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Cryptococcal meningitis

TREATMENT AND DIAGNOSIS

Joe Jarvis
NIHR Global Health Professor
London School of Hygiene and Tropical Medicine & Botswana Harvard AIDS Institute Partnership

AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN
EDCTP
European & Developing Countries Clinical Trials Partnership
Sida
UKaid from the British people
MRC Medical Research Council
wellcome

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Nabila Youssouf
Philippa Griffin
Sophia Hafeez

SGUL
Tom Harrison
Angela Loyse
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Tshepo Leeme
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Takudzwa Mtisi

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Abineli Mbewe

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Melanie Alufandika-Moyo
Henry Mzinganjira
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Conrad Muzoora
Edwin Nuwagira
Leo Atwine
Davis Muganzi
Gavin Stead

Outline

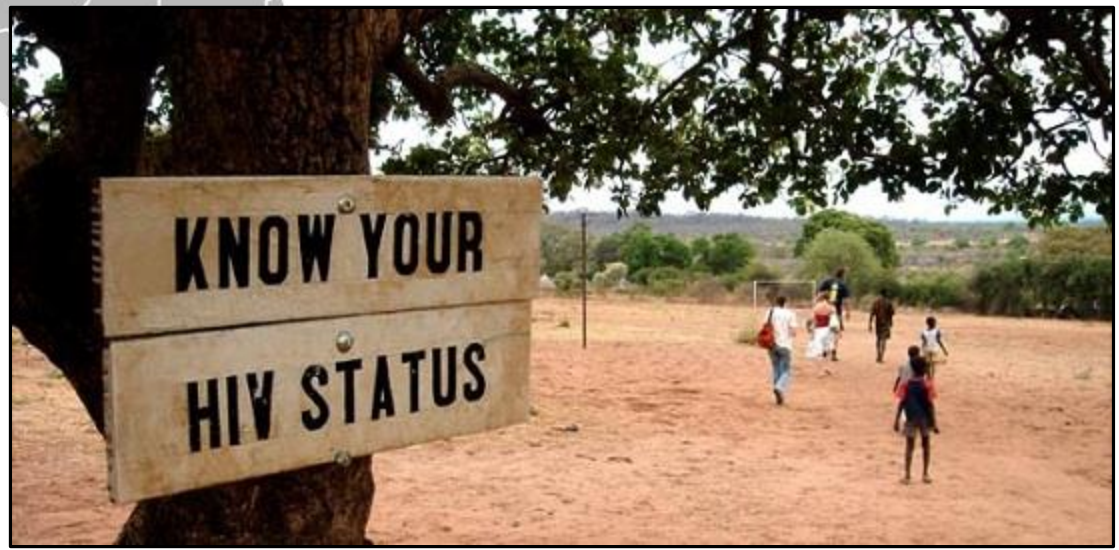
Epidemiology

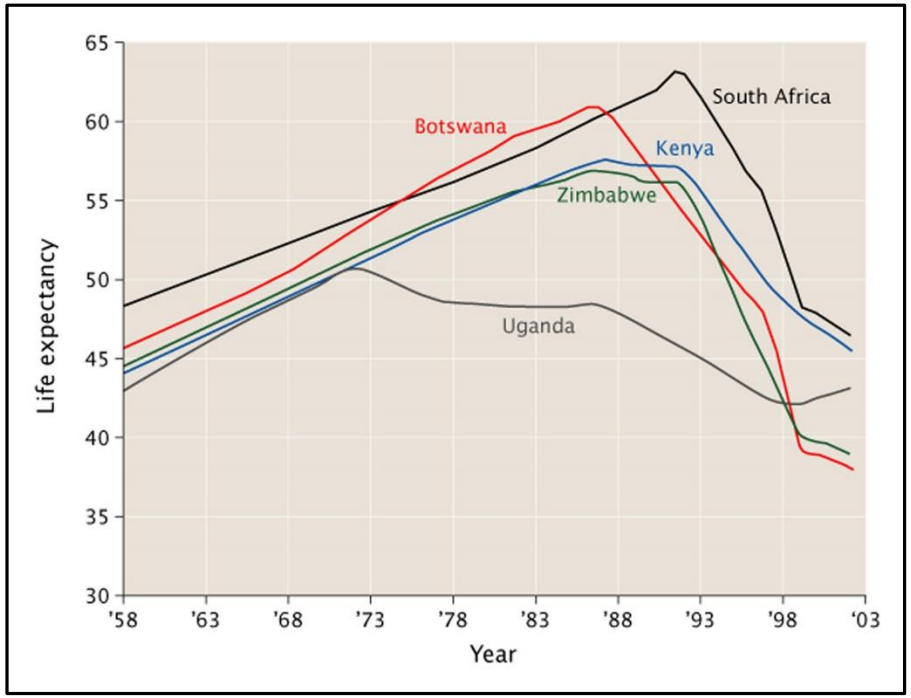
Treatment

- current treatment outcomes
- findings from recent trials
- new short-course treatments
- potential adjunctive therapies
- novel drugs

