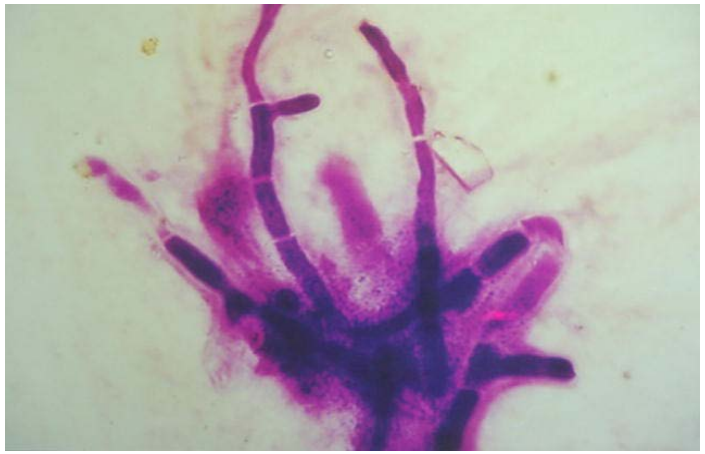
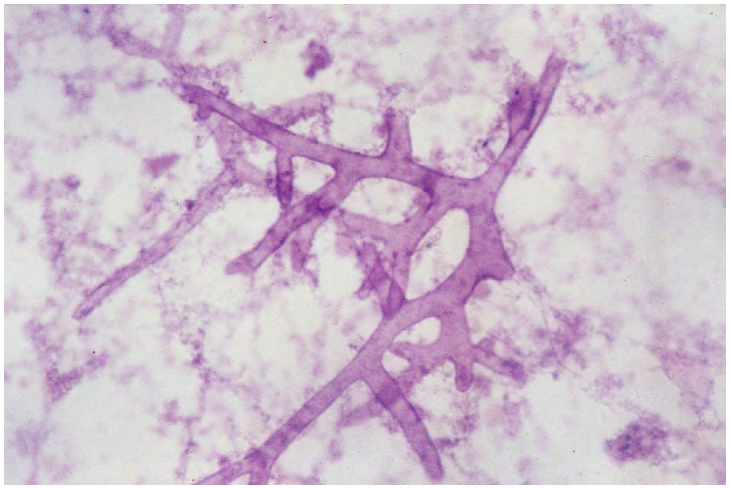
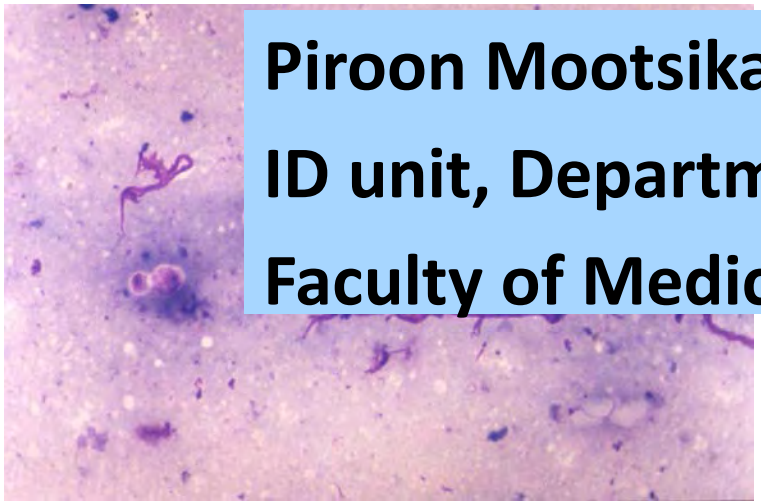




Systemic fungal infections 2019

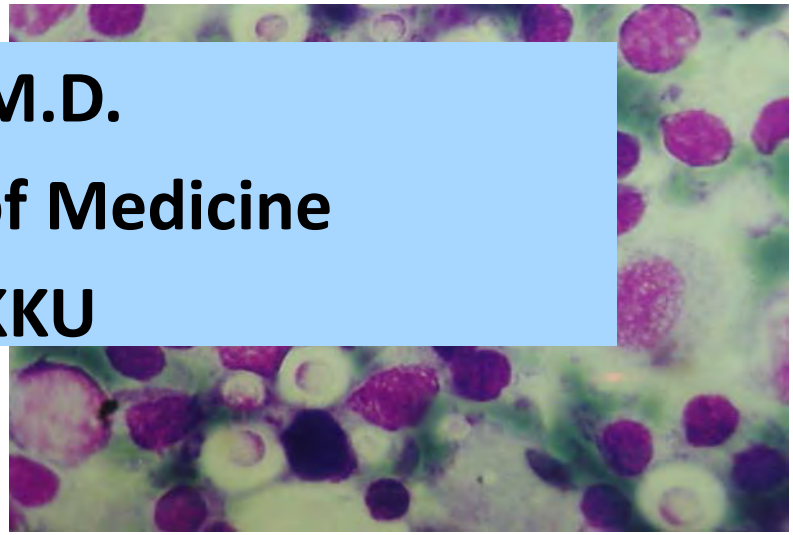
Treatment and prevention



Piroon Mootsikapun M.D.

ID unit, Department of Medicine

Faculty of Medicine, KKU



Disclosure

- **Honorarium/travel grant**
- - Pfizer, MSD, Astellas, Gilead, Novartis, LF Asia
- **Investigator**
- - Pfizer, Astellas

