Updates in Cryptococcal Meningitis Management

Caleb Skipper, MD
Assistant Professor
University of Minnesota

Last Updated: October 31, 2024

Disclosures

I will present data from several investigator initiated clinical trials, including novel drugs in development. I will also mention tests from some specific diagnostic companies.

I have no financial ties to these companies, or any other disclosures.

Disclaimer

Funding for this presentation was made possible by 1 TR7HA53202-01-00 from the Human Resources and Services Administration HIV/AIDS Bureau. The views expressed do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. *Any trade/brand names for products mentioned during this presentation are for training and identification purposes only.*

AETC AIDS Education & Training Center Program Mountain West

Data Considerations

Data in this presentation offer a limited perspective of how systemic, social, and economic factors impact health. We recognize that racism, not race, creates and perpetuates health disparities.

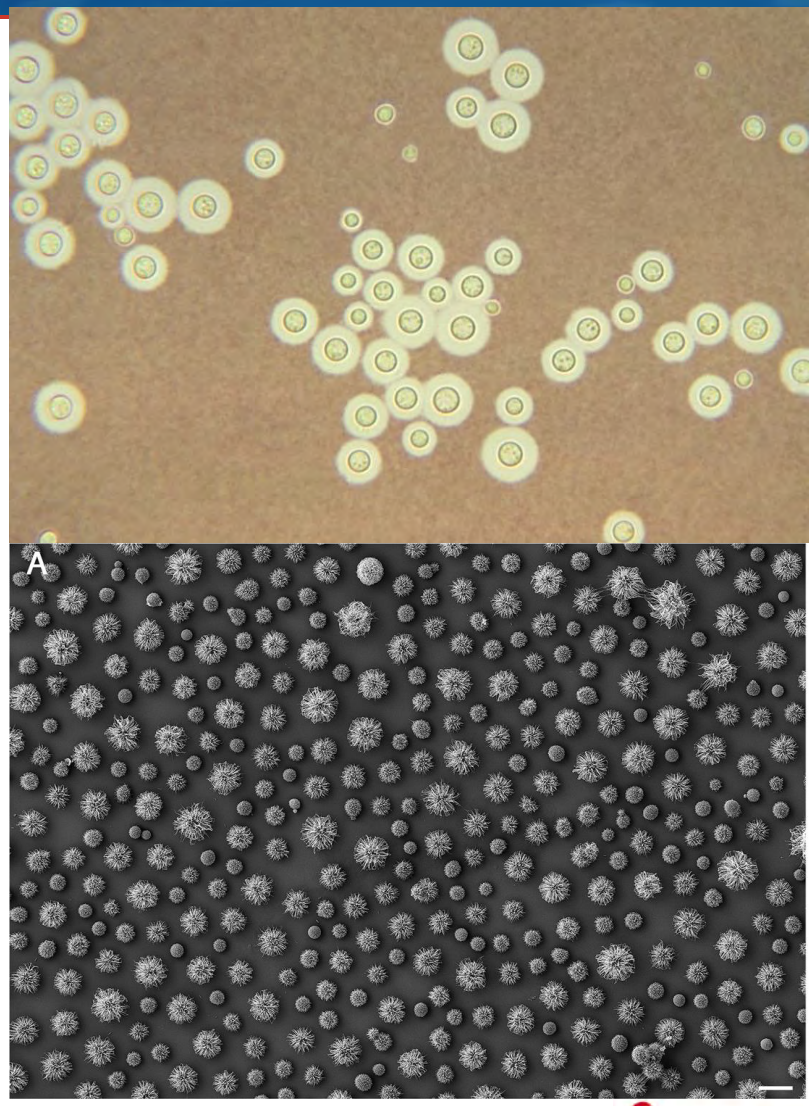
To Learn More:
https://www.cdc.gov/minorityhealth/racism-disparities

Objectives

- **<u>Outline for today</u>**
  - Introduction/refresher about cryptococcal meningitis
  - What has changed in the last several years
  - What is coming next

Cryptococcal Meningitis Intro

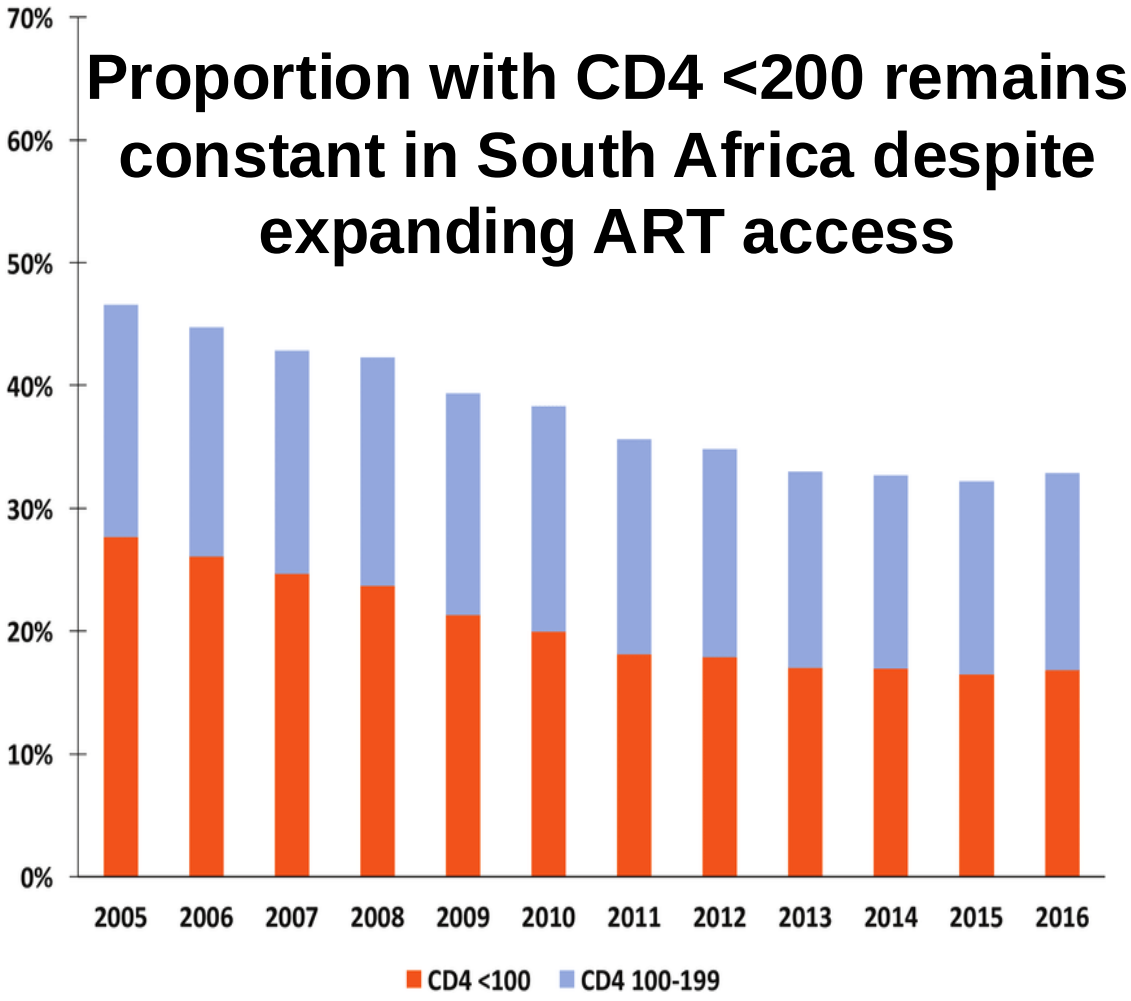
- Caused by *Cryptococcus spp., an environmental yeast*
  - *C. neoformans* is most commonly associated with HIV
  - *C. gattii* is associated with regional outbreaks
- Presentation is a sub-acute meningitis, usually slowly progressive over several weeks
- Disease is associated with immune compromised, particularly T cell deficiency
  - ~90% of cases in HIV occur in those with CD4<100 cells/uL
- Estimates are ~280,000 cases per year worldwide
  - Accounts for 15% of AIDS related deaths