Diagnostics

Challenges and opportunities


KNOW YOUR
HIV STATUS



President Festus Mogae of Botswana

UN Assembly Conference 2000

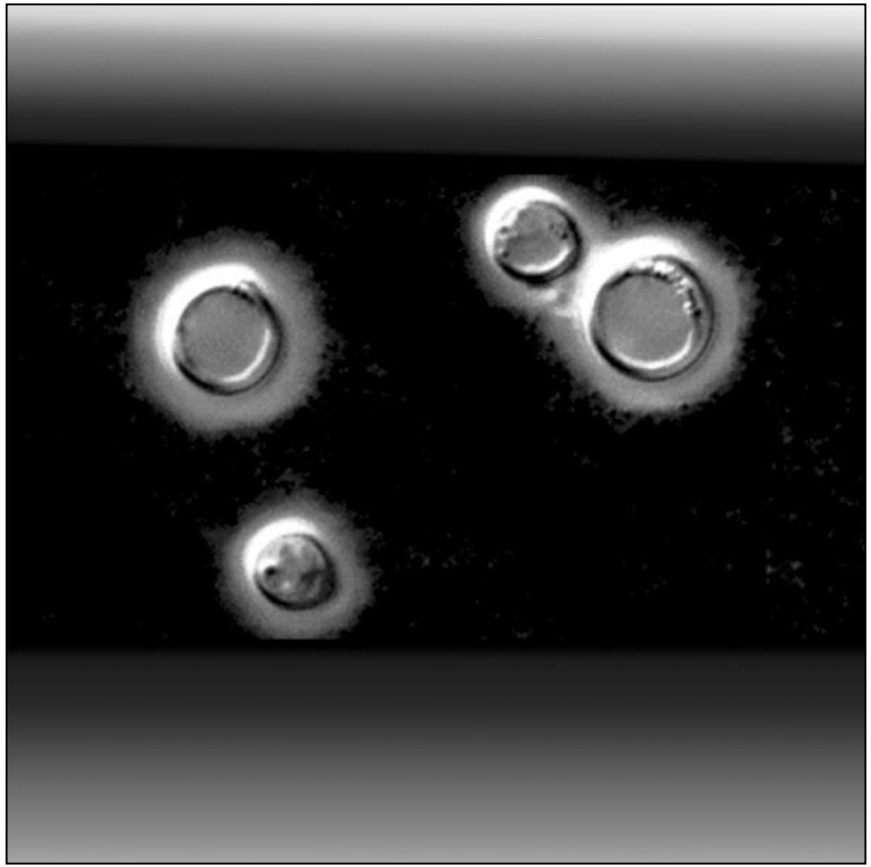
"We are threatened with extinction, People are dying in chillingly high numbers."

"One more day of delayed action is a day too late for our people. Our people are crying out for help. Let us respond while there is time."

Botswana's progress toward achieving the 2020 UNAIDS 90-90-90 antiretroviral therapy and virological suppression goals: a population-based survey

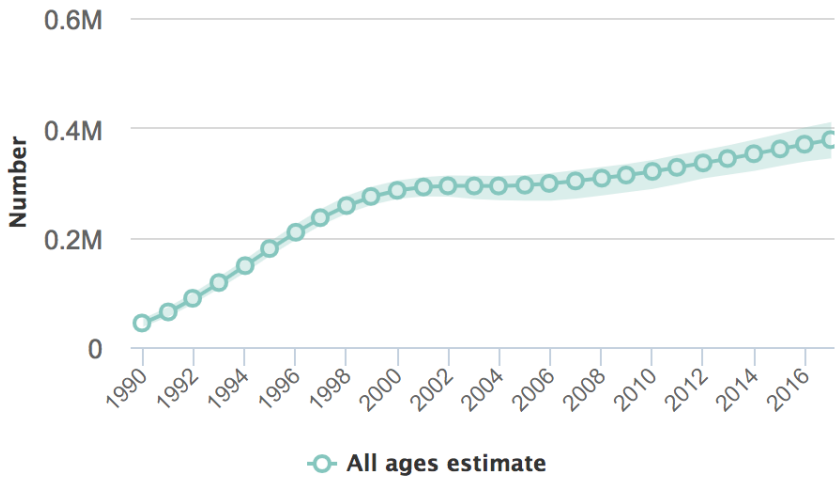
Tendani Gaolathe, Kathleen E Wirth, Molly Pretorius Holme, Joseph Makhema, Sikhulile Moyo, Unoda Chakalisa, Etienne Kadima Yankinda, Quanhong Lei, Mompati Mmalane, Vlad Novitsky, Lillian Okui, Erik van Widenfelt, Kathleen M Powis, Nealia Khan, Kara Bennett, Hermann Bussmann, Scott Dryden-Peterson, Refeletswe Lebelonyane, Shenaaz el-Halabi, Lisa A Mills, Tafireyi Marukutira, Rui Wang, Eric J Tchetgen Tchetgen, Victor DeGruttola, M Essex, Shahin Lockman, and the Botswana Combination Prevention Project study team

Findings 81% of enumerated eligible household members took part in the survey (10% refused and 9% were absent). Among 12 610 participants surveyed, 3596 (29%) were infected with HIV, and 2995 (83·3%, 95% CI 81·4–85·2) of these individuals already knew their HIV status. Among those who knew their HIV status, 2617 (87·4%, 95% CI 85·8–89·0) were receiving ART (95% of those eligible by national guidelines, and 73% of all infected people). Of the 2609 individuals receiving ART with a viral load measurement, 2517 (96·5%, 95% CI 96·0–97·0) had viral load of 400 copies per mL or less. Overall, 70·2% (95% CI 67·5–73·0) of HIV-infected people had virological suppression, close to the UNAIDS target of 73%.



