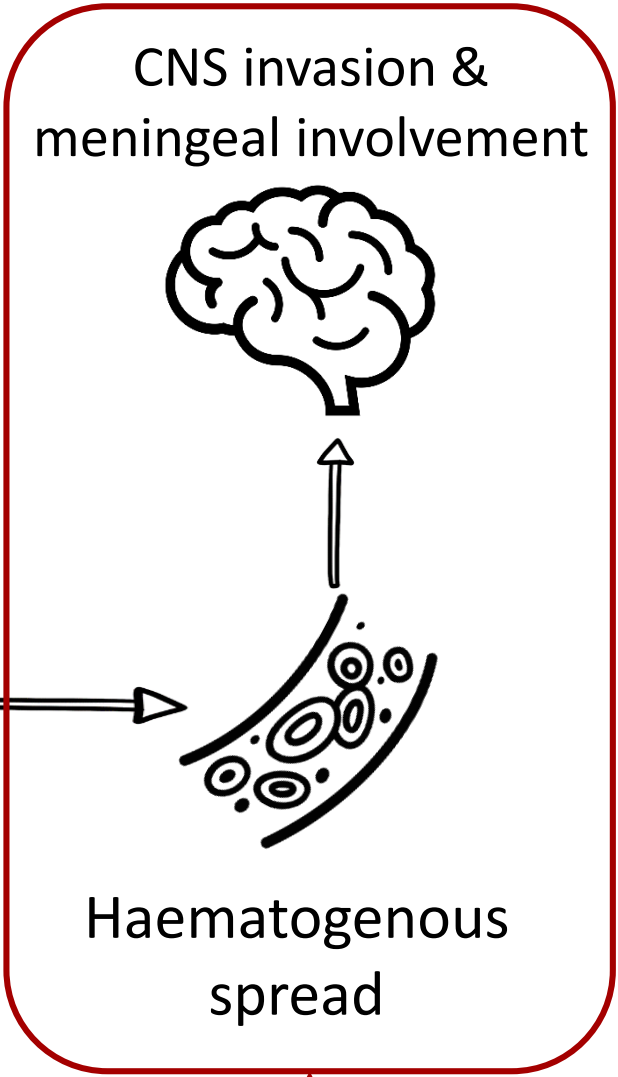


Acquired by inhalation



Dormant state (lung-LN complex)

Immune response eliminates yeast



CNS invasion & meningeal involvement

Haematogenous spread

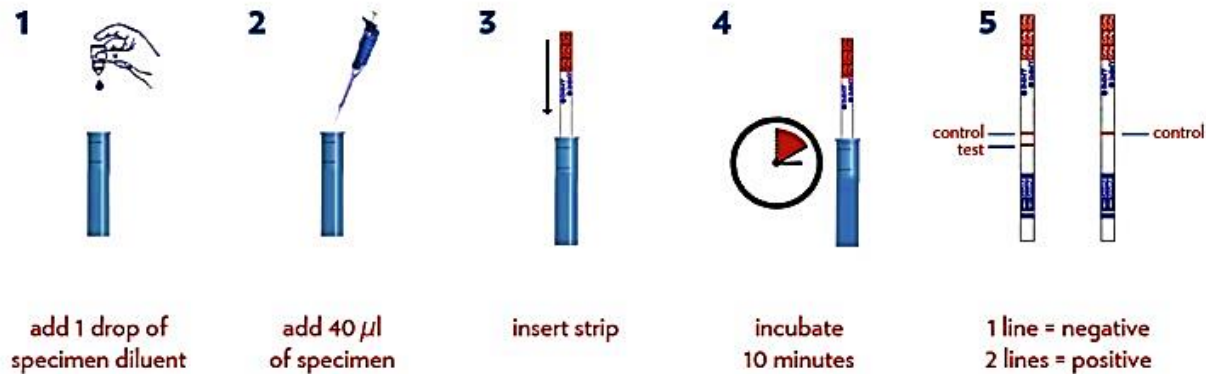
CrAg screening & pre-emptive treatment

Cryptococcal antigen testing

- Detection of capsular polysaccharide glucuronoxylomannan (GXM)
- Different assays (enzyme immunoassay, latex agglutination, lateral flow assay)
- Lateral flow assay (IMMY CrAg LFA) used for serum CrAg screening