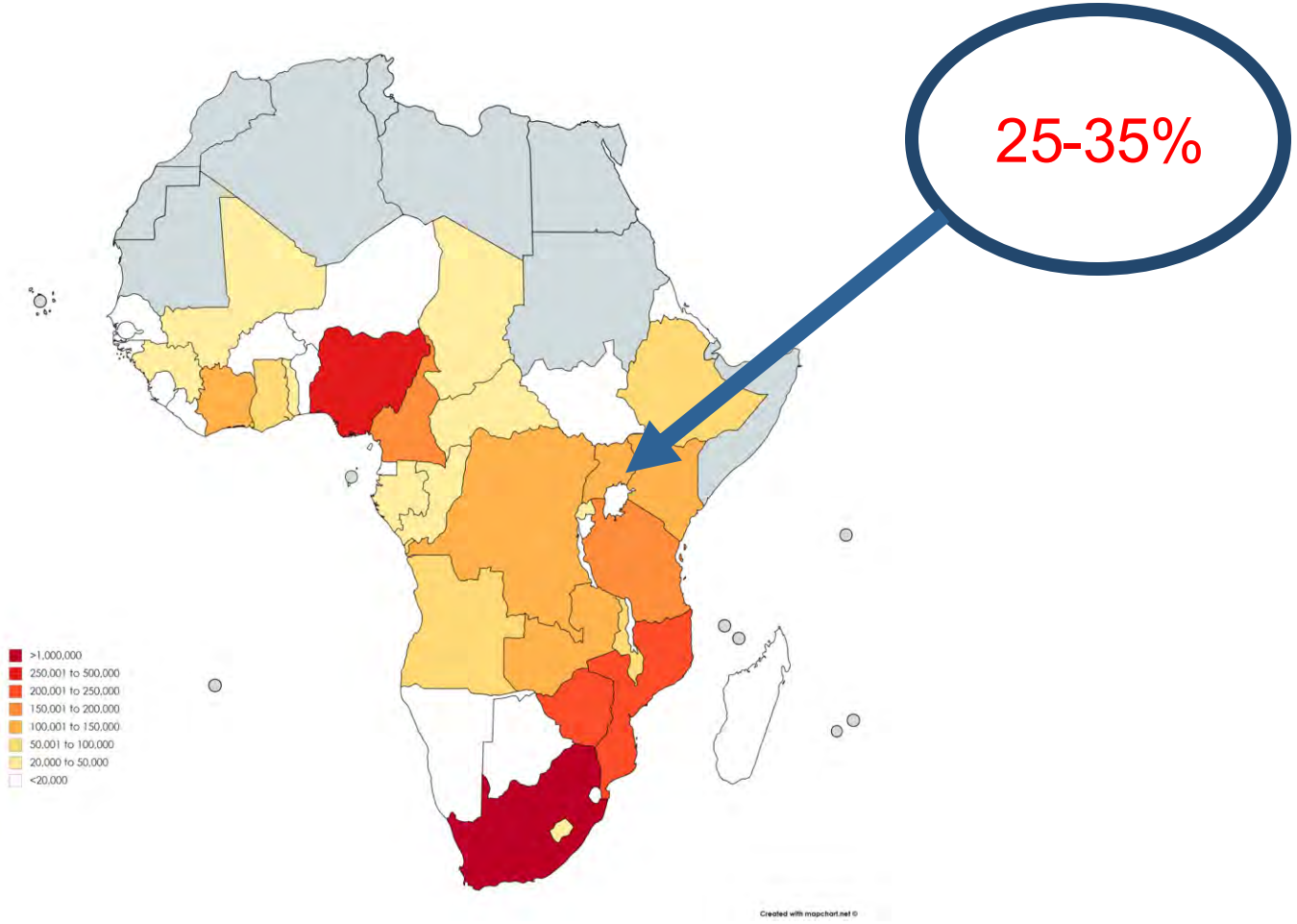


Lopez et al. Sci Rep, 2020.