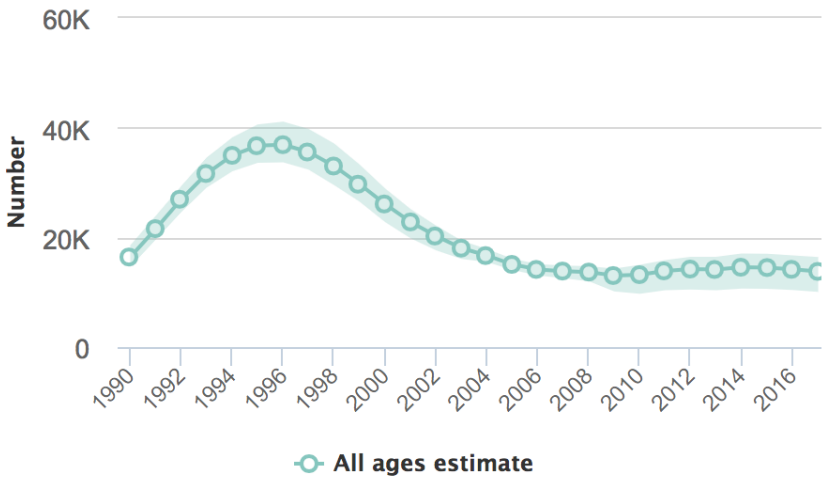
Botswana 2018

People living with HIV (all ages)



Source: UNAIDS Estimates 2018

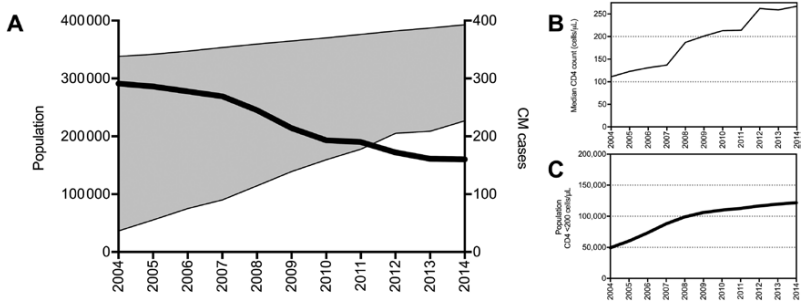
New HIV infections (all ages)



Source: UNAIDS Estimates 2018

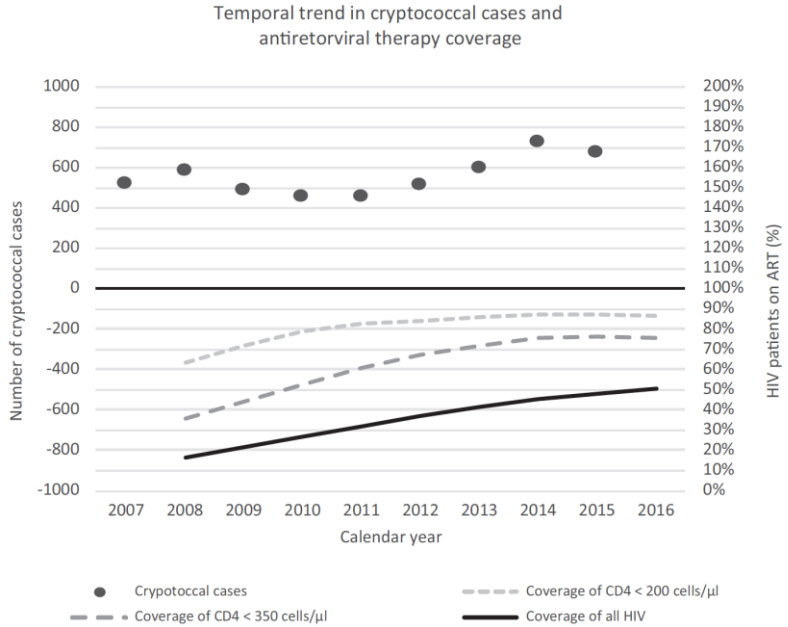
Advanced Human Immunodeficiency Virus Disease in Botswana Following Successful Antiretroviral Therapy Rollout: Incidence of and Temporal Trends in Cryptococcal Meningitis

Mark W. Tenforde,[1,2] Margaret Mokomane,[3] Tshepo Leeme,[4] Raju K. K. Patel,[5] Nametso Lekwape,[4] Chandapiwa Ramodimoosi,[3] Bonno Dube,[6] Elizabeth A. Williams,[7] Kelebeletse O. Mokobela,[6] Ephraim Tawanana,[8] Tlhagiso Pilatwe,[9] William J. Hurt,[4] Hannah Mitchell,[4] Doreen L. Banda,[4] Hunter Stone,[10] Mooketsi Molefi,[11] Kabelo Mokgacha,[9] Heston Phillips,[12] Paul C. Mullan,[13] Andrew P. Steenhoff,[4,14] Yohana Mashalla,[11] Madisa Mine,[3] and Joseph N. Jarvis[4,11,15,16]



The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa

Meg Osler,[1] Katherine Hilderbrand,[1,2] Eric Goemaere,[1,2] Nathan Ford,[1,3] Mariette Smith,[1,4] Graeme Meintjes,[5,6] James Kruger,[4] Nelesh P. Govender,[7,8] and Andrew Boulle[1,4,5]



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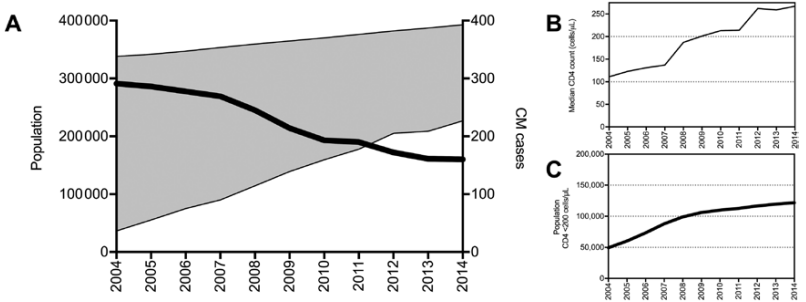