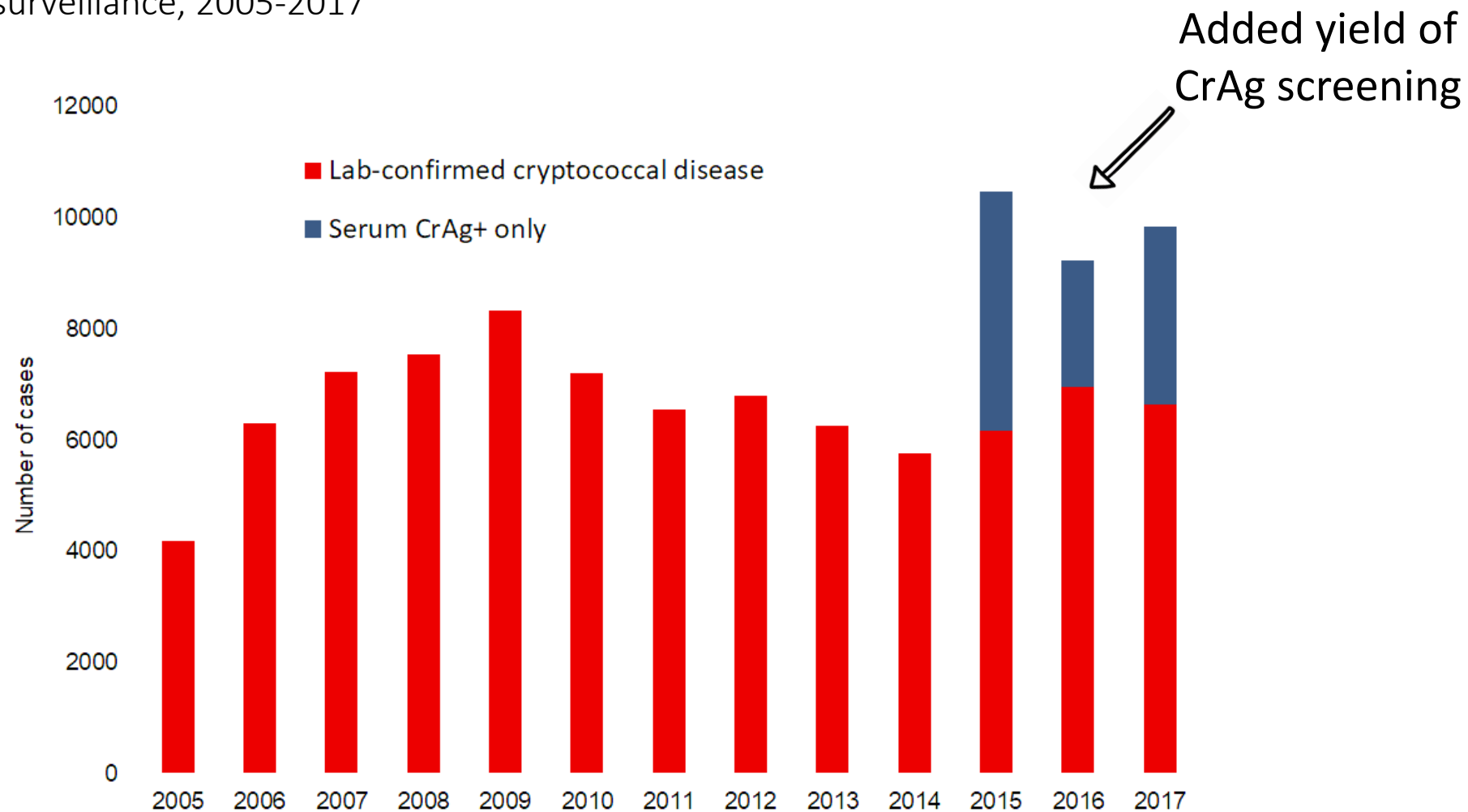


5 Easy Steps

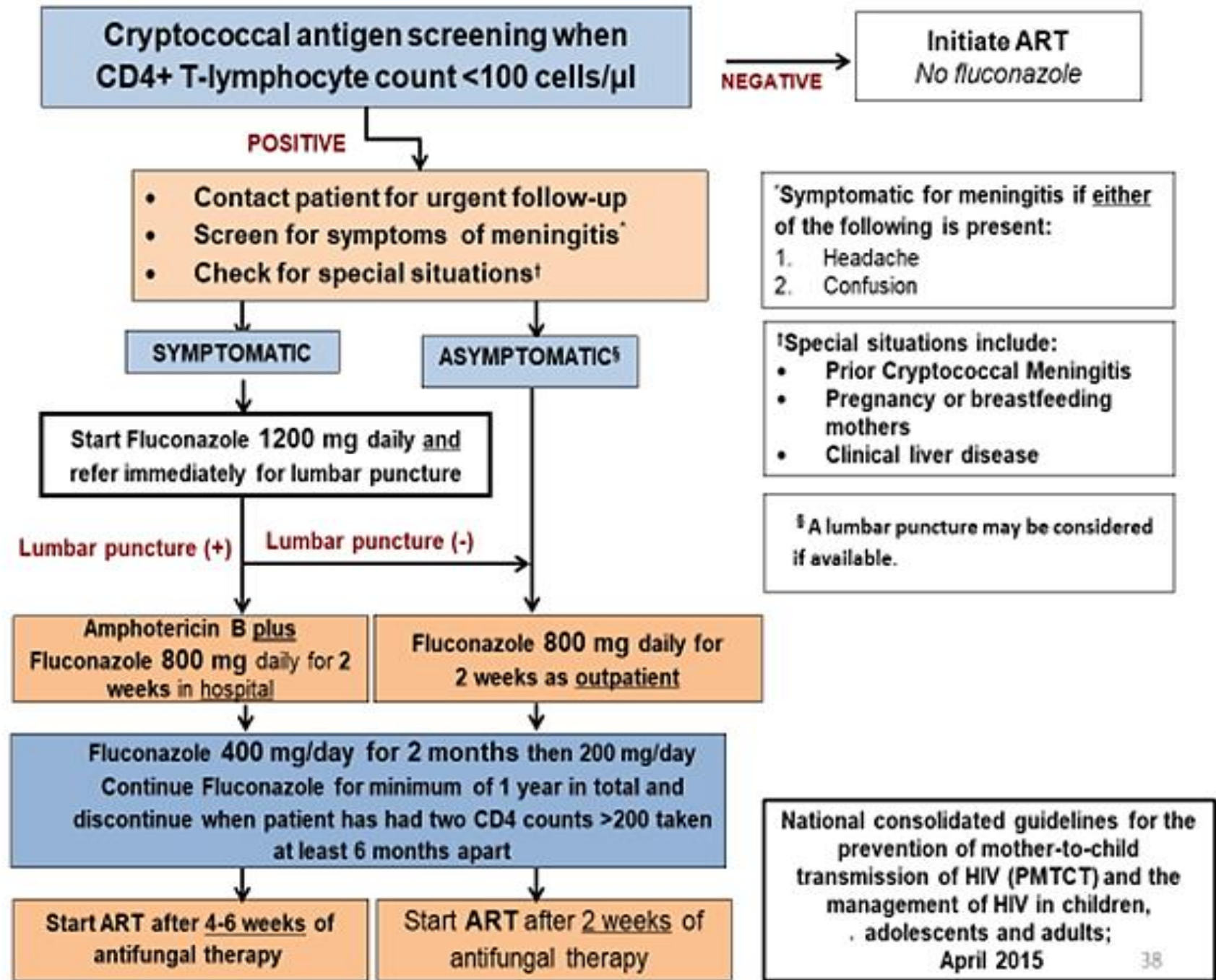


Surveillance of cryptococcal disease

GERMS-SA surveillance, 2005-2017

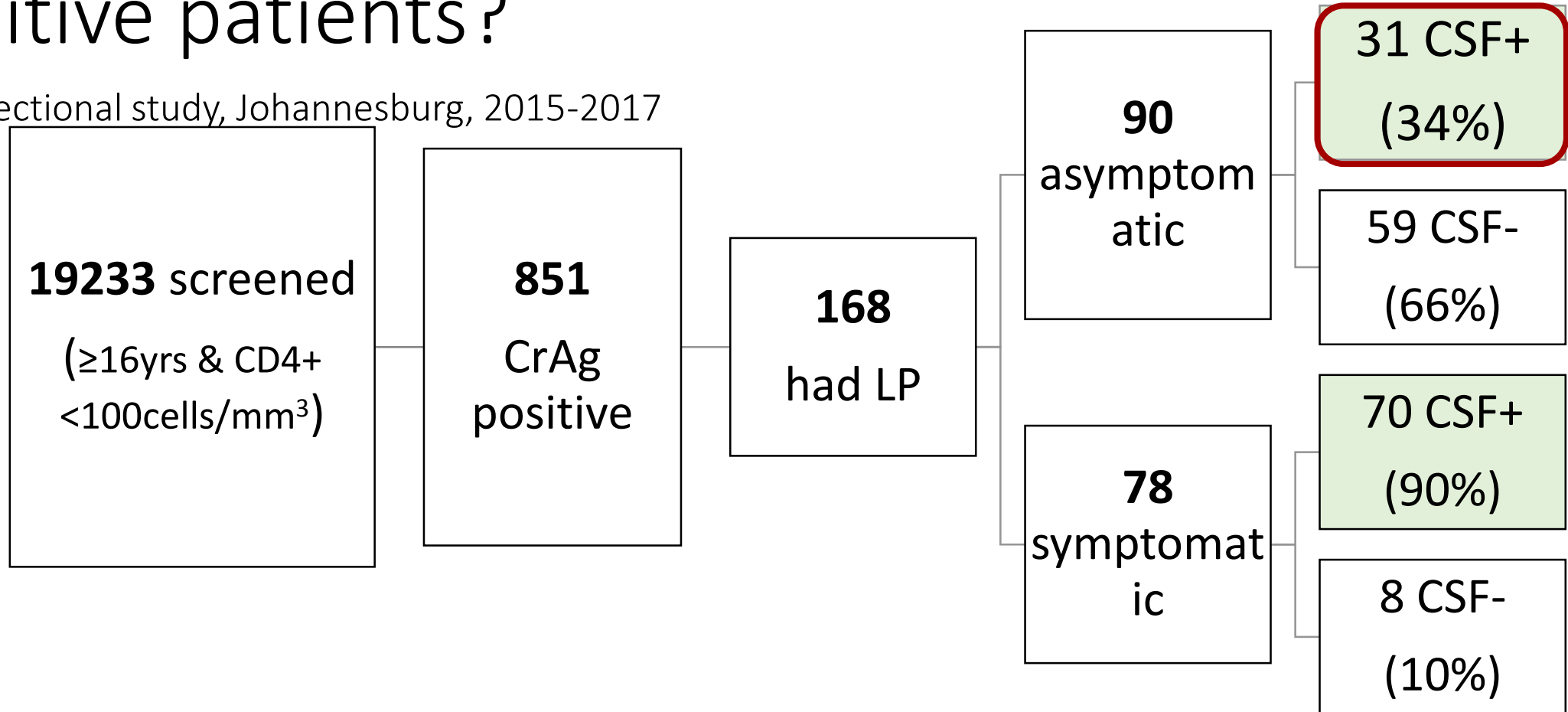


Cryptococcal screen & treat algorithm



How frequent is meningeal involvement in CrAg-positive patients?