MWAETC

Advanced HIV Disease in Africa

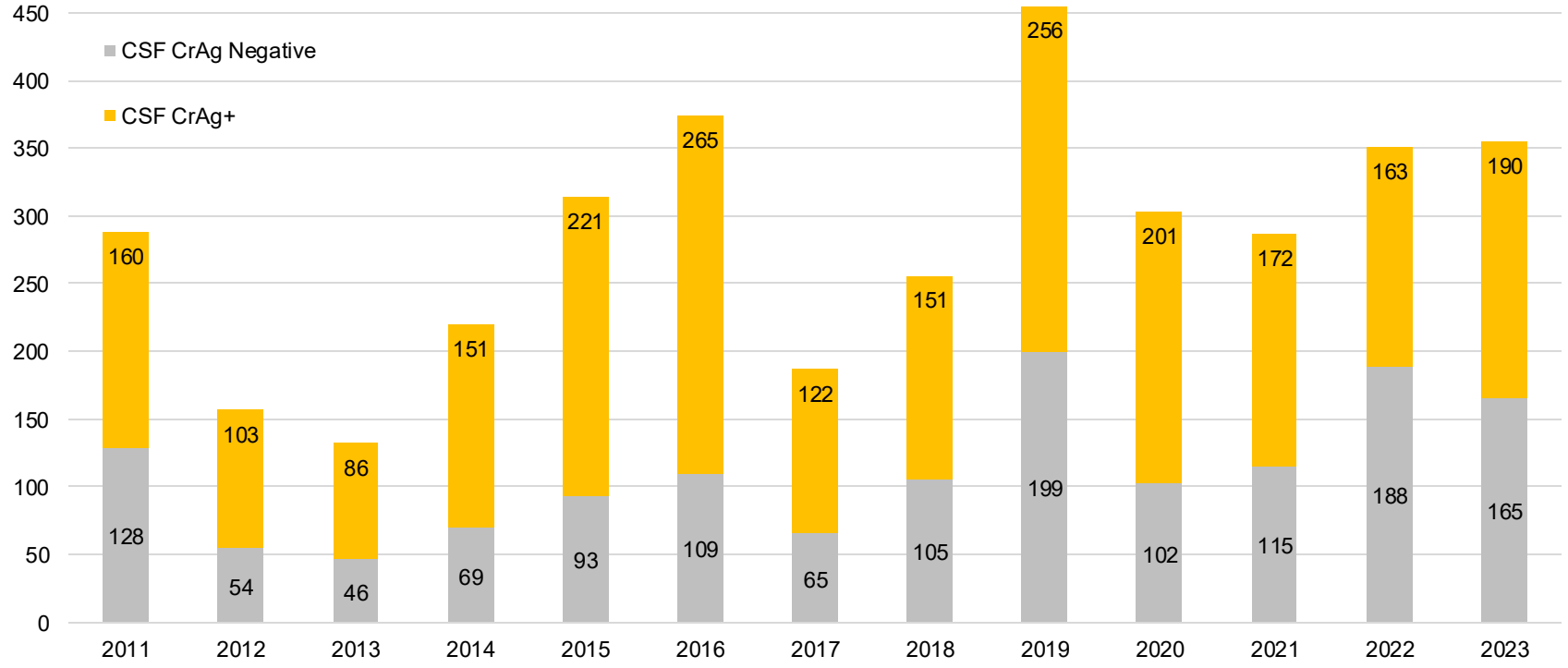




Carmona et al. *Clin Inf Dis*, 2018; Nasuuna et al. *Clin Inf Dis*, 2020; Ainembabzi et al. *Ther Adv Infect Dis*, 2024.

Cryptococcal Meningitis in Uganda

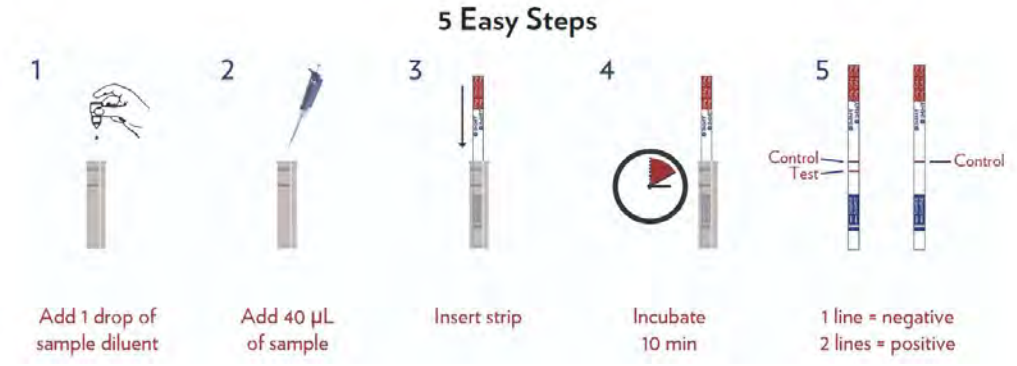
Yearly screening of persons with HIV-associated cryptococcal meningitis by the UMN-IDI study team



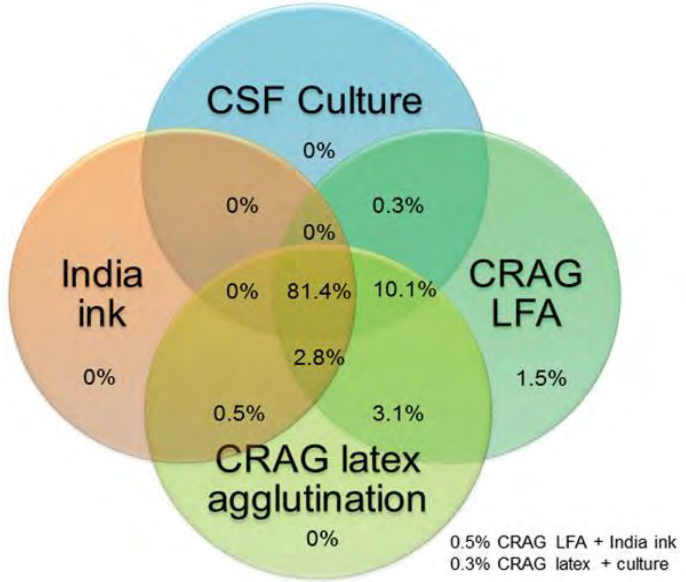
MWAETC

Cryptococcal Meningitis Management - Diagnosis

- Diagnosis
  - Diagnosis of cryptococcal meningitis (CM) is made by detection of fungus in the CSF
    - Traditionally india ink stain and fungal culture
    - Current gold standard is antigen detection
      - CrAg LFA (IMMY) had **99.3% sensitivity** & **99.1% specificity** in a multinational validation study
    - Current commercially available PCR platforms are not currently as sensitive
      - BioFire FilmArray ME (Biomerieux) had **82% sensitivity & 98% specificity** in our Uganda study



Source: immy.com/crag



Source: Boulware et al. Emerg Inf Dis, 2014.