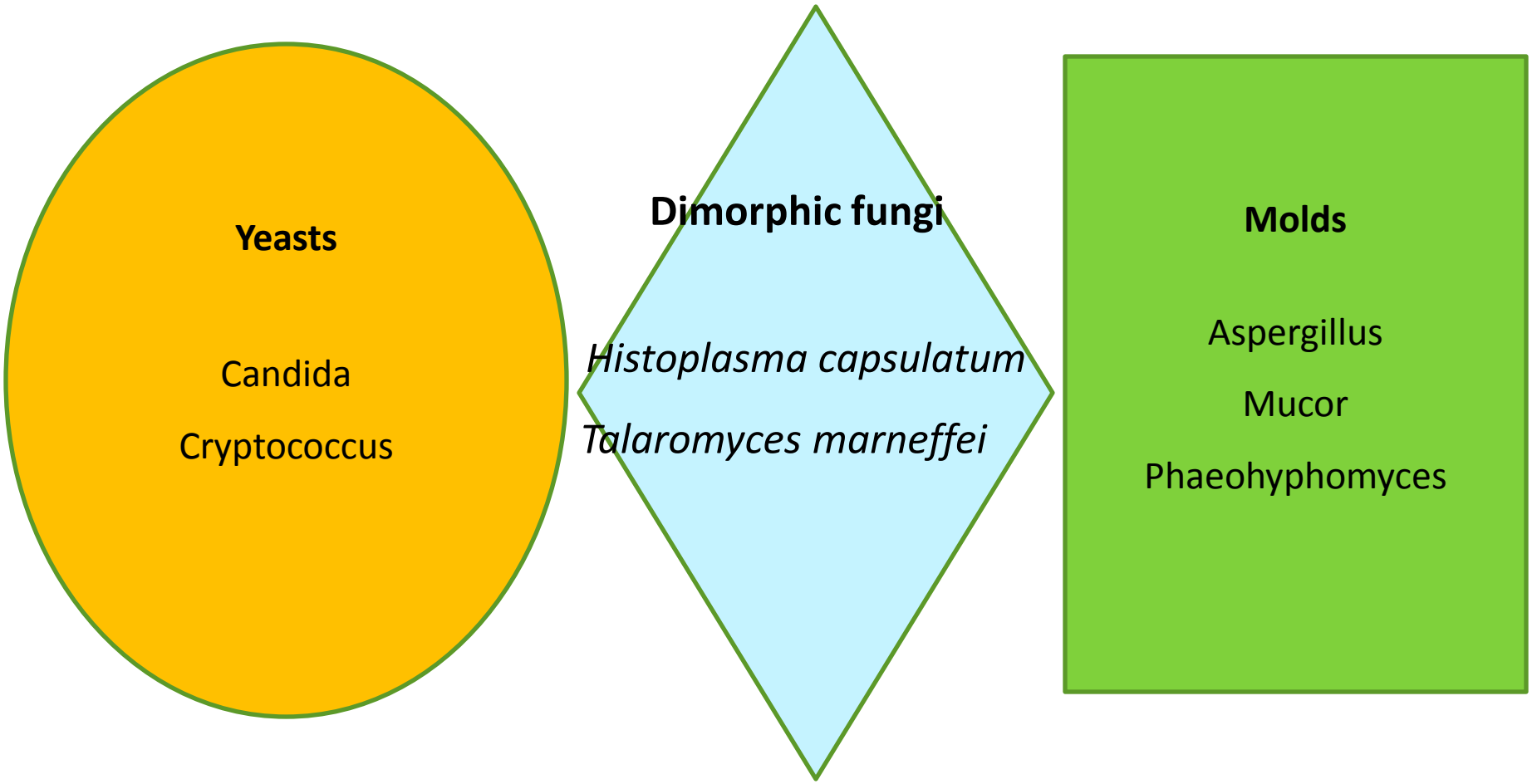
Outlines

Overview of fungal infections

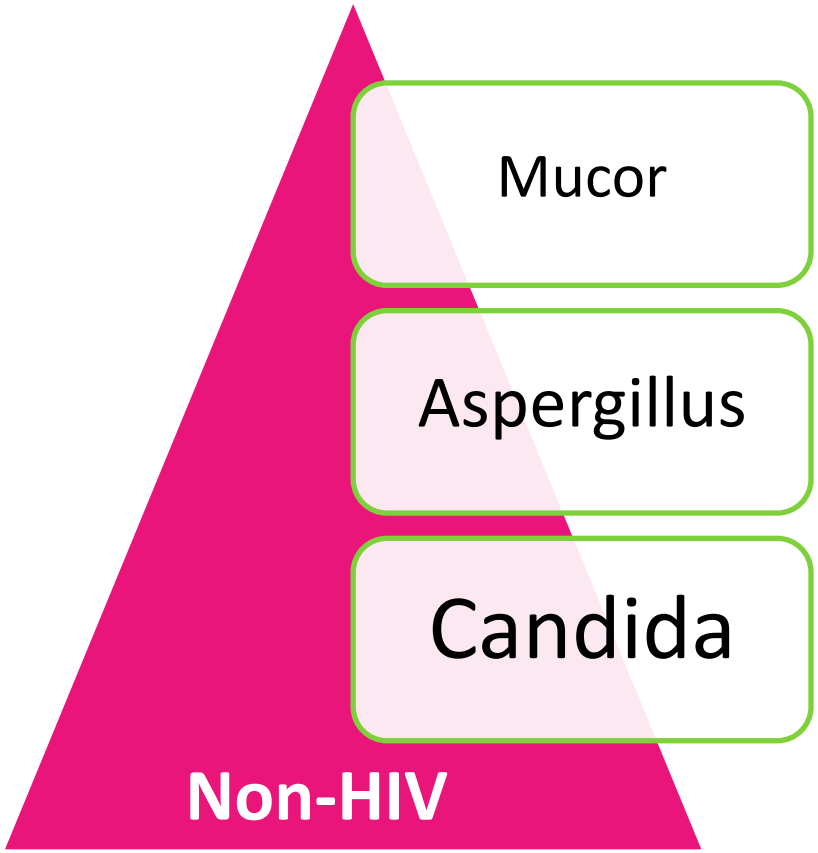
Invasive fungal infections (IFI)

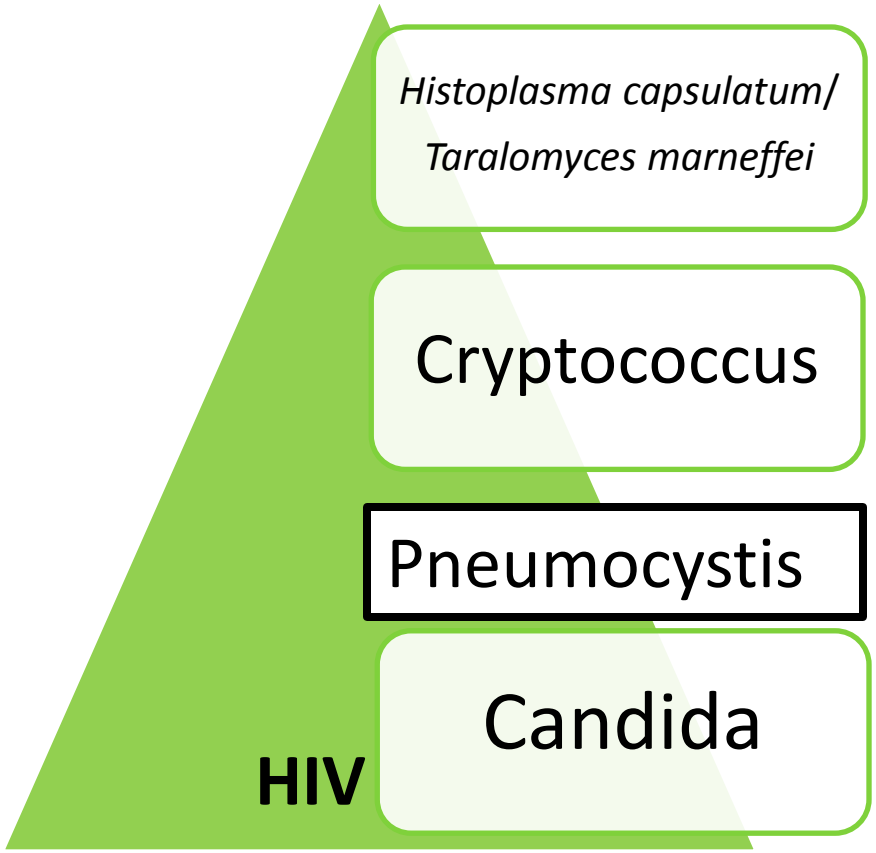
- Common IFIs
- Recent guidelines of Dx and Rx of IFI
- **HIV**
- **Non-HIV**

Common invasive fungal infections



Common invasive fungal infections





Cryptococcosis

Cryptococcal meningitis in HIV

	% (n = 678)
Fever	49.7
Headache	98.5
Median duration of headache, days	14 (7-28)
Vision loss	8.2
Seizure within 72 hours	17.5
Any CN palsy	7.8
GCS < 15	24.0
Abnormal mental status	43.9

	% (n = 678)
Median CSF pressure, cm	23 (13-38)
CSF pressure > 30 cm	32-37%
Median CSF WBC count, cells/mm3	4 (0-20)
Median CSF glucose, mg%	11 (5-15)
Median CSF protein, mg/dl	114 (5-190)
Median CSF fungal count, log10 CFU/ml	5 (3.5-5.9)
Median baseline CD4 cell count, cell/mm3	26 (10-64)

Molloy SF et al. N Engl J Med 2018;378:1004-17

Treatment of cryptococcal meningitis in HIV

Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

Table 2. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Human Immunodeficiency Virus–Infected Individuals

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)[a]	2 weeks	A-I
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)[a]	2 weeks	B-II
Fluconazole	…	B-II
Itraconazole	…	C-II
Consolidation therapy: fluconazole (400 mg per day)	8 weeks	A-I
Maintenance therapy: fluconazole (200 mg per day)[a]	≥1 year[c]	A-I

Amphotericin B 0.7-1 mg/kg/d + 5-FC 100 mg/kg/d (A-I) or fluconazole 800 mg/d (B-I) x 2 weeks -> fluconazole 400 mg/d x8 weeks (B-II) -> fluconazole 200 mg/d ≥ 1 year (A-I) until ART CD4 ≥ 100/mm3

Cryptococcal meningitis/HIV

Induction Therapy (For At Least 2 Weeks, Followed by Consolidation Therapy)

Preferred Regimens:

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus flucytosine 25 mg/kg PO QID **(AI)**

Alternative Regimens:

- Amphotericin B (deoxycholate 0.7-1.0 mg/kg/d IV) plus fluconazole 800 mg PO or IV/d **(BI)**; *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily alone **(BI)**; *or*
- Fluconazole 400 mg PO or IV daily plus flucytosine 25 mg/kg PO QID **(BII)**; *or*
- Fluconazole 800 mg PO or IV daily plus flucytosine 25 mg/kg PO QID **(BIII)**;
- Fluconazole 1200 mg PO or IV daily alone **(CI)**

Consolidation Therapy (For At Least 8 Weeks, Followed by Maintenance Th

- To begin after at least 2 weeks of successful induction therapy (defined as substantial clinical improvement and a negative CSF culture aft

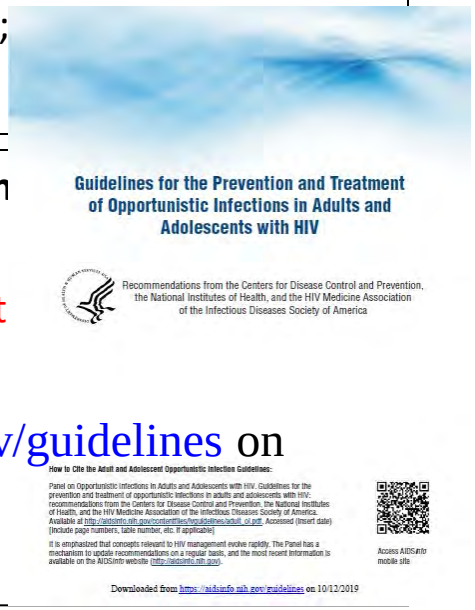
Preferred Regimen:

- Fluconazole 400 mg PO or IV once daily **(AI)**

Alternative Regimen:

- Itraconazole 200 mg PO BID **(CI)**

Adapted from https://aidsinfo.nih.gov/guidelines on 10/12/2019



The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2013;368:1291-302.