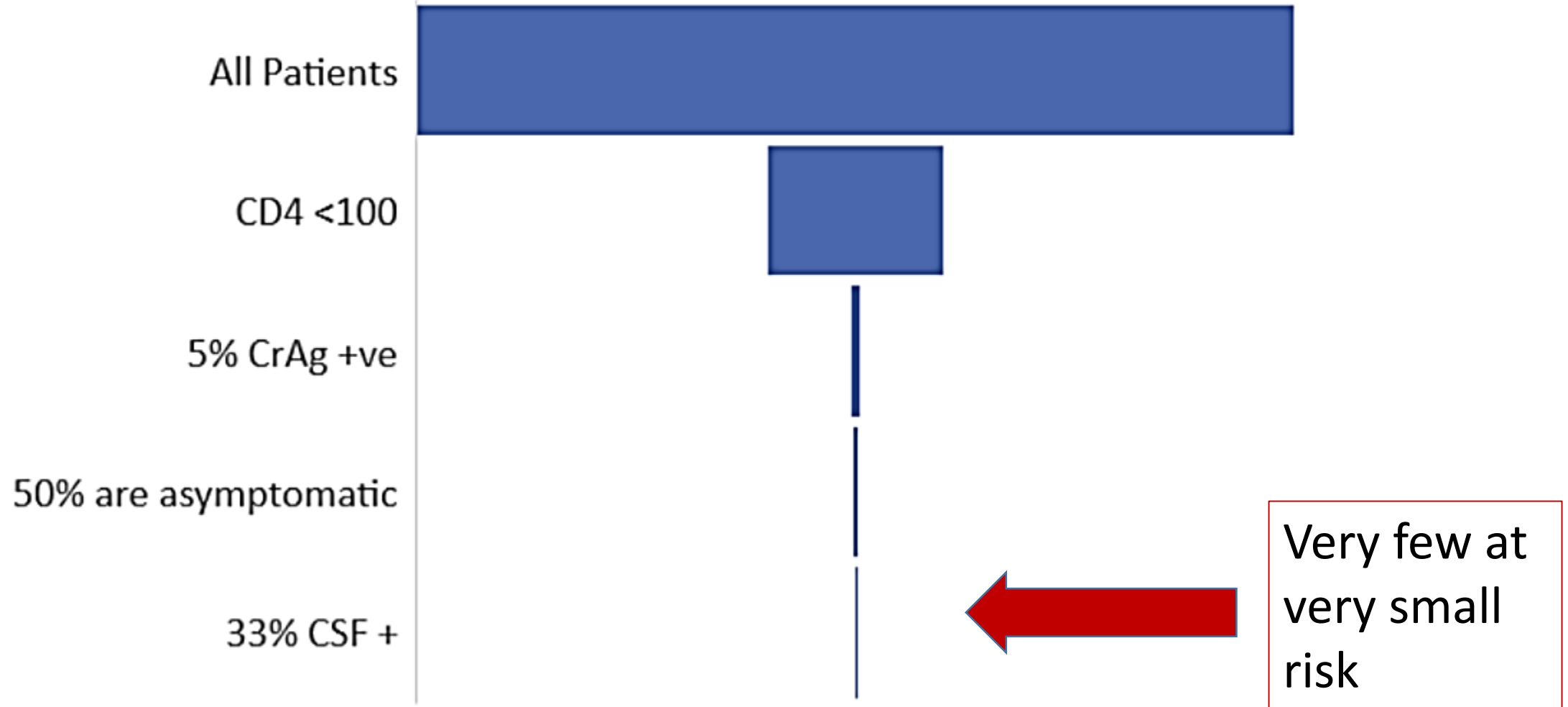
Cross-sectional study, Johannesburg, 2015-2017



* CSF+ (CCM) was defined as positive India Ink, culture or CrAg

Should we be concerned over same day initiation of ARV's and mortality related CCM?