Boulware et al. Emerg Inf Dis, 2014. Bridge et al. J Mycol Med, 2021.

MWAETC

Cryptococcal Meningitis Management - Treatment

- Management consist of antifungal therapy, control of intracranial pressure, and management of drug-induced toxicities

- Antifungal management consists of 3 primary phases
  - **Induction** – typically 14 days
  - **Consolidation** – typically 8 weeks
  - **Maintenance** – 12 months or until immune reconstitution

- All LPs should measure opening pressure
  - Enough CSF should be drained to normalize pressure (<20cm H_20)

- Aggressive management of toxicities is critical. These typically include:
  - IV fluids for kidney injury
  - Electrolyte replacement (particularly K+)
  - Anemia/cytopenia management

MWAETC

US Guidelines – Long in the Tooth (until very recently…)

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
AmBd (0.7–1.0 mg/kg per day) or liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)	4–6 weeks	B-II
Alternatives for induction therapy[b]		
AmBd plus fluconazole	…	B-I
Fluconazole plus flucytosine	…	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
Alternatives for maintenance therapy[b]		
Itraconazole (400 mg per day)[d]	≥1 year[c]	C-I
AmBd (1 mg/kg per week)[d]	≥1 year[c]	C-I

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate; HAART, highly active antiretroviral therapy.

[a] Begin HAART 2–10 weeks after the start of initial antifungal treatment.

[b] In unique clinical situations in which primary recommendations are not available, consideration of alternative regimens may be made—but not encouraged—as substitutes. See text for dosages.

[c] With successful introduction of HAART, a CD4 cell count ≥100 cells/μL, and low or nondetectable viral load for ≥3 months with minimum of 1 year of antifungal therapy.

[d] Inferior to the primary recommendation.

IDSA GUIDELINES

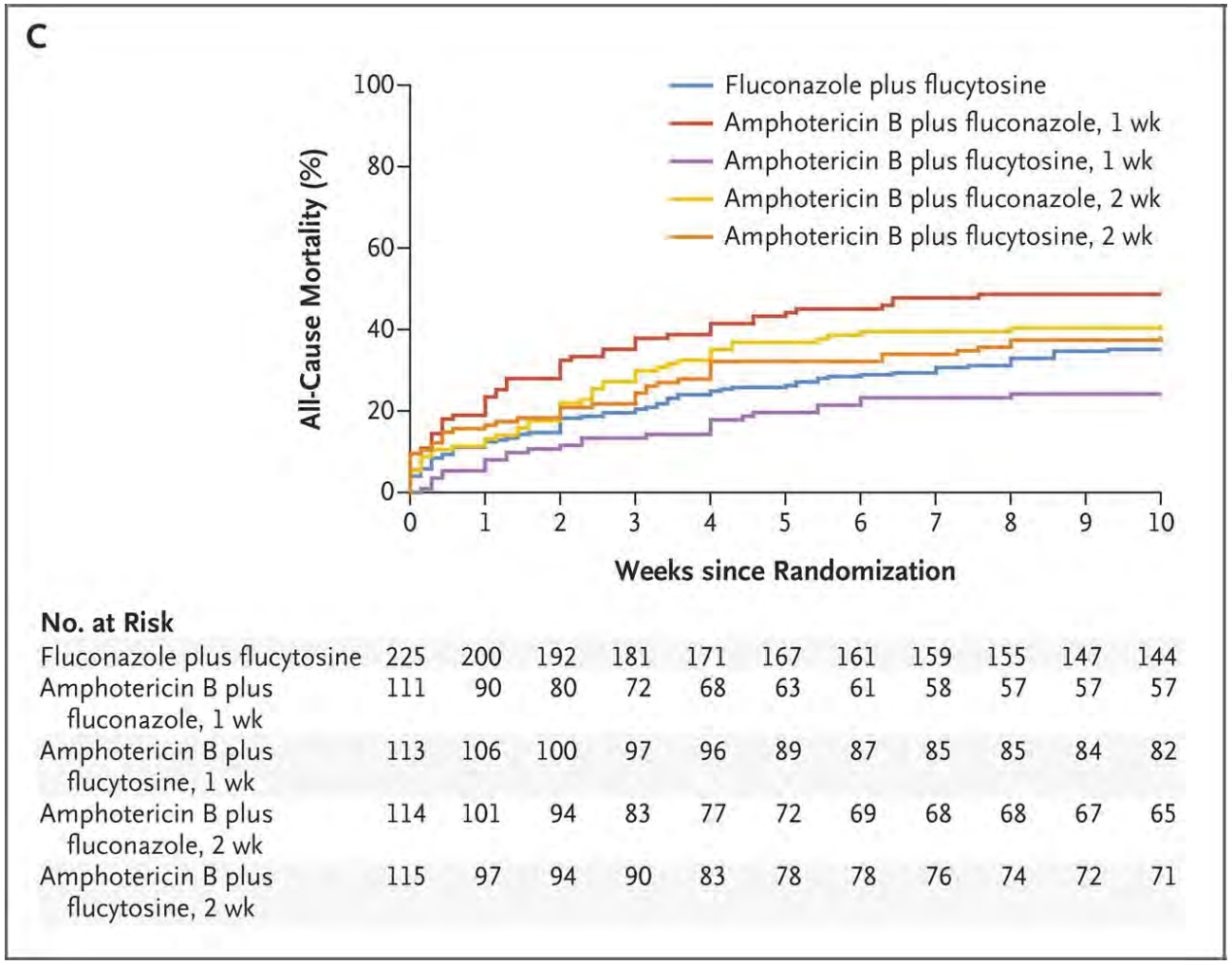
Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