ORIGINAL ARTICLE

Combination Antifungal Therapy for Cryptococcal Meningitis

AMB 1 mg/kg/d x 4 wk -> FLU 400 mg/d x 6 wk	AMB 1 mg/kg/d + 5-FC100 mg/k/d x 2 wk -> FLU 400 mg/d x 8 wk	AMB 1 mg/kg/d + FLU 800 mg x 2 wk -> FLU 400 mg/d x 8 wk

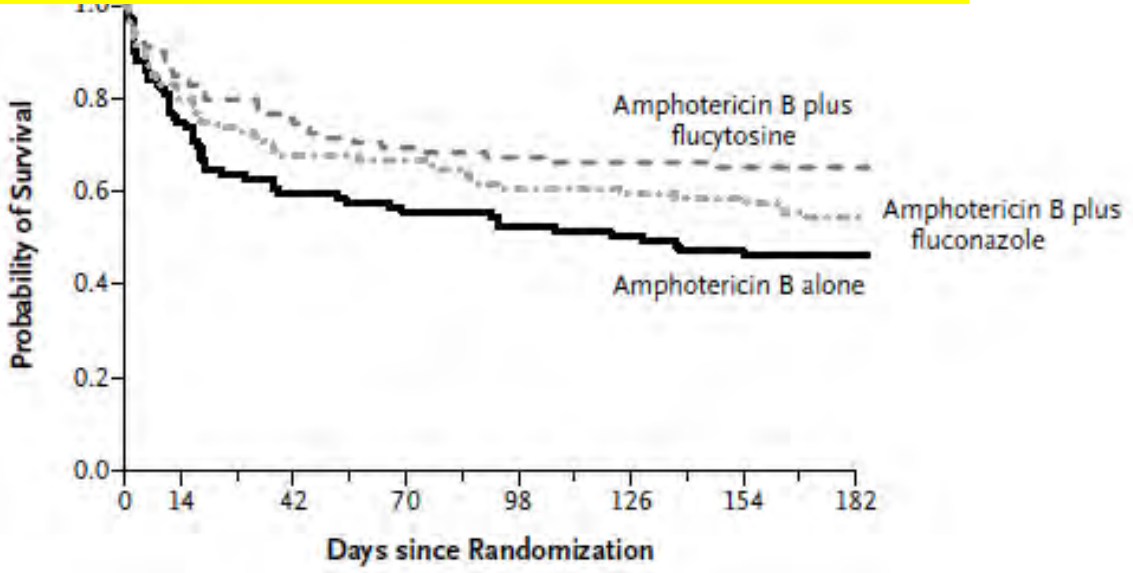
Table 2. Primary and Key Secondary Outcomes.*

Outcome	Group 1, Amphotericin B (N=99)	Group 2, Amphotericin B and Flucytosine (N=100)	Group 3, Amphotericin B and Fluconazole (N=99)
Coprimary outcomes			
Death by day 14			
No. of deaths	25	15	20
Probability of survival (95% CI)	0.75 (0.67 to 0.84)	0.85 (0.78 to 0.92)	0.80 (0.73 to 0.88)
Death by day 70‡			
No. of deaths	44	30	33
Probability of survival (95% CI)	0.56 (0.47 to 0.66)	0.69 (0.61 to 0.79)	0.67 (0.58 to 0.77)

Survival %	AMB n = 99	AMB /5-FC n =100	AMB /FLU 800 n = 99
D14	75	85	80
D70	56	69	67

A

2 WK AMB < 2 WK AMB+FLU < 2 WK AMB+5-FC



No. at Risk

Amphotericin B alone	99	74	59	54	51	49	46	30
Amphotericin B plus flucytosine	100	84	73	67	64	63	62	46
Amphotericin B plus fluconazole	99	79	67	65	59	58	57	39

Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa

1. Fluconazole 1200 mg/d + 5-FC 100 mg/kg/d for 2 wks,
2. Amphotericin B 1 mg/kg/d 1 wk + 5-FC or FLU 1200 mg/d x1wk -> FLU 1200 mg/d x1 wk
3. Amphotericin B 1 mg/kg/d 2 wks + fluconazole 1200 mg/d or 5-FC x 2 wks

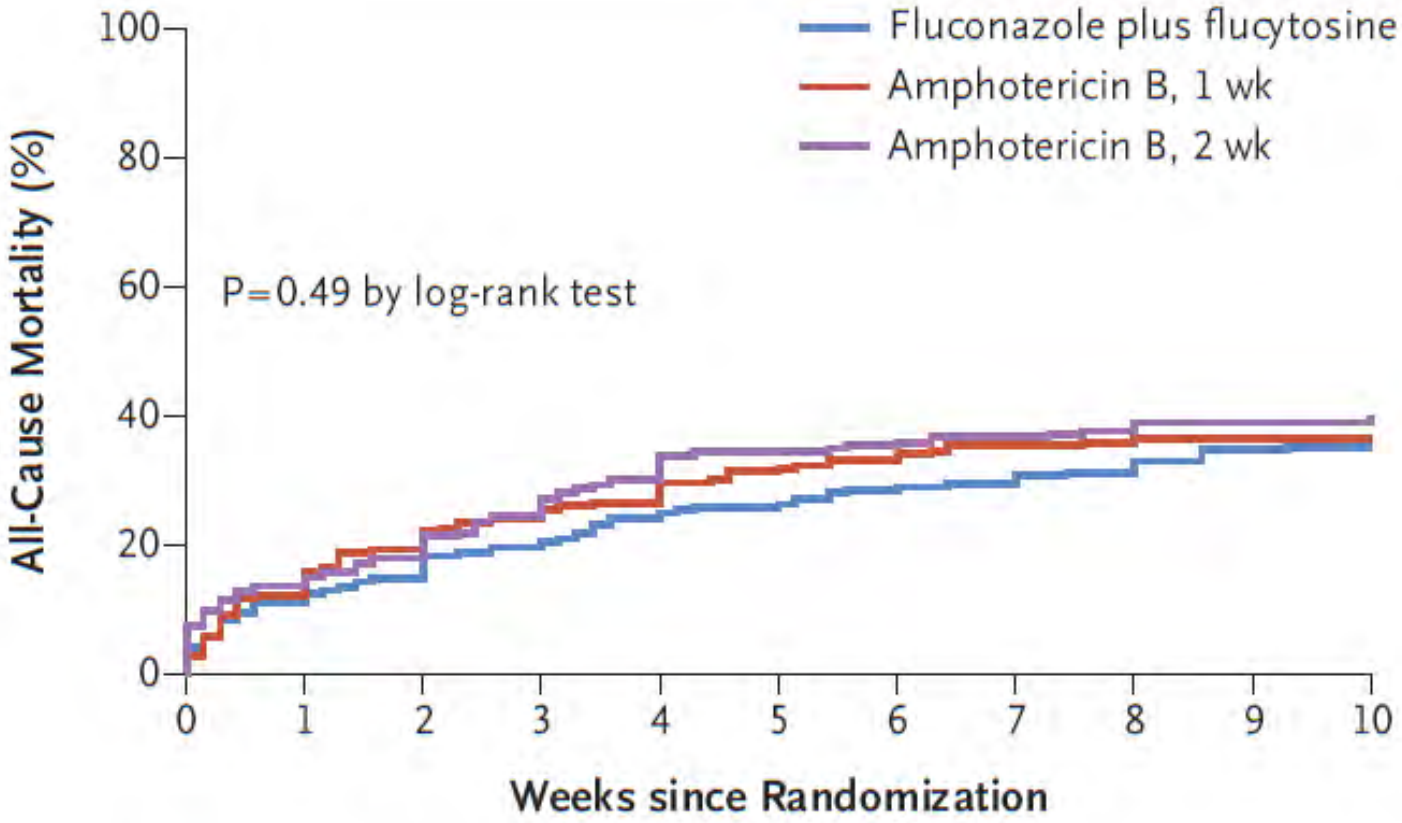
Fluconazole 800 mg/d x 2 wk -> 400 mg/d x 8wk -> 200 mg/d

	FLU + 5-FC 2 WK	AMB 1 WK	AMB 2 WK	DIFF AMB1WK/AMB2WK
Mortality at D14	18.2%	21.9%	21.4%	0.48 (−7.11 to 8.06)
Mortality at D70	35.1%	36.2%	39.7%	−3.58 (−12.51 to 5.35)