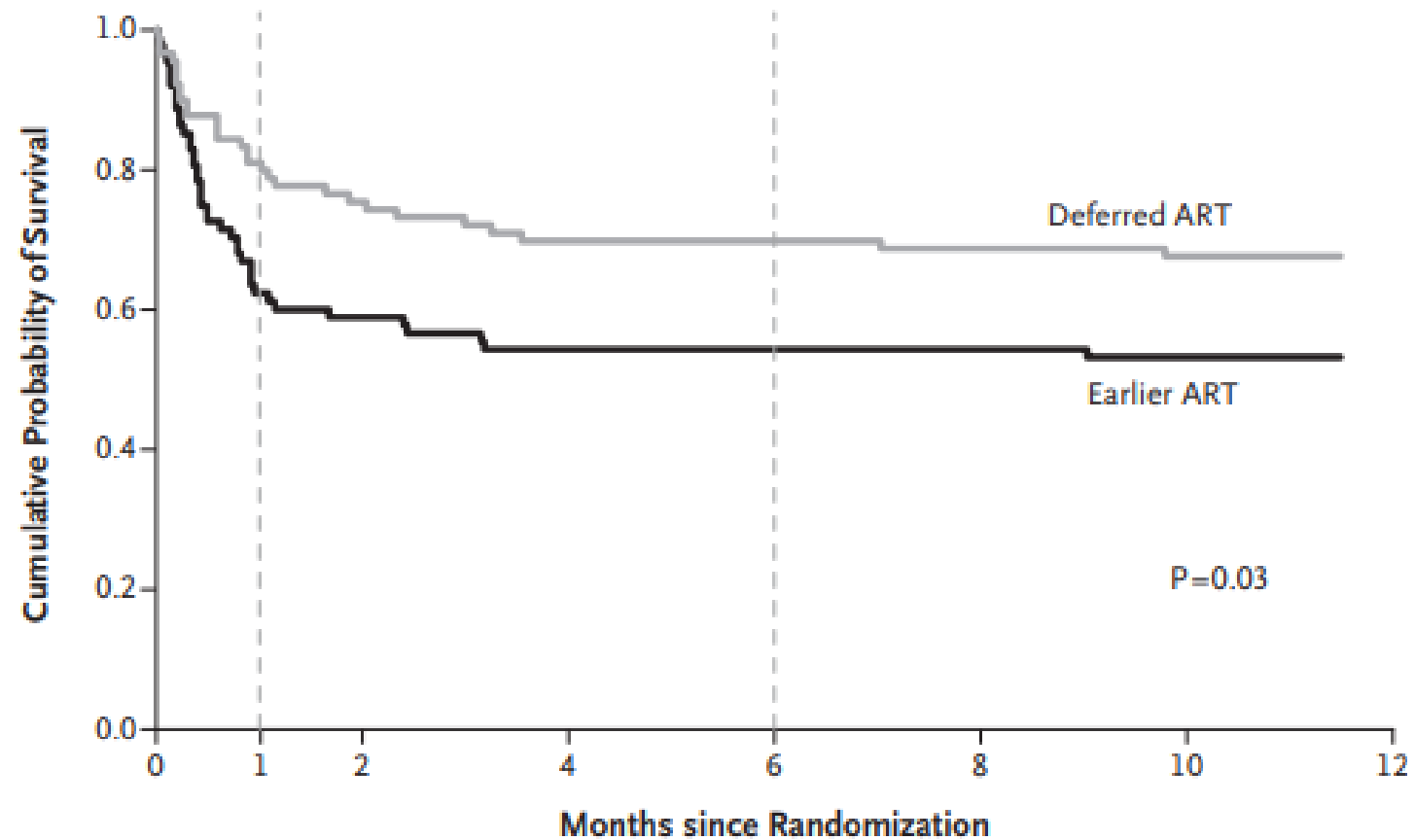
SDI without CrAg



Cryptococcal Optimal ART Timing (COAT) trial

- Multi-site randomised controlled trial showed that initiation of ART 1 - 2 weeks ($n=88$) vs 5 weeks after diagnosis ($n=89$) was associated with a significantly higher 6-month mortality (hazard ratio for death 1.73 (95% confidence interval 1.06 - 2.82))
- This finding applied to all categories of HIV-infected patients, including those with a CD4⁺ count <50 cells/mm³
- Therefore, the accepted, considered and safe approach is that ART be introduced 4 - 6 weeks after antifungal therapy is started

A Overall Survival



No. at Risk

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

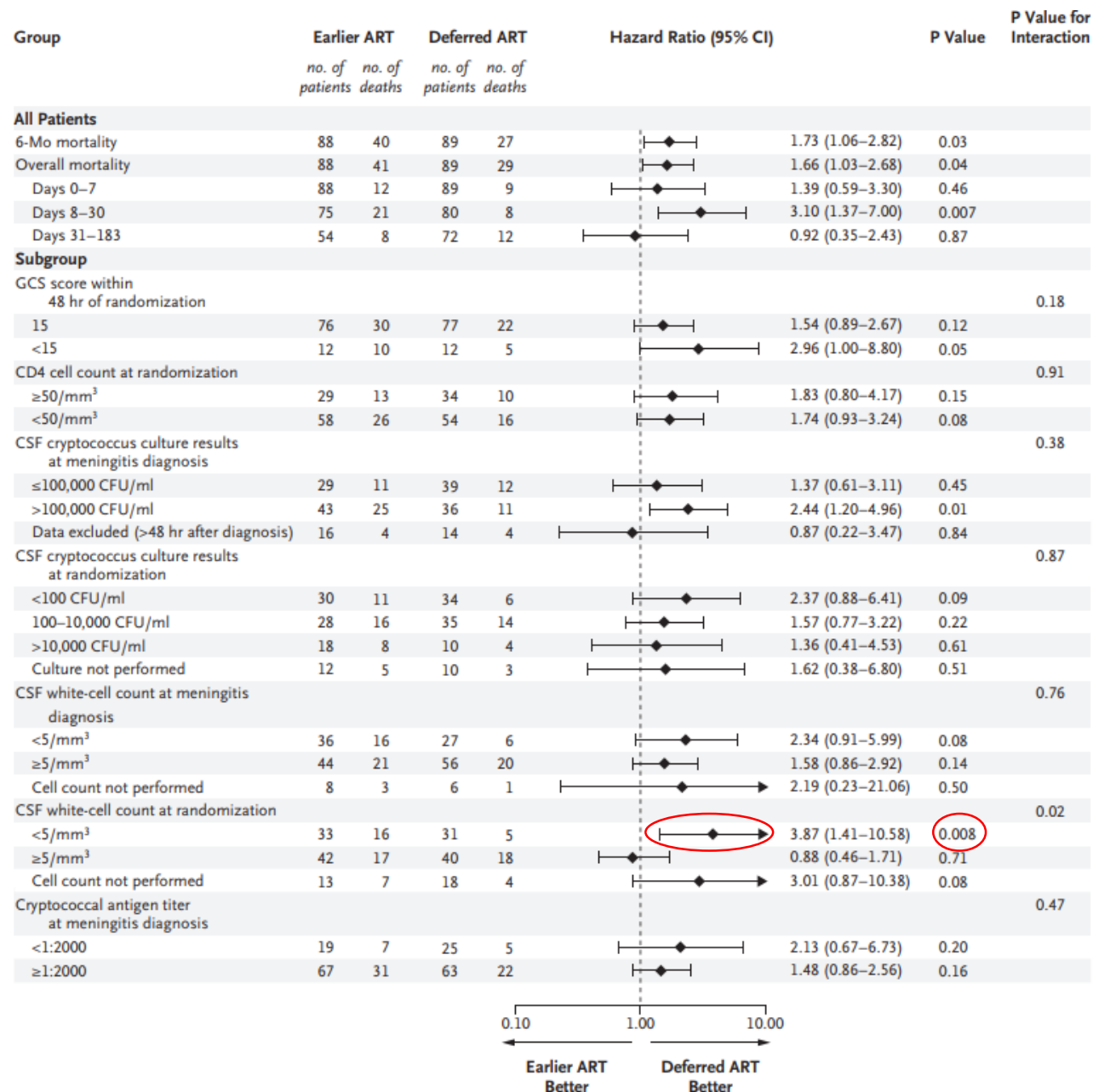
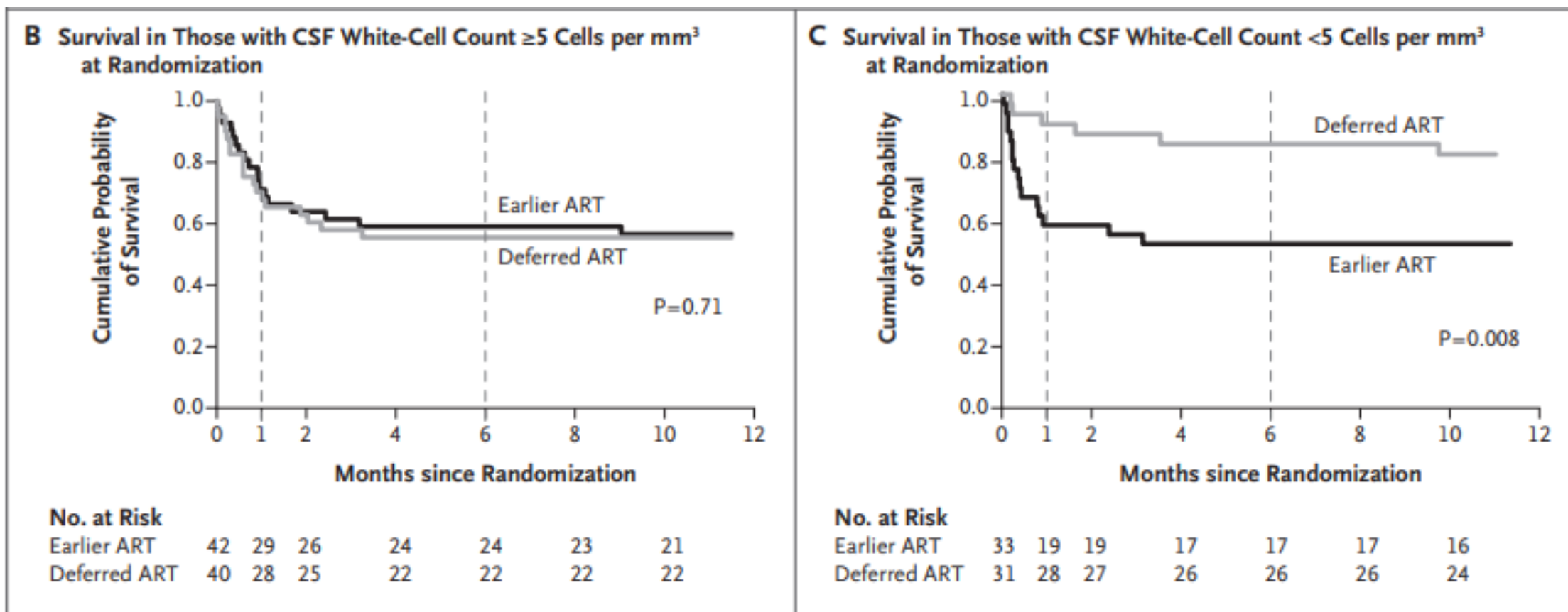