John R. Perfect,[1] William E. Dismukes,[2] Francoise Dromer,[11] David L. Goldman,[3] John R. Graybill,[4] Richard J. Hamill,[5] Thomas S. Harrison,[14] Robert A. Larsen,[6,7] Olivier Lortholary,[11,12] Minh-Hong Nguyen,[8] Peter G. Pappas,[2] William G. Powderly,[13] Nina Singh,[10] Jack D. Sobel,[10] and Tania C. Sorrell[15]

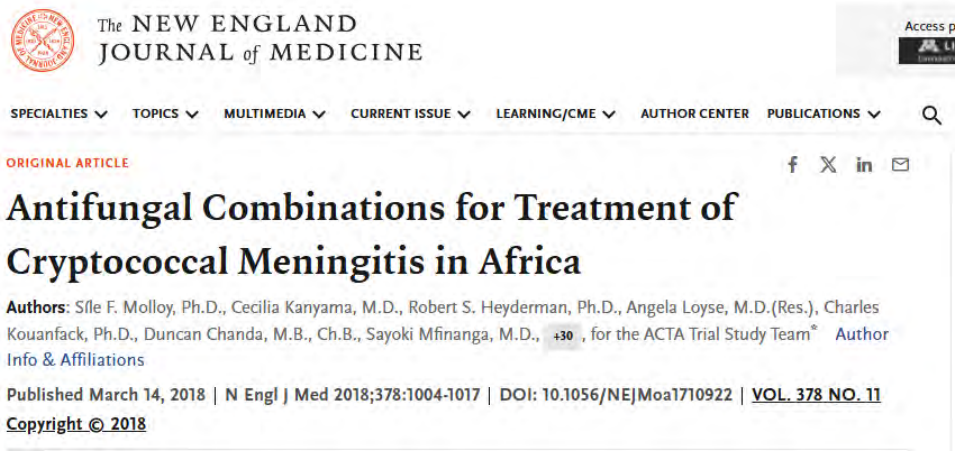
Perfect et al. CID, 2010.

MWAETC

Major Study Breakthroughs – ACTA Trial (N=721)



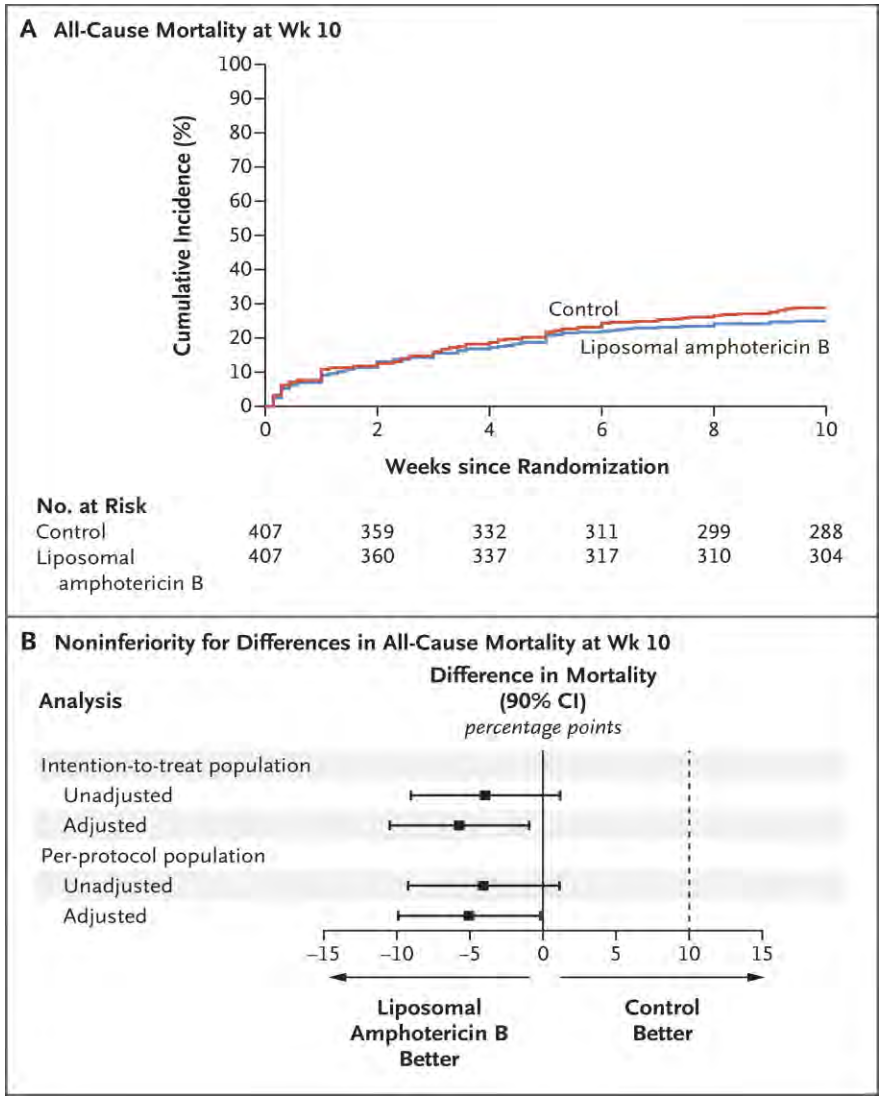
No. at Risk											
Fluconazole plus flucytosine	225	200	192	181	171	167	161	159	155	147	144
Amphotericin B plus fluconazole, 1 wk	111	90	80	72	68	63	61	58	57	57	57
Amphotericin B plus flucytosine, 1 wk	113	106	100	97	96	89	87	85	85	84	82
Amphotericin B plus fluconazole, 2 wk	114	101	94	83	77	72	69	68	68	67	65
Amphotericin B plus flucytosine, 2 wk	115	97	94	90	83	78	78	76	74	72	71