	AMB + 5-FC	AMB + FLU	HR	P-value
Mortality at D14	16.3%	21.1%	0.56	0.006
Mortality at D 70	31.1%	45.0%	0.62	0.002

Molloy SF et al. N Engl J Med 2018;378:1004-17

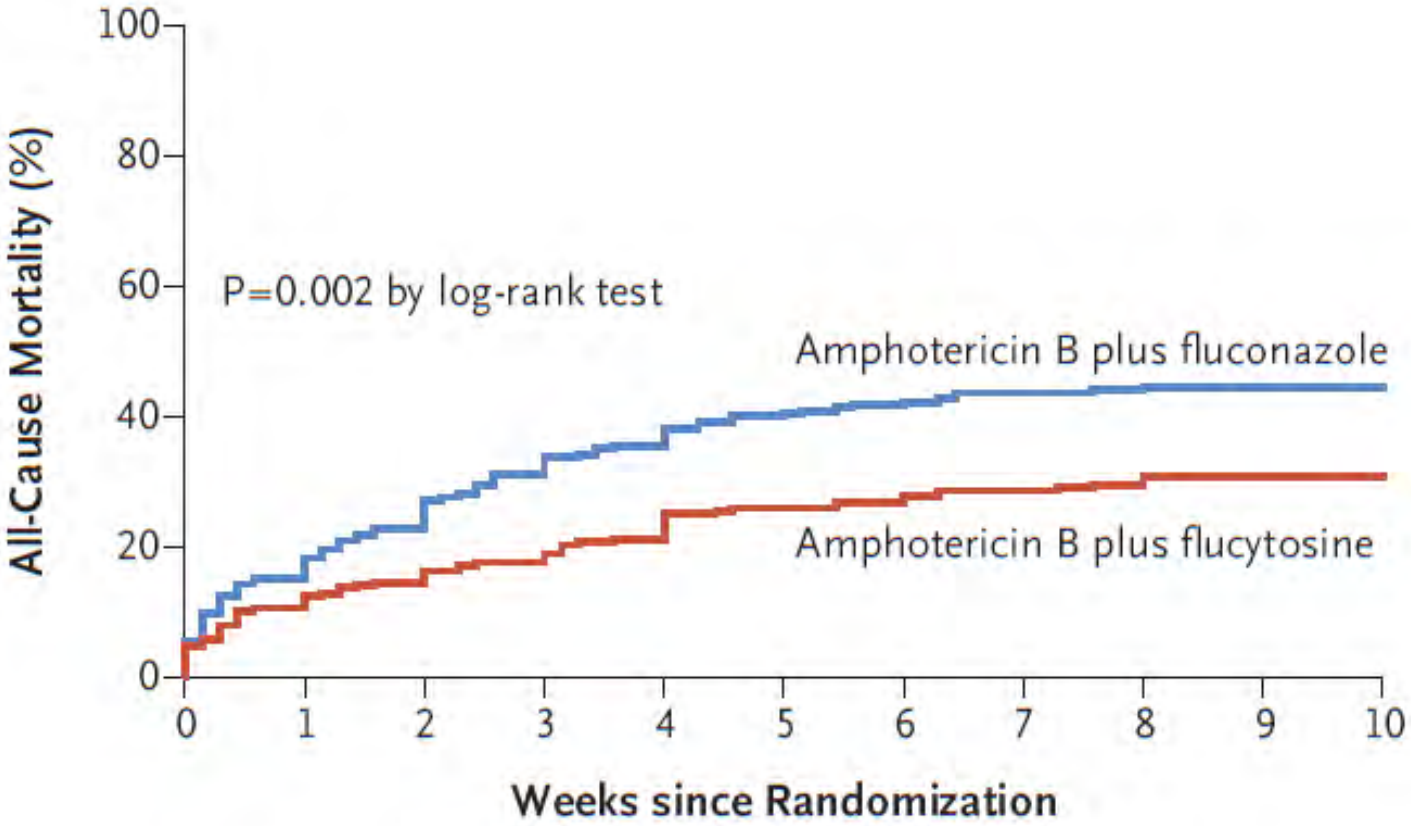
A



No. at Risk

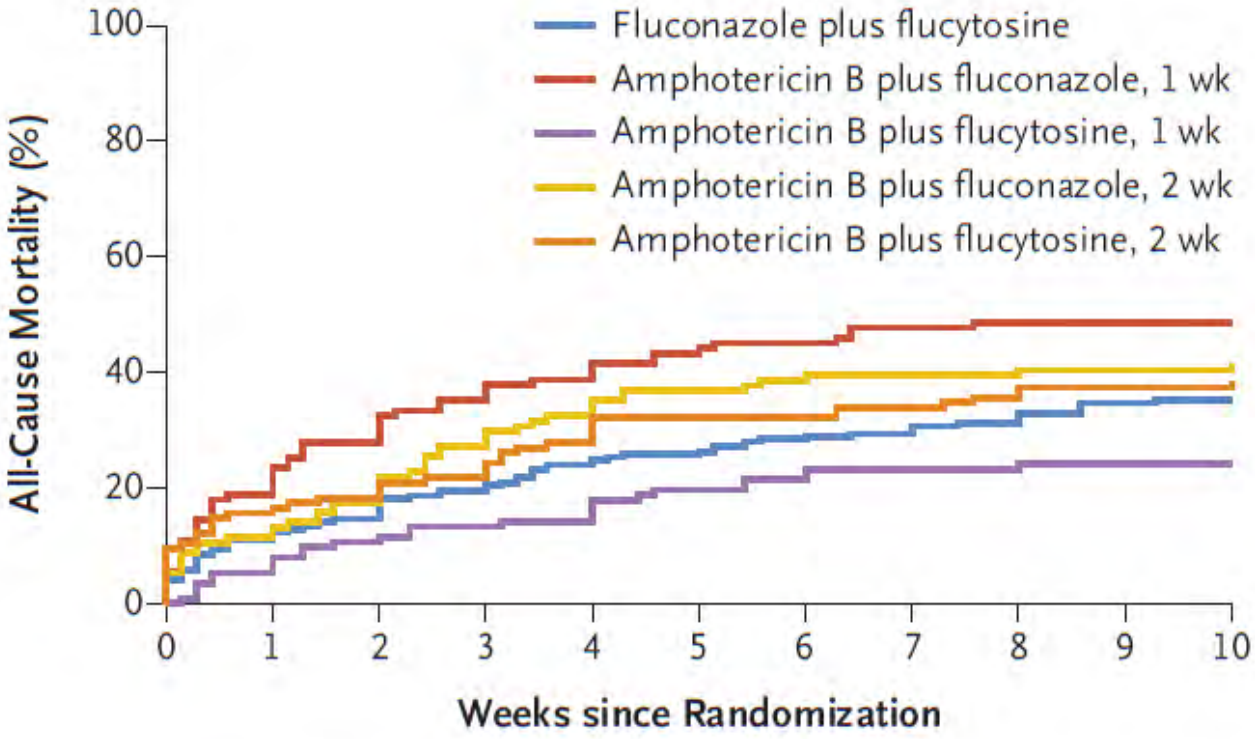
Fluconazole plus flucytosine	225	200	192	181	171	167	161	159	155	147	144
Amphotericin B, 1 wk	224	196	180	169	164	152	148	143	142	141	139
Amphotericin B, 2 wk	229	198	188	173	160	150	147	144	142	139	136

B



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

C



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

Treatment of cryptococcal meningitis

Induction

The following is recommended as the preferred induction regimen:

- For adults, adolescents and children, a short-course (one-week) induction regimen with 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, 12 mg/kg/day for children and adolescents, up to a maximum dose of 800mg daily), is the preferred option for treating cryptococcal meningitis among people living with HIV *(strong recommendation, moderate certainty evidence for adults, low-certainty evidence for children and adolescents)*

The following induction regimens are recommended as alternative options depending on drug availability:

- Two weeks of fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents) + flucytosine (100 mg/kg/day, divided into four doses per day) *(strong recommendation, moderate-certainty evidence).*

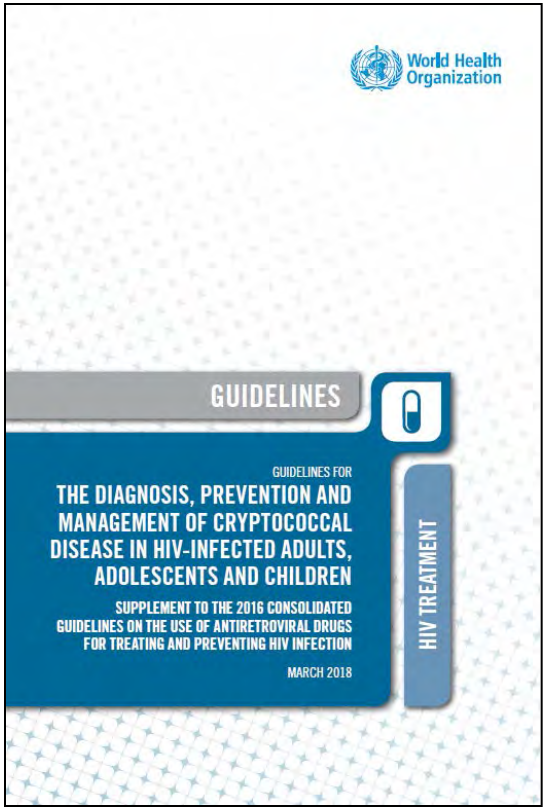
- Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) *(strong recommendation, moderate-certainty evidence).*

Consolidation

Fluconazole (800 mg daily for adults, 6–12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) is recommended for the consolidation phase (for eight weeks following the induction phase) *(strong recommendation, low-certainty evidence).*

Maintenance (or secondary prophylaxis)

Fluconazole (200 mg daily for adults, 6 mg/kg/day for adolescents and children) is recommended for the maintenance phase *(strong recommendation, high-certainty evidence).*



AMB + FLU 800 mg/d 1 wk -> 800 mg/d vs
AMB + FLU 1200 mg/d 1 wk -> 1200 mg/d?