Figure 3. Subgroup Analyses of Mortality.

What really influenced the findings?



Prognosis

- The prognosis is also influenced by the ability to manage the underlying disease and to detect and treat elevated intracranial pressure
- However this is generally very poorly managed:
 - Poor understanding of consequences by junior doctors
 - Feel that patient has a poor prognosis anyway
 - “No manometers available”

Summary of poor prognostic factors

- Ability to control the patient's underlying disease
- Burden of yeasts at presentation
- Level of the patient's sensorium at presentation
- Strongly positive India ink examination
- High polysaccharide antigen titre (1 :1024)
- Poor inflammatory response in the CSF

Pathophysiology of Hydrocephalus

- Polysaccharide capsule released from the cell wall upon lysis
- Clogging of arachnoid villi
- Impairs CSF drainage
- Continued production of CSF

Poiseuille's Law

$$\Delta p = \frac{8\mu l Q}{\pi r^4}$$

- p = is the difference in pressure between the 2 ends of a fluid filled tube
- l = length
- r = internal radius
- μ = viscosity of the fluid
- Q = volumetric flow rate

Using CSF flow rate to calculate ICP

- 32 patients with CCM had 89 LP's with 22G spinal needle
- ICP was first measured with a manometer and then CSF flow rate in drops/min counted

TABLE 1. Flow Rate of CSF With a Cutoff Value of ≥ 40 Drops/Min Compared with a Reference Standard of Manometry

	Raised ICP >25 on Manometry	Normal ICP ≤ 25 on Manometry	Total
≥ 40 drops/min	49	9	57
< 40 drops/min	5	26	32
Total	54	35	89

Using CSF flow rate to calculate ICP

- Using 40 drops/minute cut-off, sensitivity was 91% for detecting raised ICP > 25 cm of H₂O
- Only 5% of LPs misclassified with drop rate as “normal” when ICP actually elevated
- When manometers not available, ICP can be accurately estimated with CSF drops/min with possible threshold of >40 drops/min

Managing raised intracranial pressure

- Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient to reduce the CSF pressure to $<20\text{cm H}_2\text{O}$ or halving the baseline pressure if extremely high
- If pressure initial opening pressure is high, daily LP's should be performed until opening pressure is normal for 2 days
- The persistence or recurrence of symptoms or signs of raised ICP should determine the frequency of repeat therapeutic LP

How effective is our current
treatment for CCM?

Are we doing enough?

Treatment

- Combination therapy for the management of cryptococcal meningitis has been extremely well studied
- The combination of amphotericin B and flucytosine has become standard therapy for meningitis, and in patients without AIDS it reliably sterilizes CSF after 2 weeks of therapy
- In HIV treatment consists of 3 phase:
 - Induction
 - Consolidation
 - Maintenance

Treatment

- Treatment of cryptococcal meningitis in resource-limited settings is challenging
- The international standard induction treatment of 2 weeks of amphotericin B deoxycholate plus flucytosine is not available in most African clinical centres
- Amphotericin B deoxycholate requires intravenous administration and close laboratory monitoring and is associated with phlebitis, secondary infections, anaemia and renal impairment.

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*

Open-label, phase 3, randomized, non-inferiority, multicentre trial (9 centres-Malawi, Zambia, Tanzania & Cameroon)

What were they assessing?

3 treatment strategies

- oral regimen
- 1-week amphotericin B regimen
- 2 weeks
- As well as two alternative partner drugs for amphotericin B regimen (fluconazole or flucytosine)

678 Eligible
(721 enrolled)

224
1 week
Ampho

225
Oral Fluc +
5FC

229
2 week
Ampho

111
1 week Ampho +
Fluc

113
1 week Ampho +
5FC

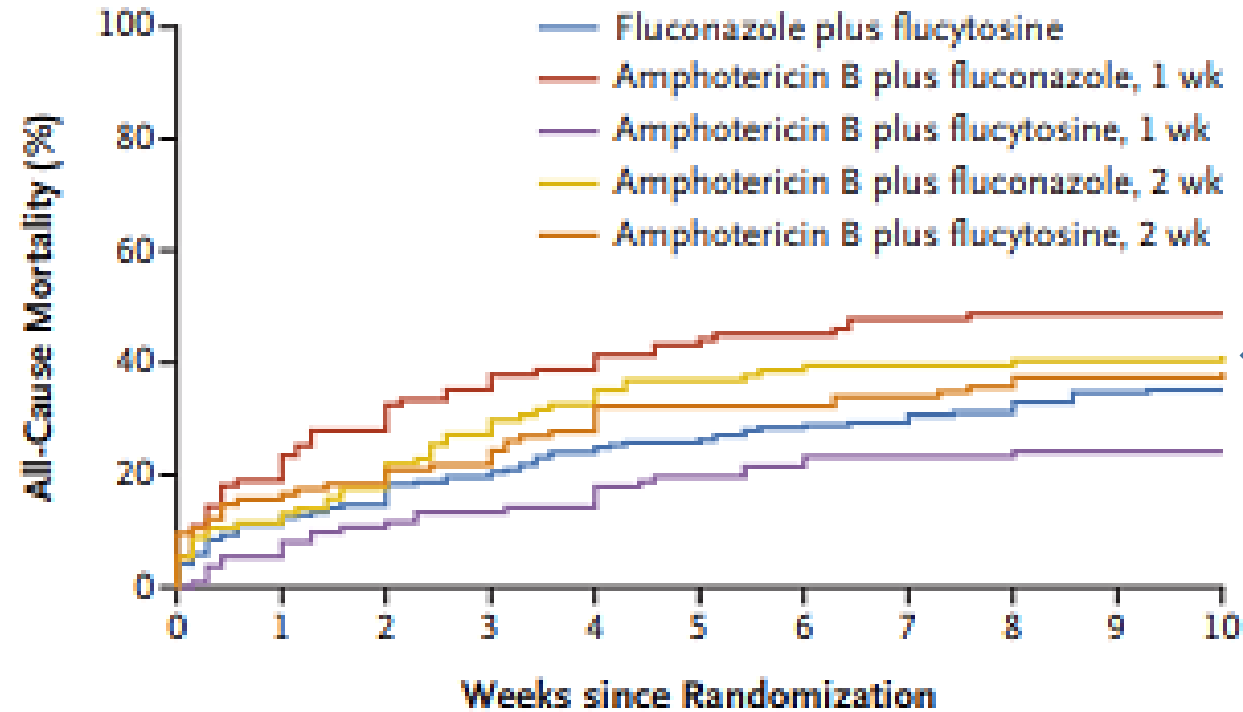
114
2 week Ampho
+ Fluc

115
2 week Ampho +
5FC

Table 2. Unadjusted Analysis of Mortality and Rate of Fungal Clearance in CSF According to Treatment Strategy in the Intention-to-Treat Population.*