Clinical Infectious Diseases® 2017;00(00):1–8

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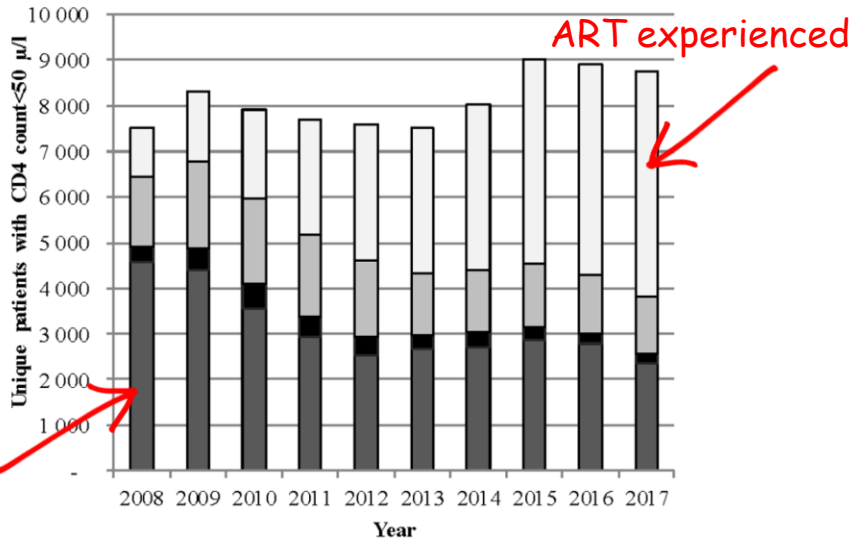


Clinical Infectious Diseases® 2018;66(S2):S118–25

Background

- 36% acute mortality in Vietnam

  Day et al. NEJM 2013;368:1291-302

- 41% acute mortality in Africa and Asia

  Beardsley et al. NEJM 2016;374:542-54

- 15% of all HIV-related mortality

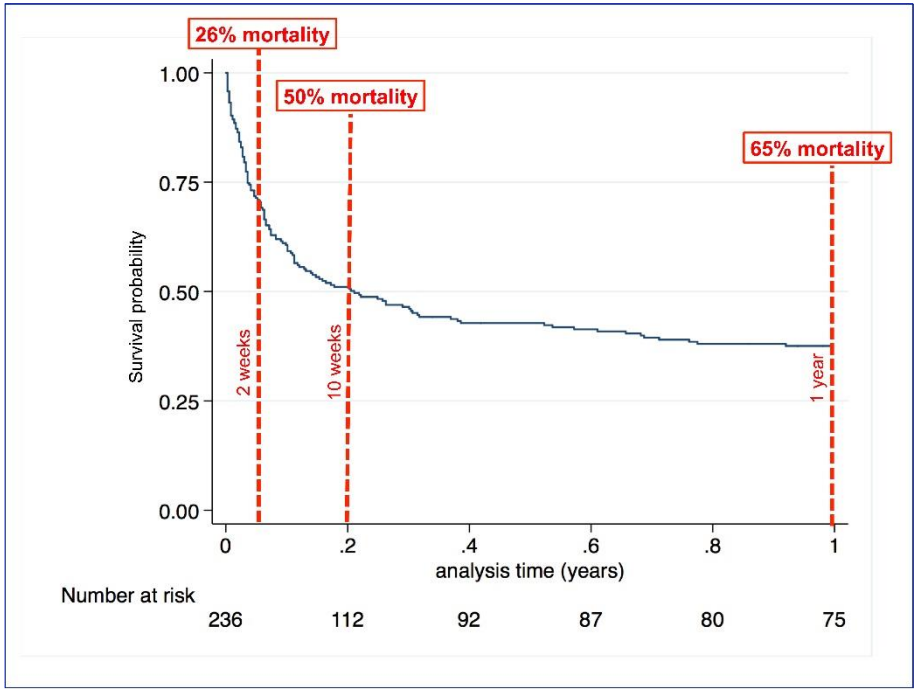
  Rajasingham et al. Lancet ID 2017; pii: S1473-3099(16)30243-8

Mortality rates with current antifungal therapy are unacceptably high

Princess Marina Hospital, Gaborone

Amphotericin B 1mg/kg plus Fluconazole 800mg daily for 14 days

Universal ART access



Tshepo Leeme et al. Mortality due to HIV-associated Cryptococcal Meningitis in Botswana in the ART Era. CROI 2017, Seattle WA.

Patel RKK, Leeme T*, et al*. Open Forum Infectious Diseases. 2018. Epub 23 Oct.