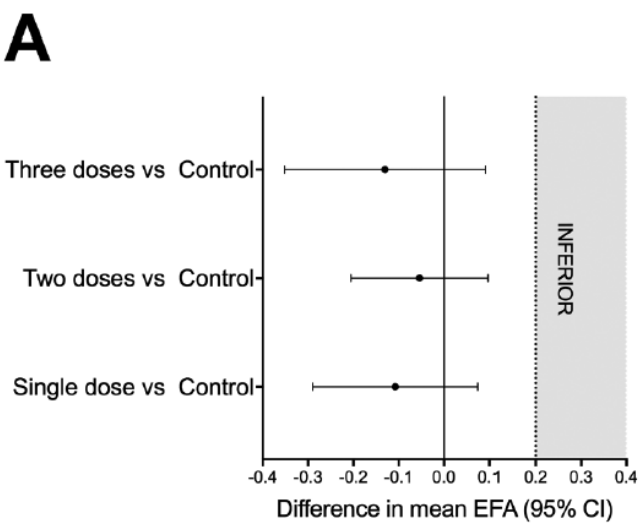
AMB + FLU + 5-FC vs AMB + FLU or 5-FC ?

Short-course High-dose Liposomal Amphotericin B for Human Immunodeficiency Virus–associated Cryptococcal Meningitis: A Phase 2 Randomized Controlled Trial

1. L-AMB 10 mg/kg D1 + FLU 1200 mg/d x14 d
2. L-AMB 10 mg/kg D1, 5 mg/kg D3 + FLU 1200 mg/d x14 d
3. L-AMB 10 mg/kg D1, 5 mg/kg D3, D7 + FLU 1200 mg/d x14 d
4. L-AMB 3 mg/kg/d x 14 d + FLU 1200 mg/d x14 d

Then Fluconazole 800 mg/d x 8 wk -> 200 mg/d

	Diff in mean EFA from control log10CFU/mL/day
L-AMB 10 mg/kg D1 N = 16	- 0.11 (95% CI, –.29 to .07)
L-AMB 10 mg/kg D1, 5 mg/kg D3 N = 18	–0.05 (95% CI, –.20 to .10)
L-AMB 10 mg/kg D1, 5 mg/kg D3, D7 N = 18	–0.13 (95% CI, –.35 to .09)
L-AMB 3 mg/kg/d x 14 d N = 17	–0.41 (CONTROL)



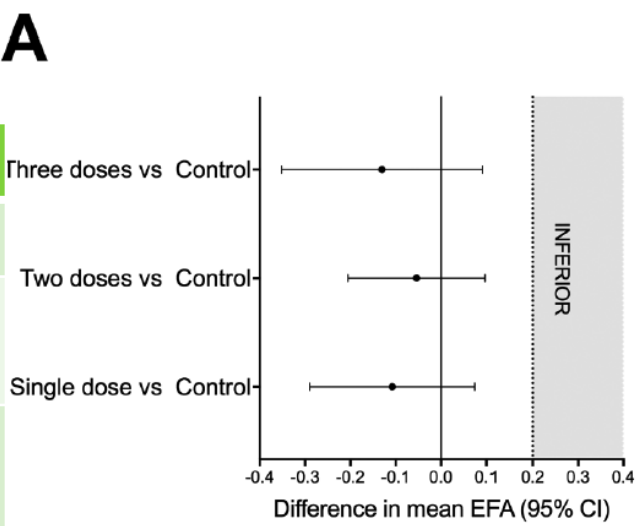
Clin Infect Dis 2019;68(3):393–401

Short-course High-dose Liposomal Amphotericin B for Human Immunodeficiency Virus–associated Cryptococcal Meningitis: A Phase 2 Randomized Controlled Trial

1. L-AMB 10 mg/kg D1 + FLU 1200 mg/d x14 d
2. L-AMB 10 mg/kg D1, 5 mg/kg D3 + FLU 1200 mg/d x14 d
3. L-AMB 10 mg/kg D1, 5 mg/kg D3, D7 + FLU 1200 mg/d x14 d
4. L-AMB 3 mg/kg/d x 14 d + FLU 1200 mg/d x14 d

Then Fluconazole 800 mg/d x 8 wk -> 200 mg/d

	All	control	1 LMB	2 AMB	3AMB
EFA log10	-0.49	-0.41	-0.52	-0.47	-0.54
2 WK MR	15%	10%	11%	15%	25%
10 WK MR	29%	29%	22%	15%	50%



Clin Infect Dis 2019;68(3):393–401

STUDY PROTOCOL Open Access

AMBIsome Therapy Induction OptimisatioN (AMBITION): High Dose AmBisome for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: Study Protocol for a Phase 3 Randomised Controlled Non-Inferiority Trial

- The trial will compare CM induction therapy with
  (1) a single dose (10 mg/kg) of L-AmB + fluconazole (1200 mg/day) and flucytosine (100 mg/kg/day) x 2 wk
  (2) amphotericin B deoxycholate (1 mg/kg/day) + 5-FC (100 mg/kg/day) X 7 d -> fluconazole (1200 mg/day) x 7 d
- Primary outcome – all cause mortality wk 10 (non-inferiority)

Lawrence et al. Trials (2018) 19:649;1-13

SERTALINE IN CM

The Antidepressant Sertraline Provides a Promising Therapeutic Option for Neurotropic Cryptococcal Infections

sonable CNS penetration. Here we demonstrate that sertraline (Zoloft), the most frequently prescribed antidepressant, displays potent antifungal activity against *Cryptococcus neoformans*, the major causative agent of fungal meningitis. In *in vitro* assays, this neurotropic drug is fungicidal to all natural *Cryptococcus* isolates tested at clinically relevant concentrations. Furthermore, sertraline interacts synergistically or additively with fluconazole against *Cryptococcus*. Importantly, consistent with our *in vitro* observations, sertraline used alone reduces the brain fungal burden at an efficacy comparable to that of fluconazole in a murine model of systemic cryptococcosis. It works synergistically with fluconazole in reducing the fungal burden in brain, kidney, and spleen. In contrast to its potency against *Cryptococcus*, sertraline is less effective against strains of *Candida* species and its inter-