Outcome	Oral Regimen (N = 225)	1-Wk Amphotericin B (N = 224)	2-Wk Amphotericin B (N = 229)	Difference (95% CI)†	
				Oral Regimen vs. 2-Wk Amphotericin B	1-Wk Amphotericin B vs. 2-Wk Amphotericin B
Mortality at 2 wk					
No. of deaths	41	49	49		
% (95% CI)	18.2 (13.2 to 23.3)	21.9 (16.5 to 27.4)	21.4 (16.1 to 26.7)	-3.18 (-10.50 to 4.15)	0.48 (-7.11 to 8.06)
Mortality at 4 wk					
No. of deaths	56	66	77		
% (95% CI)	24.9 (19.2 to 30.5)	29.5 (23.6 to 35.5)	33.6 (27.5 to 39.7)	-8.74 (-17.06 to -0.41)	-4.16 (-12.71 to 4.39)
Mortality at 10 wk					
No. of deaths	79	81	91		
% (95% CI)	35.1 (28.9 to 41.3)	36.2 (30.0 to 42.7)	39.7 (33.5 to 46.2)	-4.63 (-13.52 to 4.27)	-3.58 (-12.51 to 5.35)
Fungal clearance‡					
No. of patients	182	179	182		
Clearance rate — log ₁₀ CFU/ml/day	-0.26±0.18	-0.40±0.24	-0.42±0.25	0.10 (0.07 to 0.13)§	0.01 (-0.01 to 0.04)¶

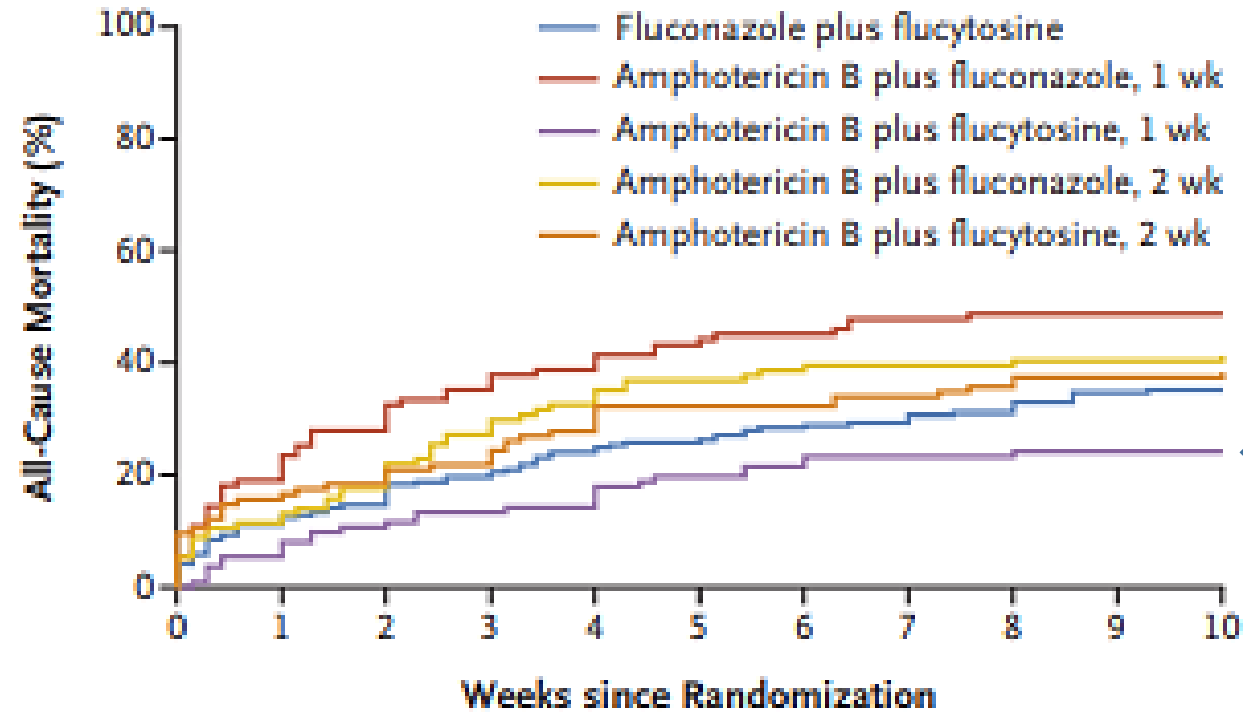
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No. at Risk

Fluconazole plus flucytosine	225	200	192	181	171	167	161	159	155	147	144
Amphotericin B plus fluconazole, 1 wk	111	90	80	72	68	63	61	58	57	57	57
Amphotericin B plus flucytosine, 1 wk	113	106	100	97	96	89	87	85	85	84	82
Amphotericin B plus fluconazole, 2 wk	114	101	94	83	77	72	69	68	68	67	65
Amphotericin B plus flucytosine, 2 wk	115	97	94	90	83	78	78	76	74	72	71