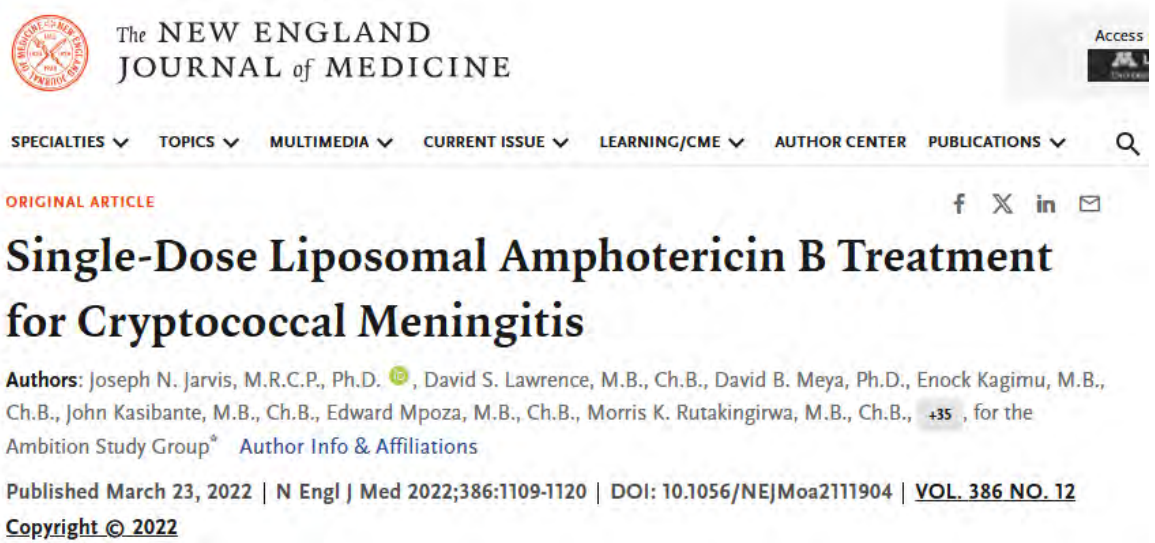


- Randomized, non-inferiority trial across 2 experimental arms and 1 control
  - 4 countries across Africa
- Primary endpoint was all-cause mortality at 2 weeks
  - Key secondary endpoint was partner drug comparison at 10 weeks

Molloy et al. NEJM, 2018.

Major Study Breakthroughs – AMBITION Trial (N=844)





- Randomized, non-inferiority trial comparing:
  - Liposomal amphotericin once (10mg/kg) + flucytosine & fluconazole for 14 days

  vs
  - Amphotericin deoxycholate + flucytosine for 7 days
- Primary endpoint was all-cause mortality at 10 weeks

Jarvis et al. NEJM, 2022.

WHO Guidelines 2022

Treating people with cryptococcal meningitis (2022 recommendations)

Induction therapy

A single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) should be used as the preferred induction regimen for treating people with cryptococcal meningitis.
Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children

Alternative induction regimens

If liposomal amphotericin is not available:
A seven-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by seven days of fluconazole (1200 mg daily for adults and 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).
Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children and adolescents

If no amphotericin formulation is available:
14 days of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) and flucytosine (100 mg/kg per day, divided into four doses per day).
Strong recommendation; moderate-certainty evidence

Note: fluconazole and flucytosine is the only recommended oral combination regimen and has been associated with lower mortality compared with amphotericin B deoxycholate and fluconazole *(3)*.

If flucytosine is not available:
14 days of liposomal amphotericin B (3–4 mg/kg per day) and fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).
Strong recommendation; moderate-certainty evidence

If liposomal amphotericin B and flucytosine are not available:
14 days of amphotericin B deoxycholate (1 mg/kg per day) and fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).
Strong recommendation; moderate-certainty evidence

Note: flucytosine-containing regimens are superior, and steps should be taken to ensure access to this drug.

https://www.who.int/publications/i/item/9789240052178

MWAETC

US Guidelines slow to adopt

HIV.gov (OARAC) Guidelines

Recommendations for Treating Cryptococcosis

Treating CNS and/or Disseminated Disease

Treatment consists of three phases: induction, consolidation, and maintenance therapy.

Induction Therapy (Duration: 2 Weeks, Followed by Consolidation Therapy)

- Irrespective of which regimen is used, patients must be followed carefully in the hospital for at least 7 days and ideally 14 days **(AII).** LP should be performed at Day 7 and Day 14 to ensure an appropriate clinical response and culture sterility. If increased ICP is documented, daily LP should be performed until the pressure is decreased into the normal range and symptoms have abated **(AII).**

Preferred Regimens

- In the United States and other settings where daily monitoring of electrolytes and kidney function and administration of electrolytes and IV fluid is possible:
  - Liposomal amphotericin B 3–4 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks **(AII)**
- In resource-limited health care systems, as recommended by the World Health Organization:
  - Liposomal amphotericin B 10 mg/kg IV as a single dose on Day 1, followed by flucytosine 25 mg/kg PO four times a day plus fluconazole 1,200 mg PO daily for 2 weeks **(AI)**