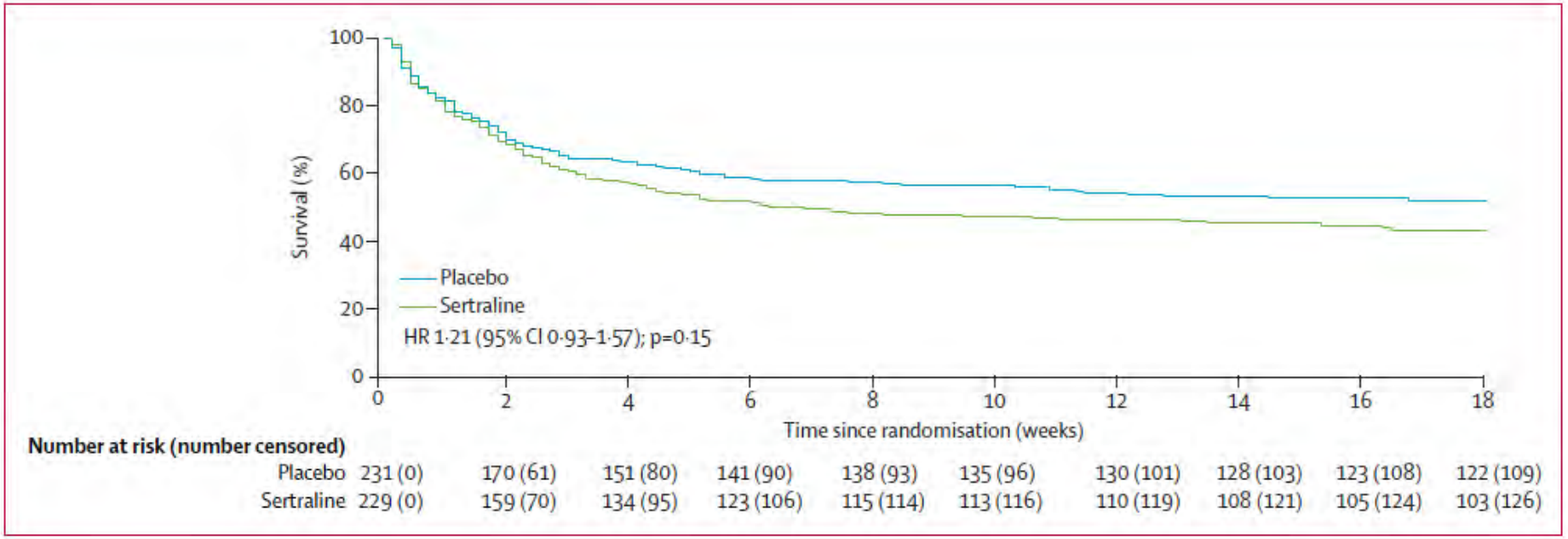
Zhal B et al. AAC 2012;56:3758-66

Adjunctive sertraline for HIV-associated cryptococcal meningitis: a randomised, placebo-controlled, double-blind phase 3 trial

Amphotericin B 0.7-1 mg/kg/d + FLU 800 mg/d 2 wk-> FLU 400 mg/d x 8 wk ->200 mg/d

Sertraline 400 mg/d x 2wk
-> 200 mg/d x 12 wks n =229

Placebo n =231



Lancet Infect Dis 2019;19: 843–51

Adjunctive sertraline for HIV-associated cryptococcal meningitis: a randomised, placebo-controlled, double-blind phase 3 trial

Amphotericin B 0.7-1 mg/kg/d + FLU 800 mg/d 2 wk-> FLU 400 mg/d x 8 wk ->200 mg/d

Sertraline 400 mg/d x 2wk
-> 200 mg/d x 12 wks n =229

Placebo n =231

	Sertraline (n=229)	Placebo (n=231)	p value*
EFA† by general linear regression, $-\log_{10}$ CFU/mL per day ‡	0·43 (0·37–0·50)	0·47 (0·40–0·54)	0·49
EFA† by mixed-effects regression, $-\log_{10}$ CFU/mL per day	0·33 (0·30–0·36)	0·33 (0·30–0·35)	0·56
2-week CSF sterility§	90/204 (44%)	101/216 (47%)	0·59
Grade 4 or 5 adverse events¶	72 (31%)	75 (32%)	0·98
Readmission to hospital‡	30 (13%)	29 (13%)	0·53
Serotonin syndrome‡	0	0	..
Culture-positive relapse	2 (1%)	2 (1%)	..

Lancet Infect Dis 2019;19: 843–51

Management of amphotericin-induced phlebitis among HIV patients with cryptococcal meningitis in a resource-limited setting: a prospective cohort study

- 1L saline IV x2 hr -> AMB infusion 4 hr -> 1L saline x2 hr after
- Rotate iv access q 3 days
- KCl 16 mEq/d during induction phase of AMB

Table 2 Duration of amphotericin B therapy and timing of Phlebitis during Cryptococcal meningitis

Characteristic	Phlebitis	No Phlebitis
N	125	571
Days of amphotericin B	14 [12, 14]	8 [4, 12]
Days in hospital	15 [14, 18]	14 [8, 16]
Time to phlebitis		
1–7 days	34 (27%)	
8–10 days	23 (18%)	
11–14 days	31 (25%)	
15–18 days	22 (18%)	
> 18 days	15 (12%)	

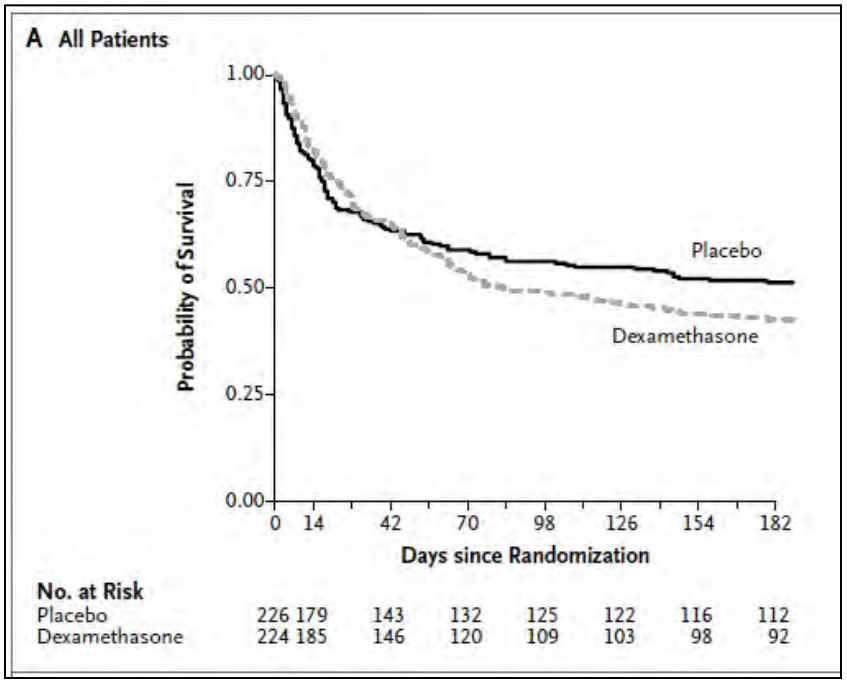
Ahimbisibwe et al. BMC Infectious Diseases (2019) 19:558
https://doi.org/10.1186/s12879-019-4209-7

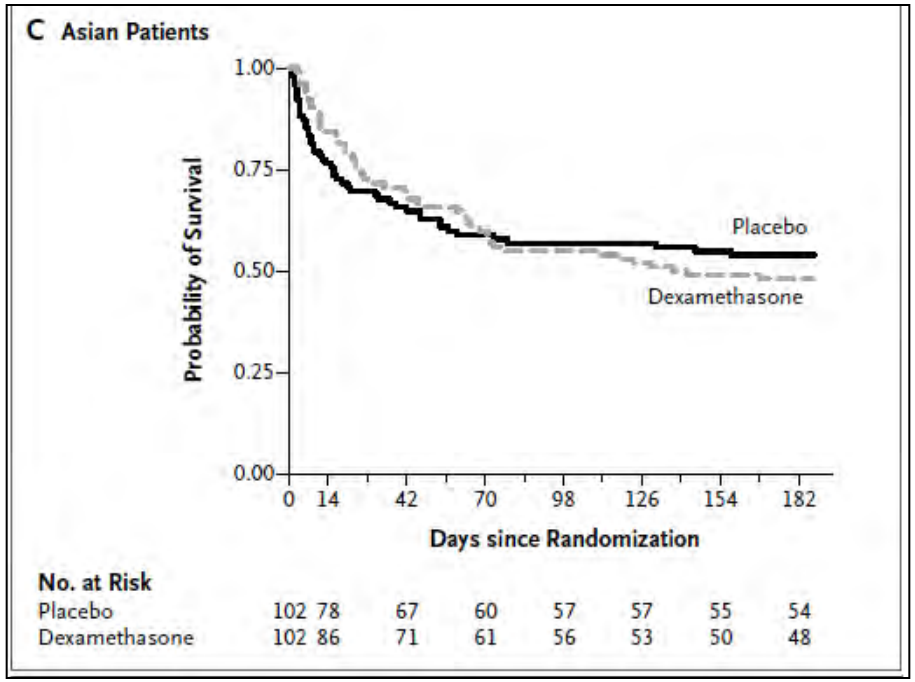
CM HIV: Increased ICP

- Elevated intracranial pressure (ICP) associated with cerebral edema, clinical deterioration, and higher risk of death
  - More likely if >25 cm H_2O
- Opening pressure always should be measured when lumbar puncture (LP) is performed
- Management of elevated ICP:
  - Daily LP with removal of CSF, or CSF shunting if LP is not effective or not tolerated
  - Corticosteroids, mannitol, and acetazolamide are not recommended

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

	DEXA	PLACEBO	HR	P-value
Mortality at 10 wks	47%	41%	1.11	0.45
Mortality at 6 mo	57%	49%	1.18	0.20
Good outcome of disability at 10 wks	13%	25%	0.42	<0.001
Adverse events	667	494		0.01





Beardsley et al. N Engl J Med 2016;374:542-54.