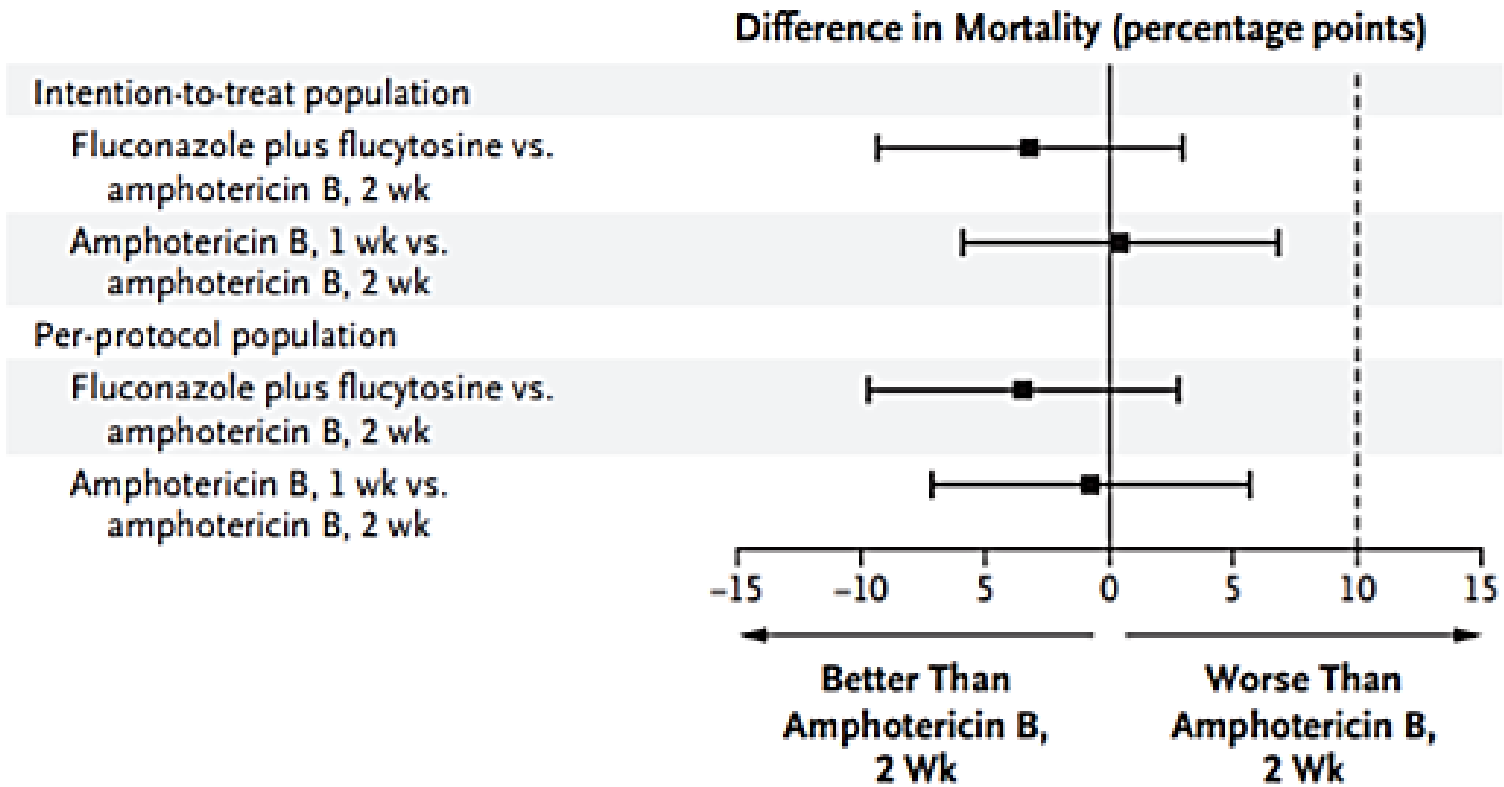
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Amphotericin B plus flucytosine, 2 wk	115	97	94	90	83	78	78	76	74	72	71

D



WHO guidelines 2018

1. Induction

Preferred induction regimen:

- 1 week amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/ day, divided into four doses per day)
- Followed by 1 week of fluconazole 1200 mg/day for adults

WHO guidelines 2018

Induction

Alternate regimen

- 2 weeks of fluconazole 1200 mg daily for adults + flucytosine 100mg/kg/day, divided into 4 doses per day
- 2 weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole 1200 mg daily for adults

WHO guidelines 2018

2. Consolidation

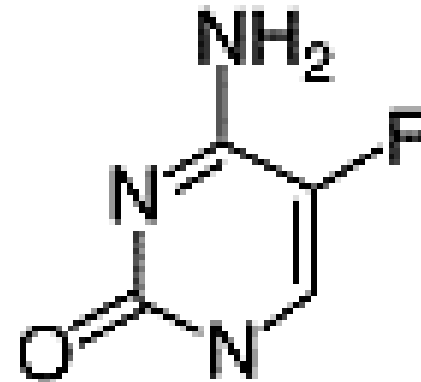
Fluconazole 800 mg daily for 8 weeks following the induction phase

3. Maintenance (or secondary prophylaxis)

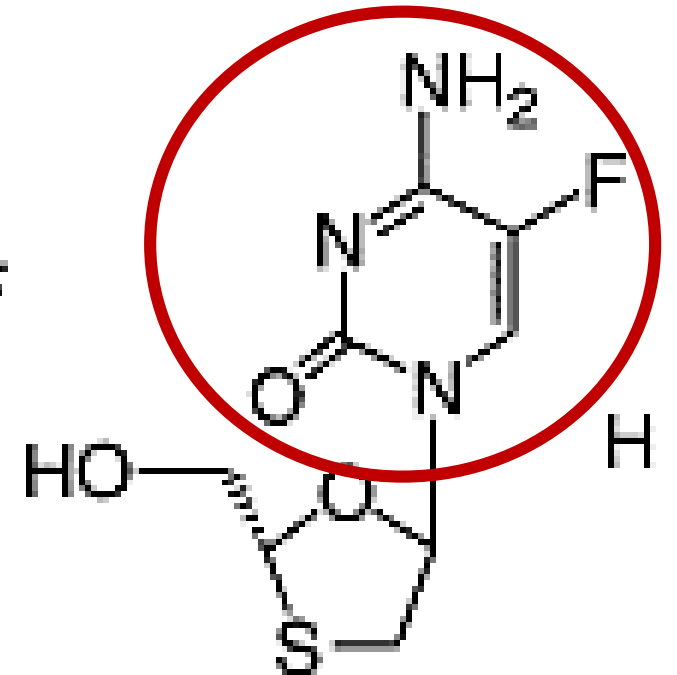
Fluconazole 200 mg daily until CD4 count ≥ 200 cells/mm³

Flucytosine

- Flucytosine is not registered and unavailable
- The cost of registration in many countries
- Advocacy is required to reduce the cost of flucytosine and simplify drug registration procedures
- The molecule is used widely as a constituent of emtricitabine, and generic manufacture is possible at low cost



Flucytosine



Emtricitabine
(Gilead) 2003

Mechanism of action

- It has no intrinsic antifungal capacity
- Taken up by susceptible fungal cells- converted into 5-fluorouracil (5-FU)
- Further converted to metabolites that inhibit fungal RNA and DNA synthesis
- Monotherapy with 5-FC is limited because of the frequent development of resistance
- Primarily renal excretion- dose adjustment required in renal failure

5-FC dose interval adjustment in renal impairment

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

Adverse effects

- *Dose dependent- normally reversible with cessation of the drug*
- Bone-marrow depression
- Hepatotoxicity
- Urticaria
- Anaphylaxis
- GI side effects
- CNS SE-hallucinations, dizziness, drowsiness
- Rise in creatinine and occasionally acute renal failure

Amphotericin B adverse effects

- Renal tubular toxicity
- Hypokalaemia and hypomagnesaemia
- Anaemia
- Causes fever, chills, rigors
- Fewer side effects with ampho B lipid preparations

Prevention of Ampho B toxicity

- All patients should receive oral potassium and magnesium supplementation unless contraindicated
- Monitor U&E, CPM and FBC
- **Rate of infusion!!!**
- Give 1 litre IV fluid minimum for prehydration daily with potassium

Managing amphotericin toxicity

- If renal failure/ doubling of baseline creatinine- hold Ampho
- If hypokalaemic aggressive potassium replacement (NB max infusion rate 10mmol/hr in a peripheral line and 20mmol/hr in central line)
- If hypomagnesemic , up to 5g per day magnesium may be required
- Transfuse as required