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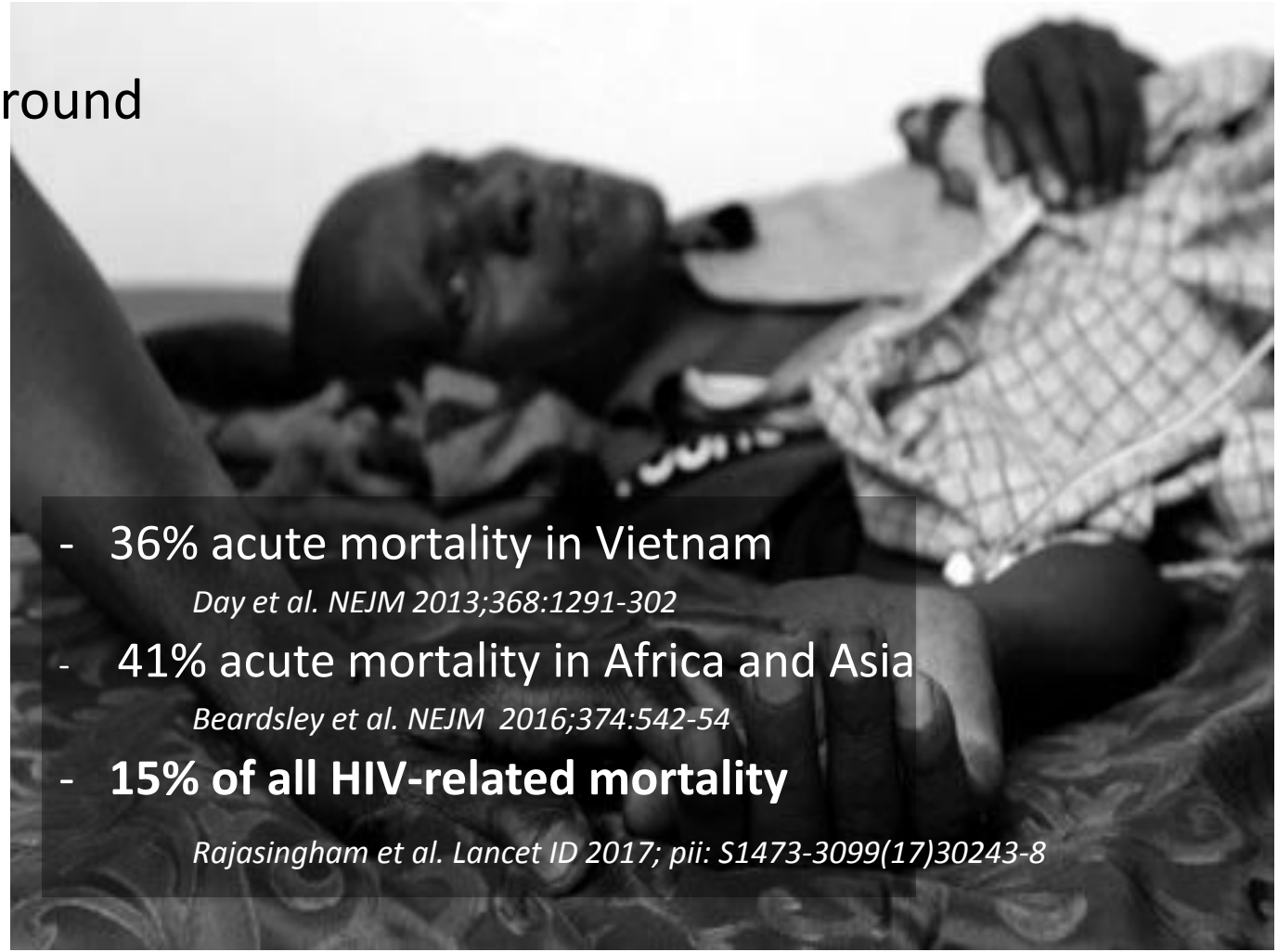

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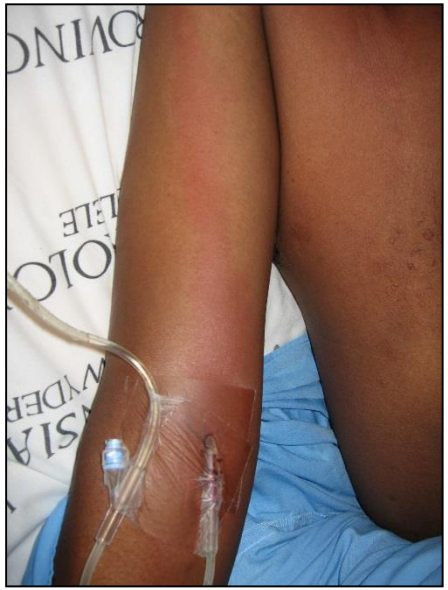
Amphotericin B deoxycholate is toxic and difficult to administer in resource-limited settings



Thrombophlebitis

Nosocomial sepsis (15%)
Rajasingham et al. Emerg Infect Dis. 2014

Infusion reactions

Anaemia (mean 2.3g/dL drop over 14 days)
Bicanic et al AAC 2015

Renal impairment

Potassium and magnesium wasting

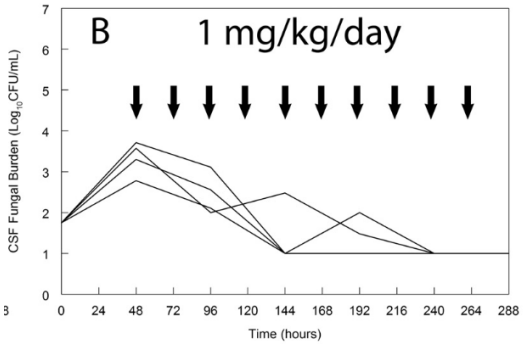
Efficacy of an Abbreviated Induction Regimen of Amphotericin B Deoxycholate for Cryptococcal Meningoencephalitis: 3 Days of Therapy Is Equivalent to 14 Days

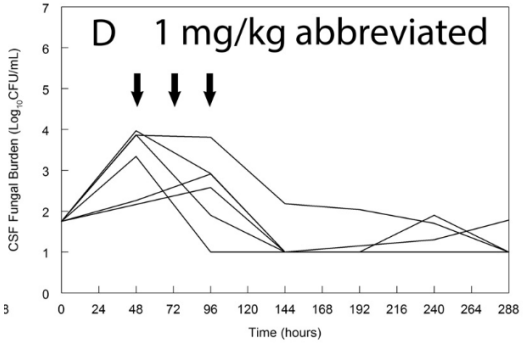
Livermore J et al. *MBio* 2014; 5(1):e00725-13.