Alternative Regimens

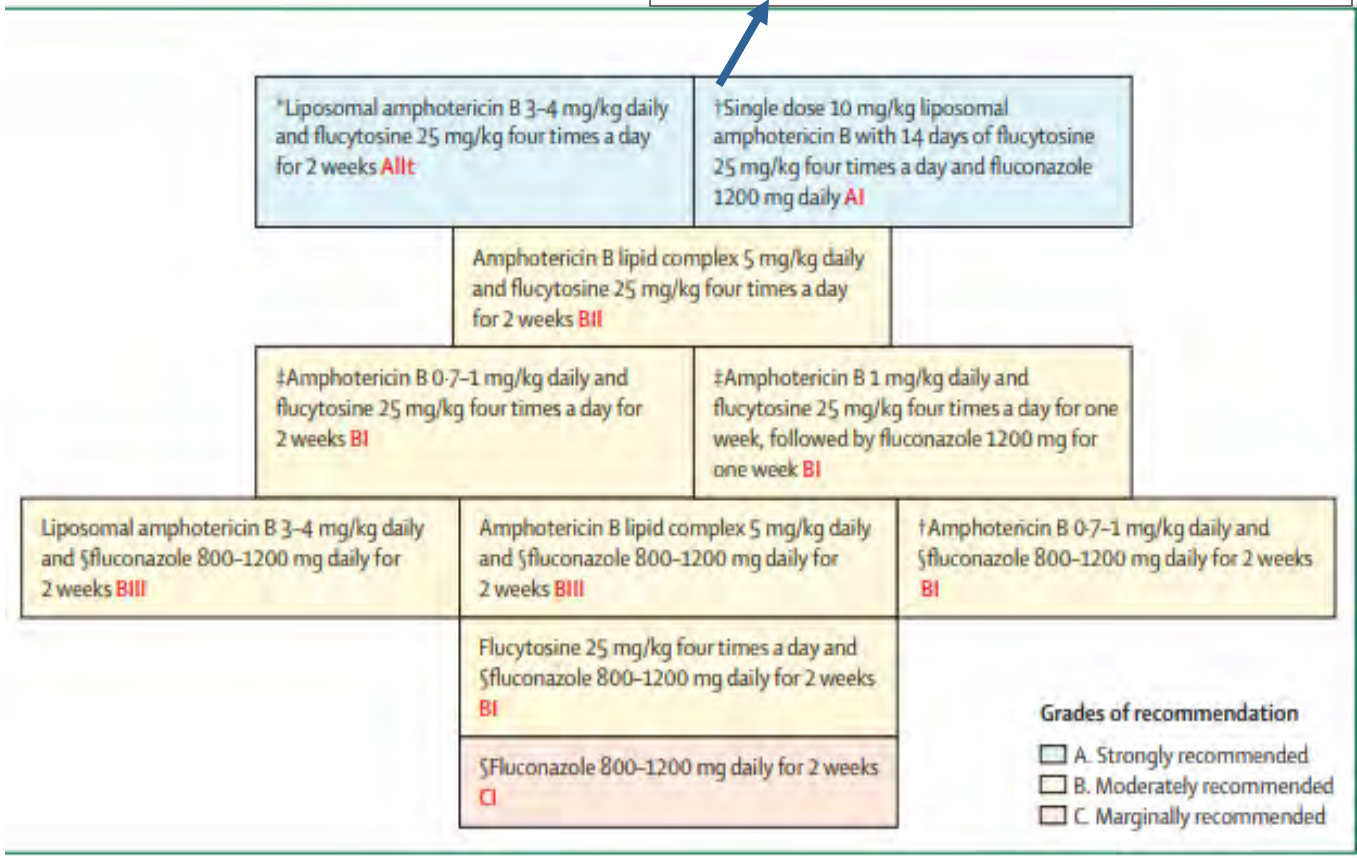
- Amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks **(BII),** *or*
- Amphotericin B deoxycholate 1 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 1 week, followed by fluconazole 1,200 mg PO daily for an additional week **(BI)**

Note: The flucytosine dose should be adjusted in renal impairment and ideally use TDM (see Table 6).

Updated: 10/29/24

IDSA (ECMM & ISHAM) Guidelines

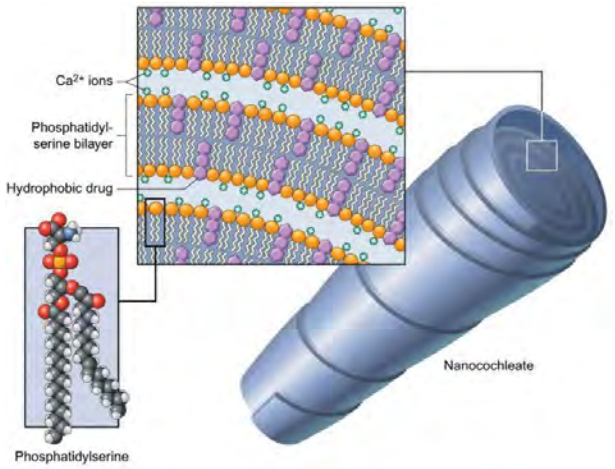
Only trialed in low-income settings

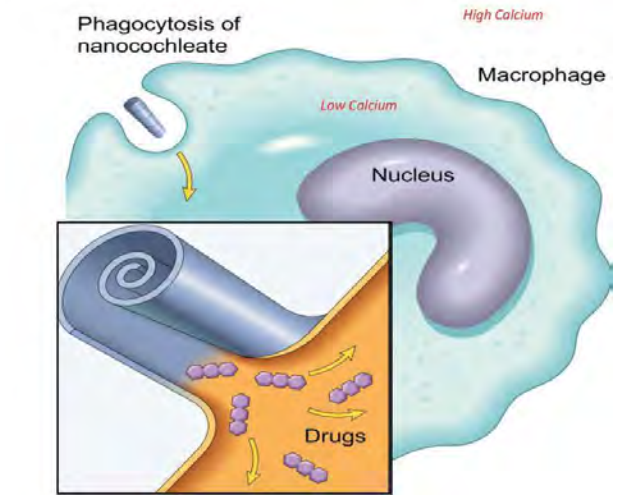


Updated: 2/9/24

MWAETC

What is coming next – oral amphotericin?! (EnACT)





AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

CLINICAL THERAPEUTICS
October 2020 Volume 64 Issue 10 10.1128/aac.00838-20
https://doi.org/10.1128/aac.00838-20

Phase I EnACT Trial of the Safety and Tolerability of a Novel Oral Formulation of Amphotericin B

Caleb P. Skipper [a,b], Mucunguzi Atukunda [a], Anna Stadelman [a,b], Nicole W. Engen [b], Ananta S. Bangdiwala [b], Katherine H. Hullsiek [b], Mahsa Abassi [b], Joshua Rhein [b], Melanie R. Nicol [b], Eva Laker [a], Darlisha A. Williams [b], Raphael Mannino [c], Theresa Matkovits [c], David B. Meya [a,b,d], David R. Boulware [b]

Skipper et al. *AAC*, 2020.

What is coming next – oral amphotericin?! (EnACT)

Oral Lipid Nanocrystal Amphotericin B for Cryptococcal Meningitis: A Randomized Clinical Trial

Boulware et al., 2023 | *Clinical Infectious Diseases*

IDSA Infectious Diseases Society of America

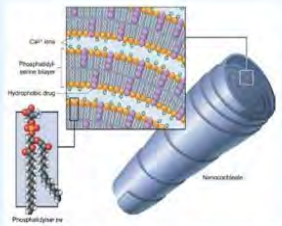
BACKGROUND: We conducted a randomized clinical trial to evaluate the antifungal efficacy of oral lipid nanocrystal (LNC) amphotericin (MAT2203) with flucytosine (5FC) in the treatment of cryptococcal meningitis.