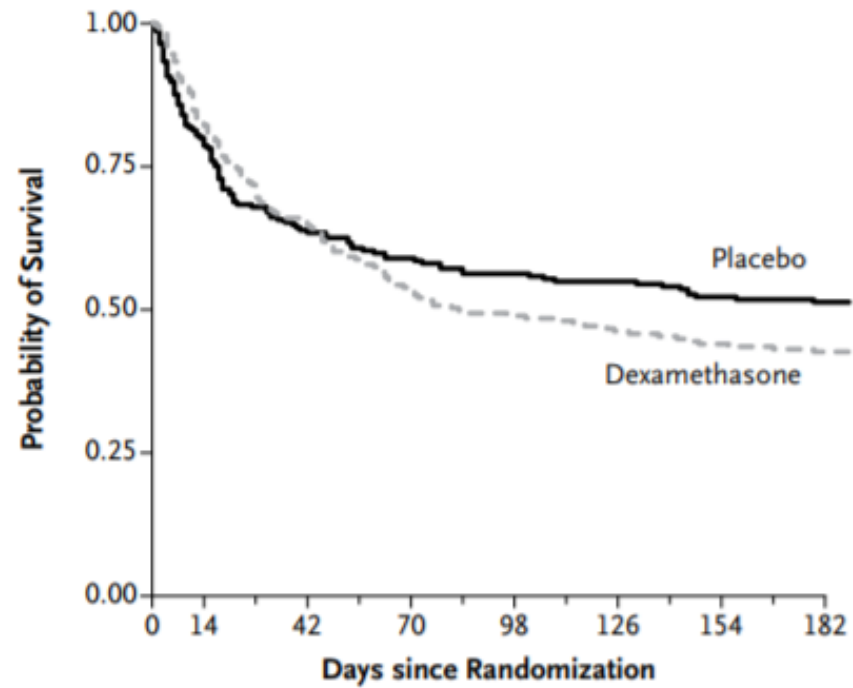
Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

J. Beardsley, M. Wolbers, F.M. Kibengo, A.-B.M. Ggayi, A. Kamali, N.T.K. Cuc, T.Q. Binh, N.V.V. Chau, J. Farrar, L. Merson, L. Phuong, G. Thwaites, N. Van Kinh, P.T. Thuy, W. Chierakul, S. Siriboon, E. Thiansukhon, S. Onsanit, W. Supphamongkholchaikul, A.K. Chan, R. Heyderman, E. Mwinjiwa, J.J. van Oosterhout, D. Imran, H. Basri, M. Mayxay, D. Dance, P. Phimmasone, S. Rattanavong, D.G. Lalloo, and J.N. Day, for the CryptoDex Investigators*

ABSTRACT

- Double-blind, randomized, placebo-controlled trial
- Adult patients with HIV-associated cryptococcal meningitis were recruited 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.

A All Patients



No. at Risk

Placebo	226	179	143	132	125	122	116	112
Dexamethasone	224	185	146	120	109	103	98	92

What about steroids?

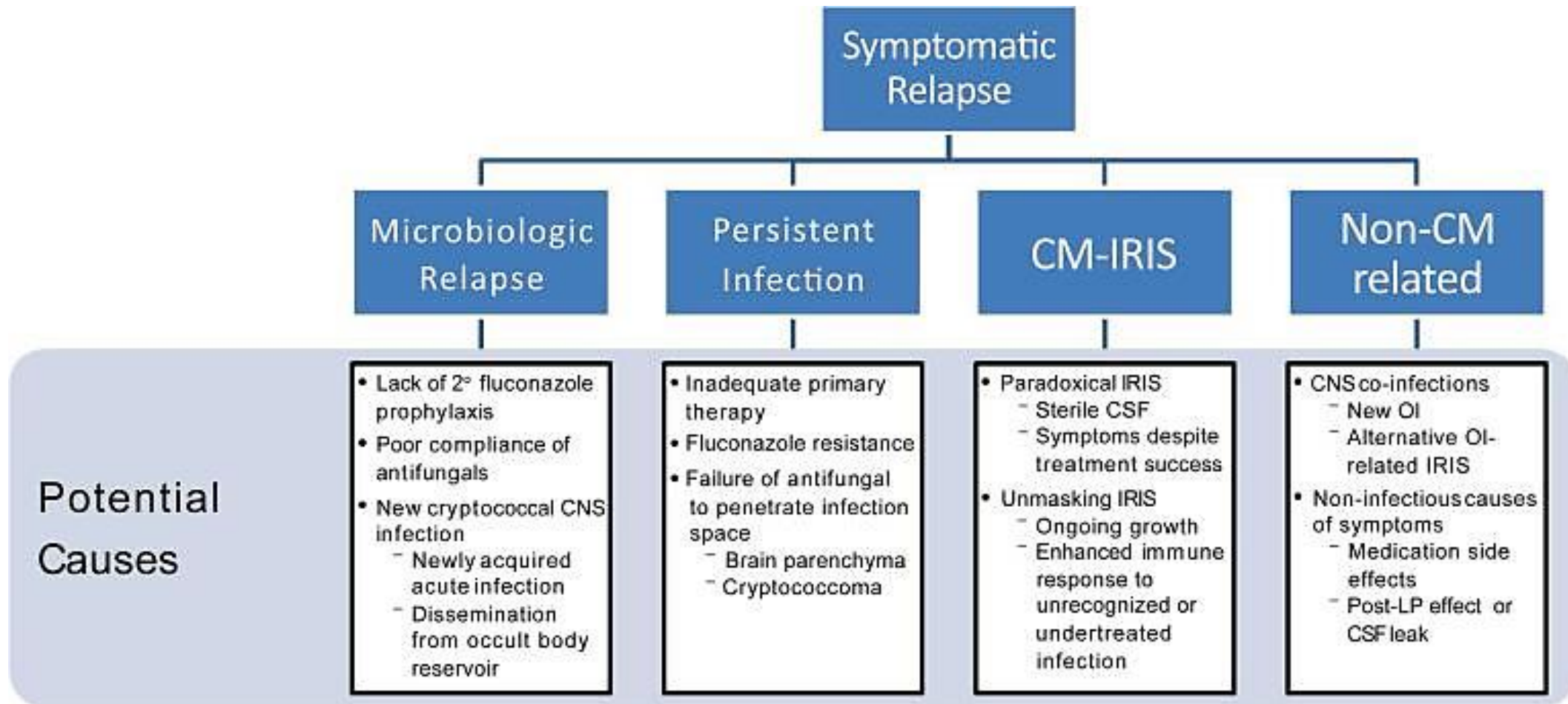
- The trial was stopped for safety reasons after the enrollment of 451 patients.
- Mortality was 47% in the dexamethasone group and 41% in the placebo group by 10 weeks
- 57% and 49%, respectively, by 6 months (hazard ratio, 1.18; 95% CI, 0.91 to 1.53; P=0.20).
- The percentage of patients with disability at 10 weeks was higher in the dexamethasone group than in the placebo group, with 13% versus 25% having a prespecified good outcome (odds ratio, 0.42; 95% CI, 0.25 to 0.69; P

Recurrence of symptoms

Cryptococcal antigen dynamics

- Studies have demonstrated that CrAg can persist in serum and CSF for months or years after successful treatment
- Persistence of CrAg not clearly associated with risk of recurrence
- Seems to relate to continuous release of capsular polysaccharide antigens from dead *C. neoformans* cells and slow elimination from serum/CSF
- Antigens too large to be filtered by kidney – taken up by macrophages and accumulate in liver/spleen (reservoir of infection)

Differential for symptomatic recurrence



References

- Mandel principles and practices of infectious disease
- WHO guidelines “The diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children”
March 2018 <https://apps.who.int/iris/bitstream/handle/10665/260399/9789342550277-eng.pdf;jsessionid=22b14fb58fe83e394f92b2c6a5aa44a?sequence=1>

Acknowledgement to Dr RJ Lessels