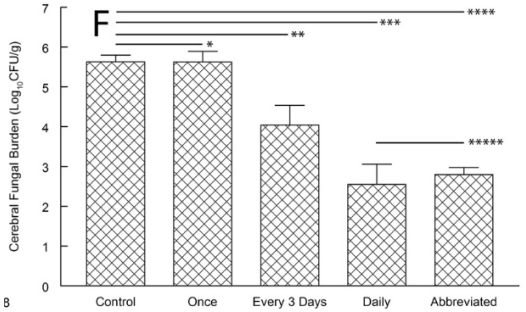
(experimental cryptococcal meningoencephalitis in rabbits)

Abbreviated Amphotericin B Deoxycholate regimens have been tested in humans in the recently completed ACTA randomized controlled trial

Toxicity of abbreviated regimes is significantly less than with standard 14-day regimens
Bicanic et al. AAC 2015







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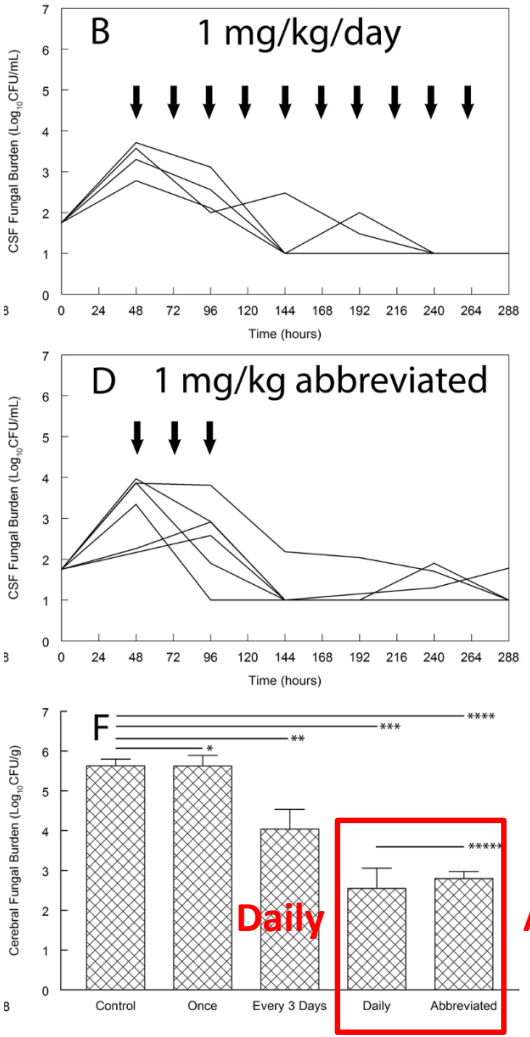
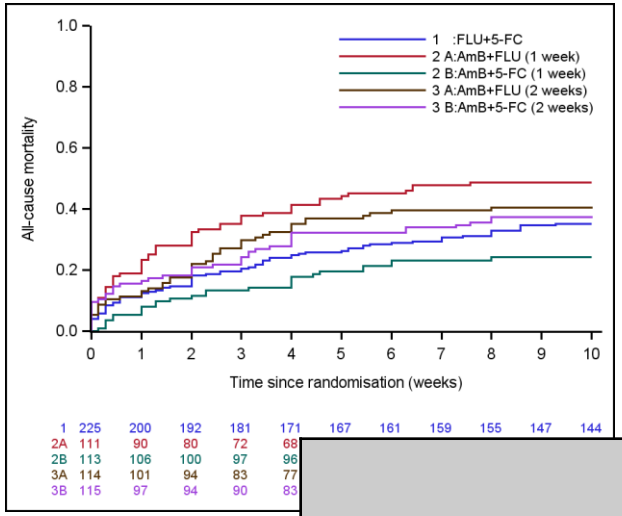


The NEW ENGLAND JOURNAL of MEDICINE

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,



1 week AmB + 5FC vs 2 weeks AmB + 5FC	
10 week mortality Hazard ratio (95% CI)	**0.56** (0.35 to 0.91)

	Oral	1 week AmB + FLU	1 week AmB + 5FC	2 weeks AmB + FLU	2 weeks AmB + 5FC
Probability of death by 10 wks % (95% CI)	**35%** (29 - 41)	**49%** (39 - 58)	**24%** (16 - 32)	**41%** (32 - 50)	**38%** (29 - 47)
	79/225	54/111	27/113	47/114	44/115

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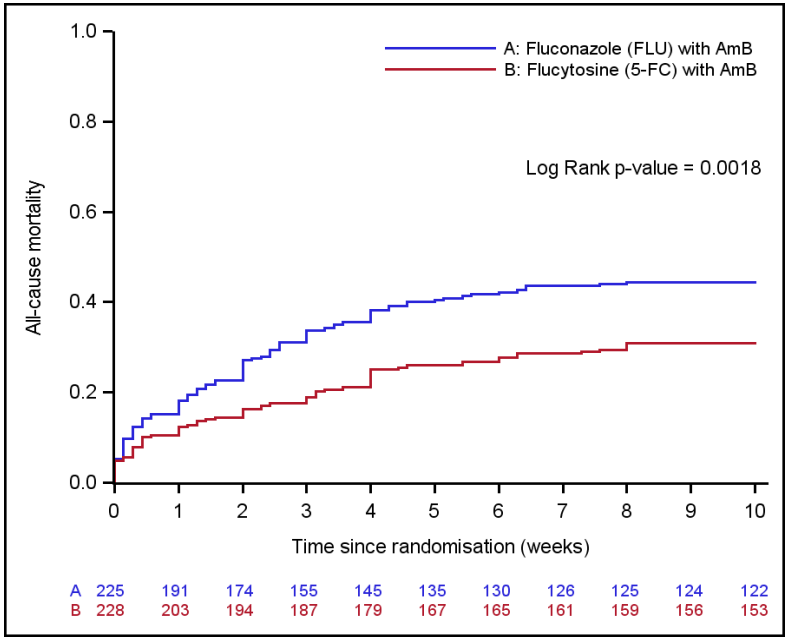


Hazard Ratio (95% CI)		
	AmB + 5FC vs AmB + FLU	**p-value (log-rank test)**
10 week mortality	**0.62** (0.45 to 0.84)	**0.002**

10 week mortality:

FLU: **45%** (101/225)

5FC: **31%** (71/228)