PARTICIPANTS: We recruited adults with HIV diagnosed with cryptococcal meningitis from three hospitals in Uganda.

METHODS

Study participants had a positive CSF CrAg, Glasgow Coma Scale score = 15, and had to be able to tolerate oral medication. Participants were randomized to either the IV amphotericin control arm or to an interventional arm.

	ARM 1: 7 doses of IV Amphotericin + 5FC	ARM 2: 2 doses of IV Amphotericin + MAT2203 + 5FC	ARM 3: Oral MAT2203 + 5FC
	N=41	N=40	N=40
18-week Survival	85%	90%	85%
2-week CSF Sterility	67.6%	62.2%	63.6%
Grade 3-4 Hgb AEs	43.9%	20%	22.5%
Grade 3-4 K+ AEs	17%	5.1%	5%



Clinical antifungal activity did not differ between oral LNC-amphotericin and IV amphotericin

CONCLUSION: Oral LNC-amphotericin B with 5FC demonstrated similar antifungal activity, similar survival, and less toxicity than IV amphotericin and 5FC. Oral LNC-amphotericin B appears to be a promising antifungal candidate to be moved forward in future clinical trials for the treatment of severe fungal infections.

Clinical Infectious Diseases https://doi.org/10.1093/cid/ciad440

Clin Infect Dis, Volume 77, Issue 12, 15 December 2023, Pages 1659–1667, https://doi.org/10.1093/cid/ciad440

OXFORD UNIVERSITY PRESS

MWAETC

What is coming next – less flucytosine? (FLOOR)

- We recently completed enrollment in a small phase II trial testing using lower dose flucytosine for HIV-associated cryptococcal meningitis

- Intervention:
  - Amphotericin deoxycholate 1mg/kg for 7 days + **5FC 50mg/kg** for 10 days, followed by fluconazole 1200mg/day from Day 8-14
- Control:
  - Amphotericin deoxycholate 1mg/kg for 7 days + 5FC 100mg/kg for 7 days, followed by fluconazole 1200mg/day from Day 8-14

- Pragmatic goal: Non-inferior outcomes, reduced toxicity, reduced costs

MWAETC

What is coming next – enhanced treatment of cryptococcal antigenemia (ACACIA)

In persons with CrAg titer <1:160

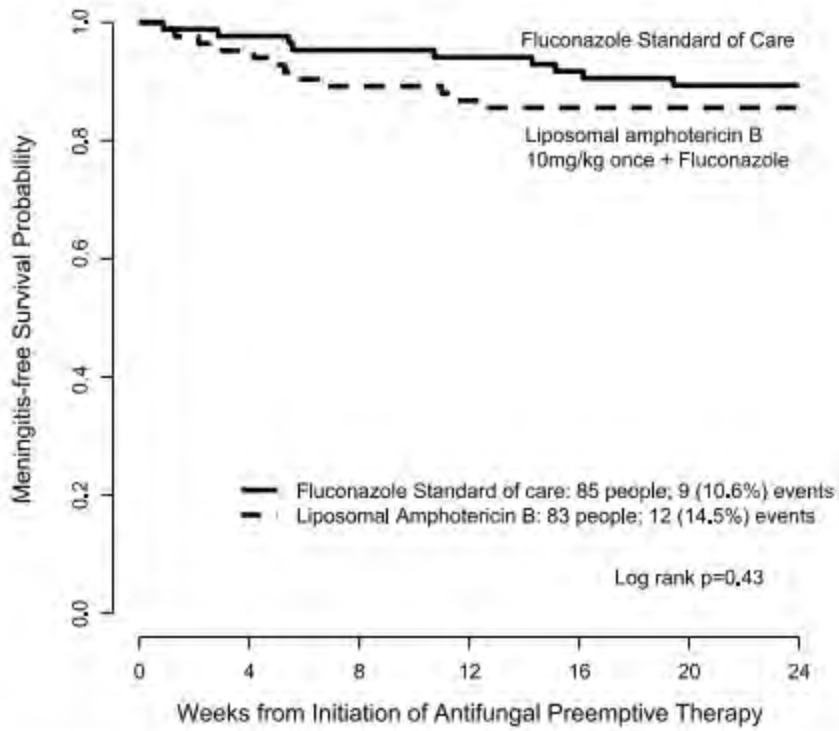


Figure 2. Kaplan-Meier curve comparing 24-week meningitis-free survival among participants assigned to liposomal amphotericin versus standard-of-care treatment. Among persons with a CrAg titer ≤1:80, there was no statistical difference in meningitis-free survival, with a hazard ratio of 1.42 (95% CI, .60–3.36; $P = .43$). Abbreviation: CrAg, cryptococcal antigen.

Clinical Infectious Diseases

MAJOR ARTICLE

Adjunctive Single-Dose Liposomal Amphotericin to Prevent Cryptococcal Meningitis in People With Human Immunodeficiency Virus (HIV)–Associated Cryptococcal Antigenemia and Low Plasma Cryptococcal Antigen (CrAg) Titers

David B. Meya,[1,2,a,@] Elizabeth Nalintya,[1,a] Caleb P. Skipper,[3] Paul Kirumira,[1] Peruth Ayebare,[1] Rose Naluyima,[1] Teopista Namuli,[1] Fred Turya,[1] Stewart Walukaga,[1] Nicole Engen,[4,@] Kathy H. Hullsiek,[4] Abduljewad Wele,[4] Biyue Dai,[4] David R. Boulware,[3] and Radha Rajasingham[3,@]

Meya et al. CID, 2024.

Summary

1. Cryptococcal meningitis remains major source of morbidity and mortality in persons with advanced HIV disease, particularly in high burden areas like sub-Saharan Africa

2. Major advancements have been made in improving induction antifungal regimens
   -- However, there remains some controversy about how clinical trial findings from Africa translate to the US

3. New antifungal drugs are coming, and active protocols are in place to study these in clinical trials

Acknowledgment

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of award 1 TR7HA53202-01-00 totaling $2,982,063 with 0% financed with non-governmental sources.

AETC AIDS Education & Training Center Program Mountain West