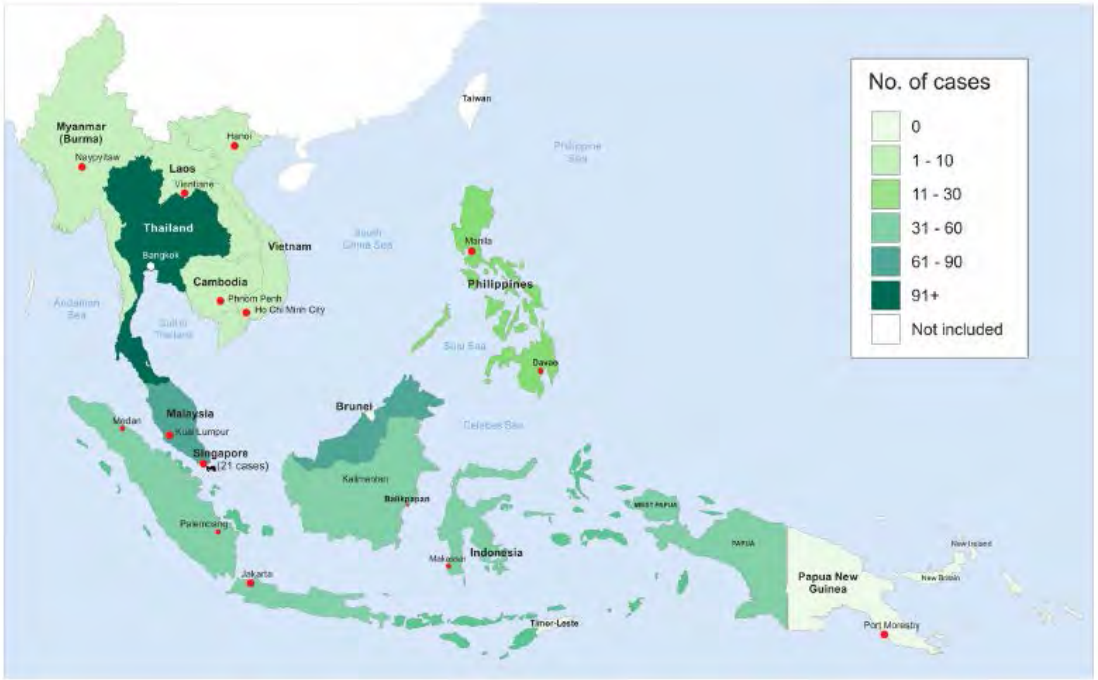
Histoplasmosis

Mapping histoplasmosis in South East Asia – implications for diagnosis in AIDS

Jacob Baker[a], Findra Setianingrum[a,b], Retno Wahyuningsih[b,c] and David W. Denning [a,d]

Table 1. Literature review of cases of histoplasmosis in South East Asia from 1932 to 2018.

Country	Number of cases	Number of cases with HIV co-infection	Number of cases of disseminated disease
Cambodia	5	5	4
Brunei	0	0	0
East Timor	0	0	0
Indonesia	48	24	28
Laos	1	0	0
Malaysia	76	8	21
Myanmar	3	2	0
Pacific Islands	1	0	0
Philippines	14	0	13
Singapore	21	9	14
Thailand	233	129	172
Vietnam	5	0	3
Total	407	177	255



Emerging Microbes & Infections
2019, VOL. 8
https://doi.org/10.1080/22221751.2019.1644539

Histoplasmosis

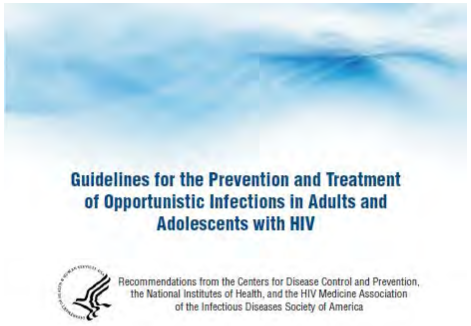
Treating Moderately Severe to Severe Disseminated Disease

Induction Therapy

Preferred Therapy:

- Liposomal amphotericin B at 3 mg/kg IV daily **(AI)**

Duration: For at least 2 weeks or until clinically improved



Maintenance Therapy

Preferred Therapy:

- Itraconazole 200 mg PO TID for 3 days, then BID for at least 12 months **(AII)**

Histoplasmosis

Long-Term Suppressive Therapy (Secondary Prophylaxis)

Indications:

• severe disseminated or CNS infection after at least 12 months of Rx **(AIII)**,

and In patients who relapsed despite appropriate initial therapy **(BIII)**

Preferred Therapy:

• Itraconazole 200 mg PO daily **(AIII)**

Alternative Therapy:

• Fluconazole 400 mg PO daily **(BIII)**

Criteria for Discontinuing Long Term Suppressive Therapy (AI):

• Received azole treatment for >1 year, *and*
• Negative fungal blood cultures, *and*
• Serum Histoplasma antigen <2 ng/mL, *and*
• CD4 count >150 cells/mm3 for ≥6 months in response to ART

Indication for Restarting Secondary Prophylaxis:

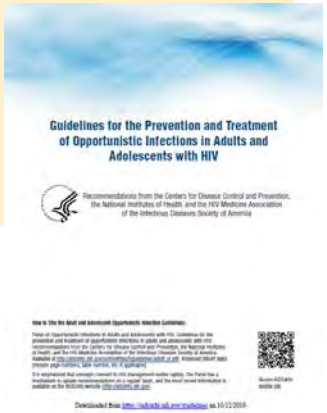
• CD4 count <150 cells/mm3 **(BIII)**

Talaromycosis marneffei in HIV

	n = 435
CD4 count cells/mm3	10 (6-27)
Positive skin culture	87.6%
Positive hemo culture	70%
ARV therapy	43%
Median duration of ART	123 days

N Engl J Med 2017;376:2329-40. DOI:10.1056/NEJMoa1613306

Talaromyces marneffei



Treating Acute Infection in Severely Ill Patients

Preferred Therapy:

- Liposomal amphotericin B, 3 to 5 mg/kg/day IV for 2 weeks; followed by itraconazole 200 mg PO BID for 10 weeks **(AII)**

Alternative Therapy:

- Voriconazole **(BII)**

Treating Mild Disease

Preferred Therapy:

- Itraconazole 200 mg PO BID for 8 weeks **(BII)**

Alternative Therapy:

- Voriconazole **(BII)**

Chronic Maintenance Therapy (Secondary Prophylaxis)

- Itraconazole 200 mg PO daily **(AI)**

Criteria for Discontinuing Chronic Maintenance Therapy:

- CD4 count >100 cells/mm3 for ≥6 months in response to ART **(BII)**

Criteria for Restarting Chronic Maintenance Therapy:

- CD4 count <100 cells/mm3 **(AIII)**, *or*
- If penicilliosis recurs at CD4 count >100 cells/mm3 **(CIII)**

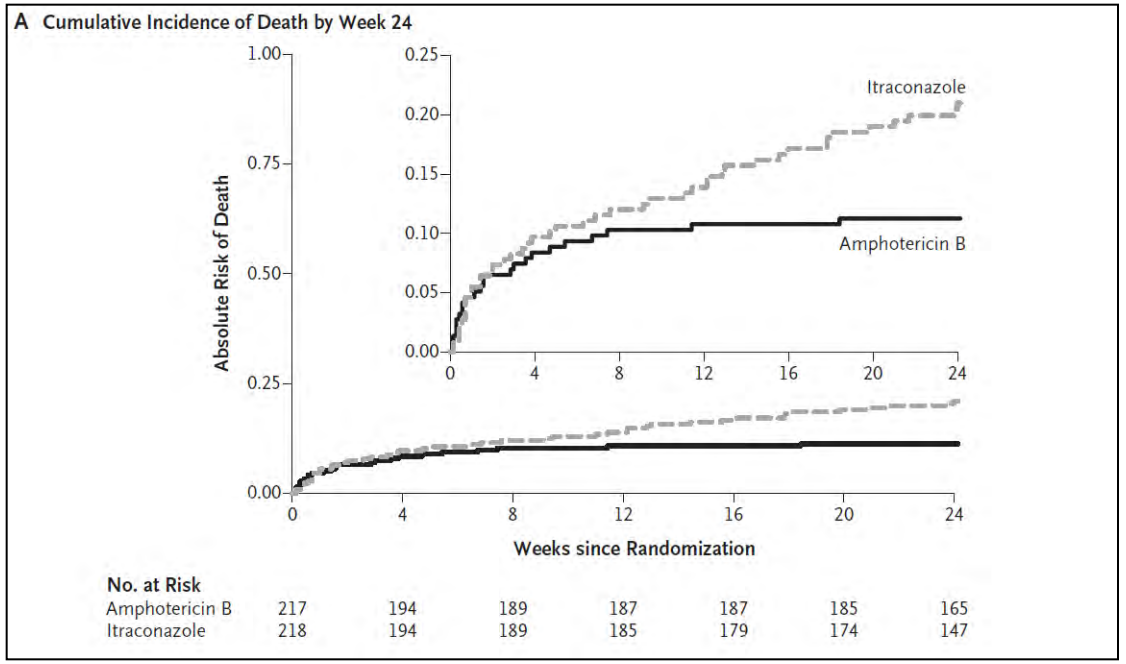
A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis

1. Amphotericin B 0.7 -1 mg/kg/d 2 wk
2. Itraconazole 600 mg/d x 3 d-> 400 mg/d x11 d

→ Itraconazole 400 mg/d x 10 wks ->200 mg/d

The risk of death at week 2 was 6.5% in AMB group and 7.4% in the ITRA group (absolute risk difference, 0.9%; 95%CI,−3.9 to 5.6; P =0.73)

the risk of death at week 24 was 11.3% in AMB group and 21.0% in the ITRA group (absolute risk difference, 9.7%; 95% CI, 2.8 to 16.6; P = 0.006)

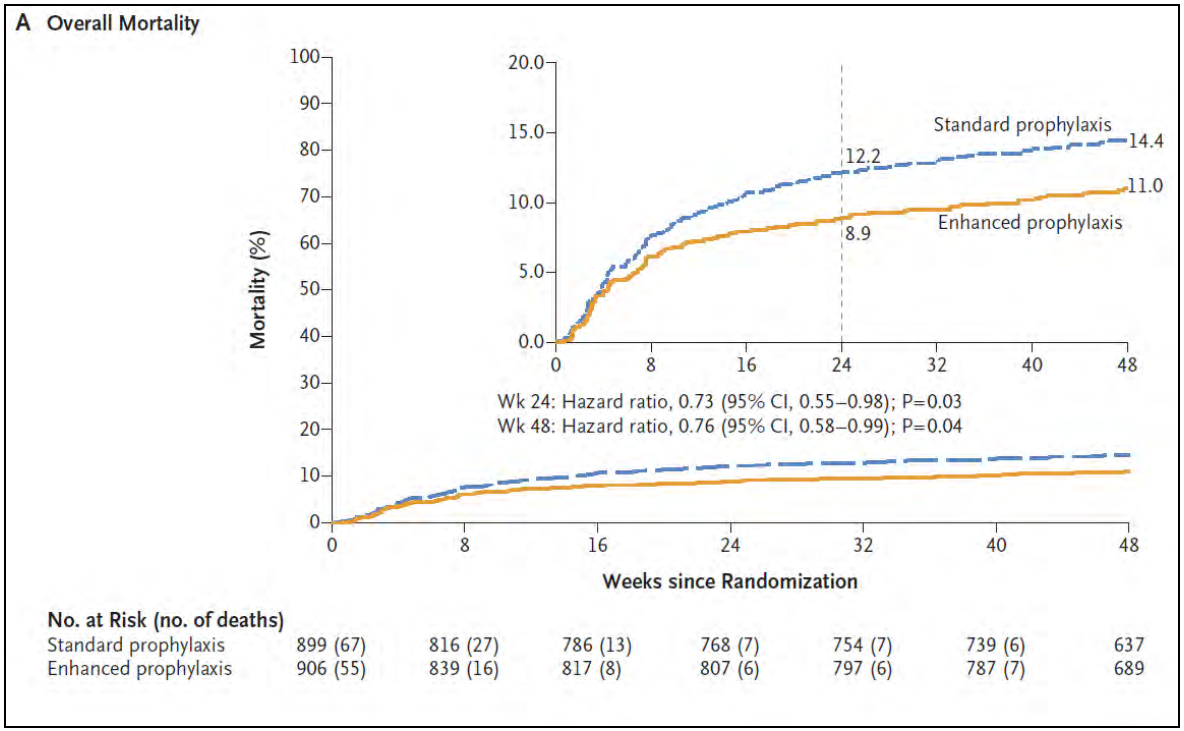


Treatment with AMB was associated with significantly faster clinical resolution and fungal clearance and significantly lower rates of relapse and IRIS than itraconazole.

N Engl J Med 2017;376:2329-40. DOI:10.1056/NEJMoa1613306

Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa

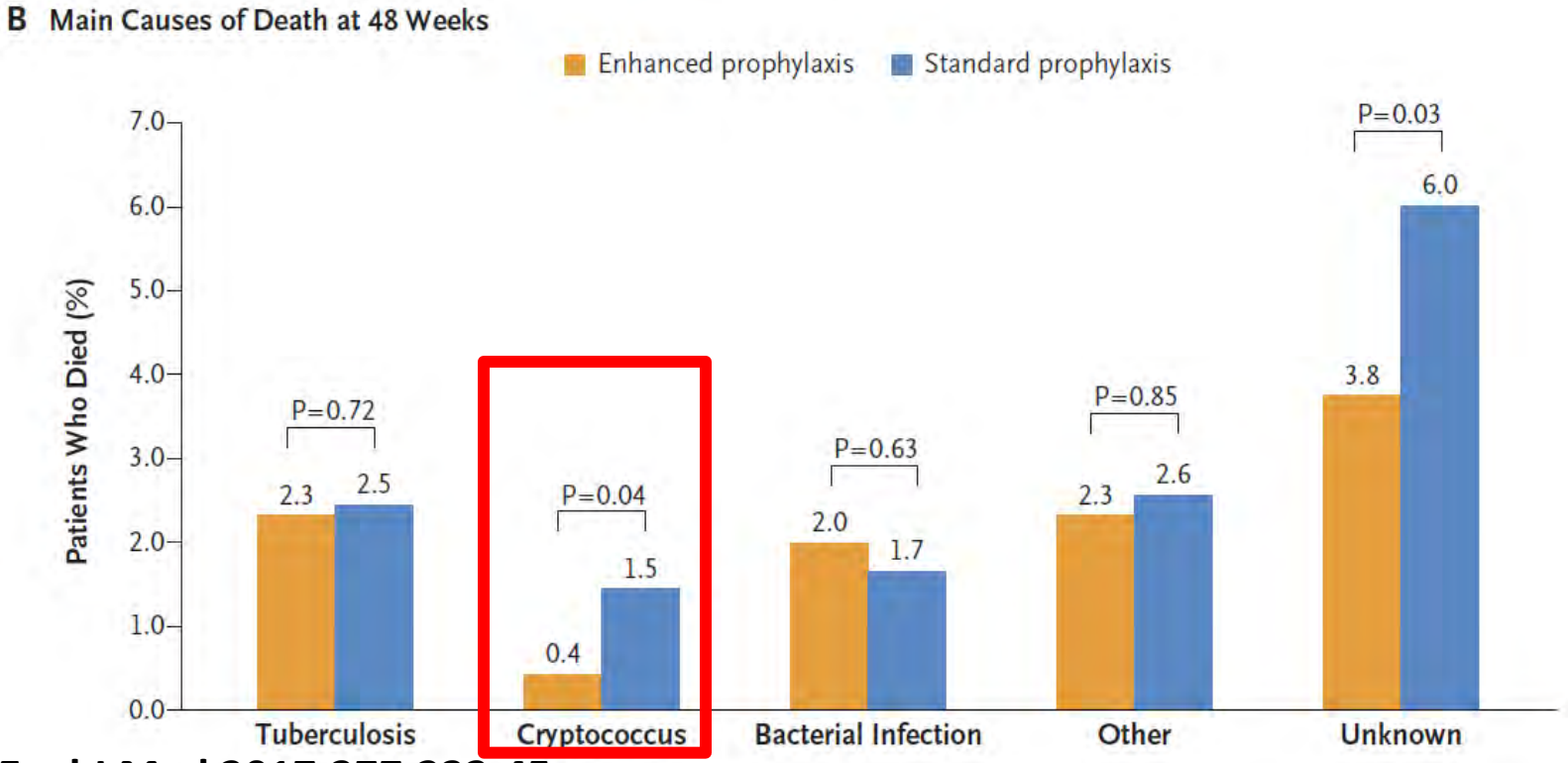
1. Standard prophylaxis: TMP/SMX 2X1 po PC
2. Enhanced prophylaxis: albendazole 400 mg po once + azithromycin 500 mg/d x 5 d + fluconazole 100 mg/d + TMP/SMX 2X1/d + INH 300 mg/d + B6 25 mg/d x 12 wks



N Engl J Med 2017;377:233-45.

Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa

1. Standard prophylaxis: TMP/SMX 2X1 po PC
2. Enhanced prophylaxis: albendazole 400 mg po once + azithromycin 500 mg/d x 5 d + fluconazole 100 mg/d + TMP/SMX 2X1/d + INH 300 mg/d + B6 25 mg/d x 12 wks



N Engl J Med 2017;377:233-45.