The NEW ENGLAND JOURNAL of MEDICINE

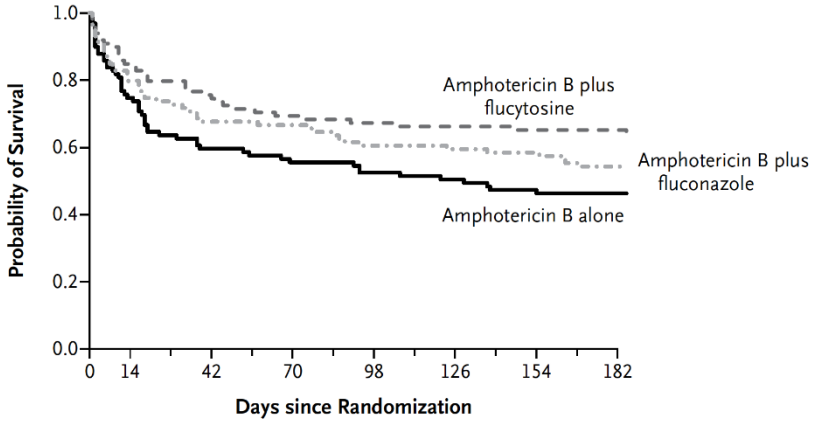
ORIGINAL ARTICLE

Combination Antifungal Therapy for Cryptococcal Meningitis

Jeremy N. Day, M.D., Ph.D., Tran T.H. Chau, M.D., Ph.D., Marcel Wolbers, Ph.D.,

N ENGL J MED 368;14 NEJM.ORG APRIL 4, 2013

A



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

What about liposomal amphotericin B?

Less nephrotoxic

- *higher doses can be given safely*

Excellent tissue penetration and long tissue half life

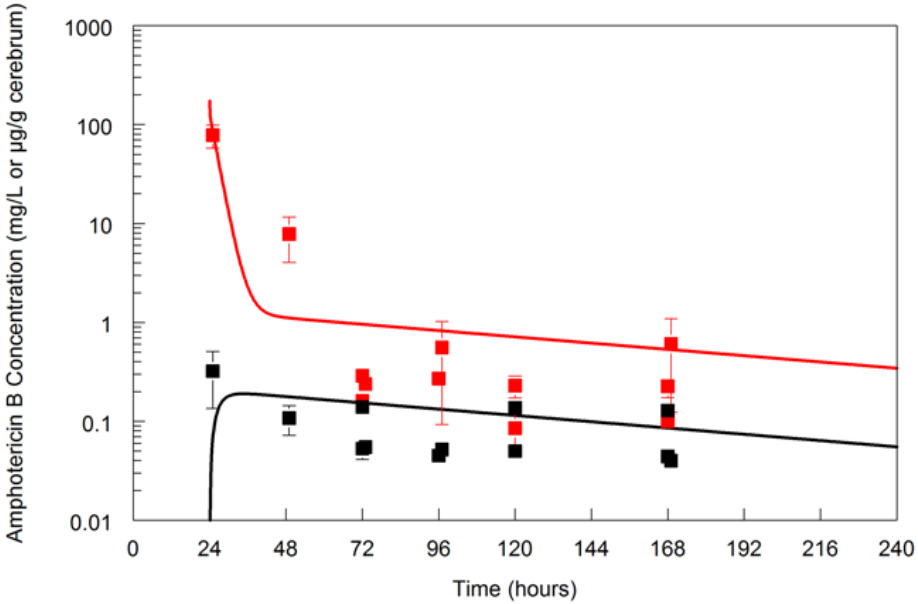
- *should be possible to deliver highly effective induction therapy with very few (1, 2, or 3) doses*

Effective long-lasting therapy with just one dose of high dose liposomal amphotericin B has been established in the treatment of visceral leishmaniasis

Use in CM previously limited by cost, but short courses and reduced pricing could make it a cost-effective option

Need to define the most effective and most cost-effective schedules

The pharmacokinetics of liposomal amphotericin B in murine **plasma (red)** and **cerebrum (black)** in cohorts of mice infected with *Cryptococcus neoformans* receiving LAmB 20 mg/kg SINGLE DOSE i.v.



The terminal half-life in the plasma and cerebrum is circa 133 hours.

Jodi M. Lestner, Laura McEntee, Adam Johnson, Joanne Livermore, Sarah Whalley, Julie Schwartz, John R. Perfect, Thomas Harrison, William Hope. AAC 2017.

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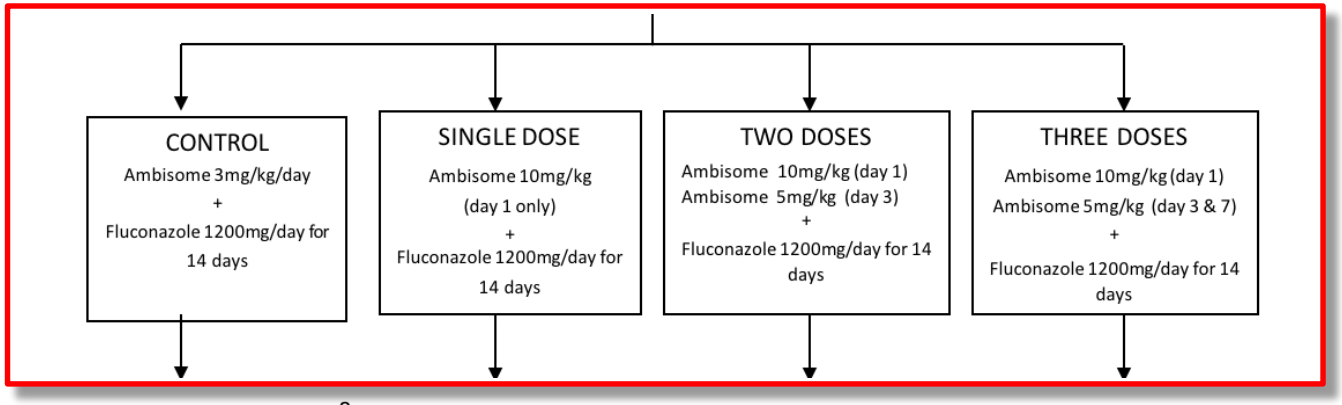
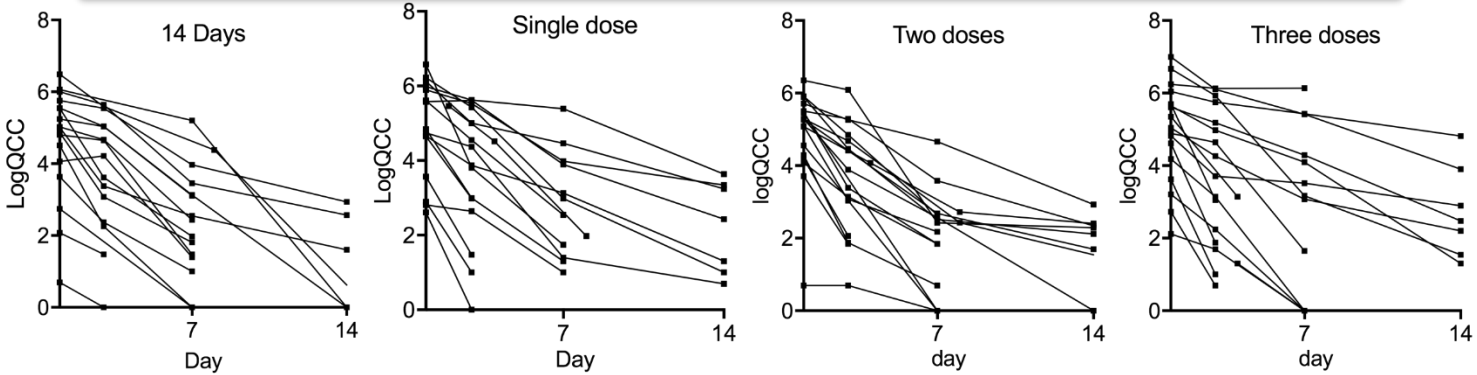
AMBIsome Therapy Induction OptimizatioN

The Ambition Phase 2 Study: Primary Endpoint EFA *(Jarvis et al. CID 2018)*





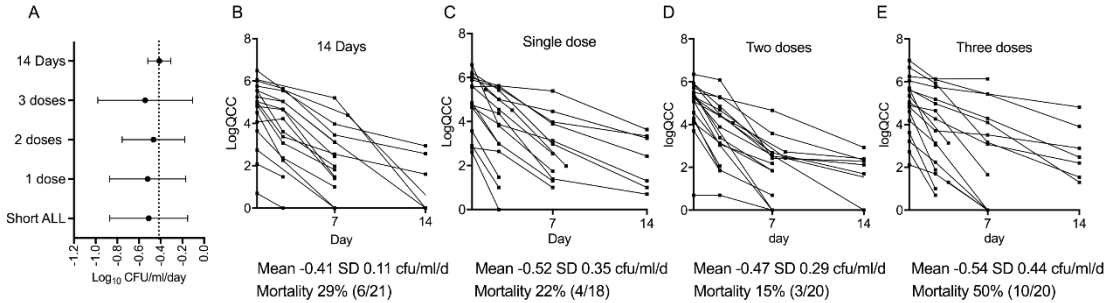
Mean -0.41 SD 0.11 cfu/ml/d
Mortality 29% (6/21)

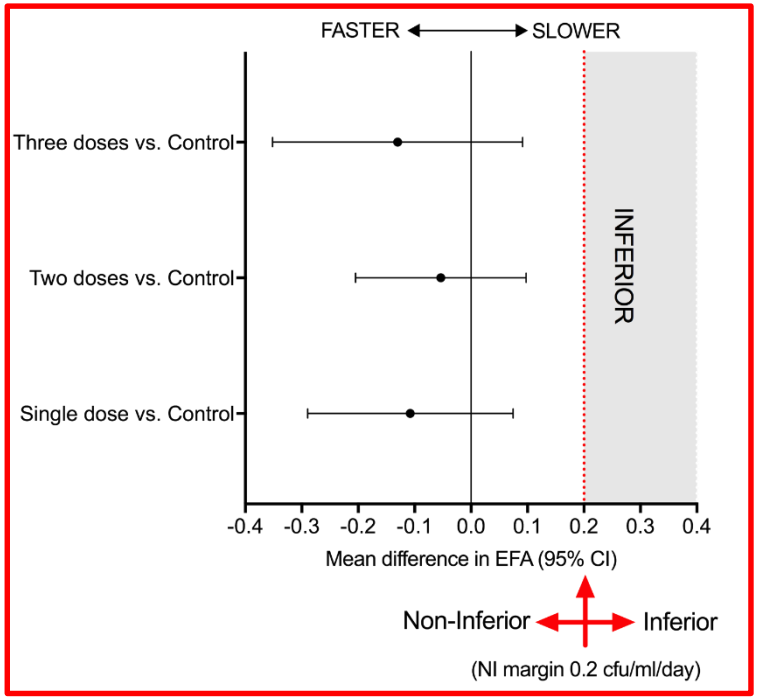
Mean -0.52 SD 0.35 cfu/ml/d
Mortality 22% (4/18)

Mean -0.47 SD 0.29 cfu/ml/d
Mortality 15% (3/20)

Mean -0.54 SD 0.44 cfu/ml/d
Mortality 50% (10/20)

The Ambition Phase 2 Study: Primary Endpoint EFA *(Jarvis et al. CID 2018)*





All 3 short course Liposomal Amphotericin B treatment arms were non-inferior to control

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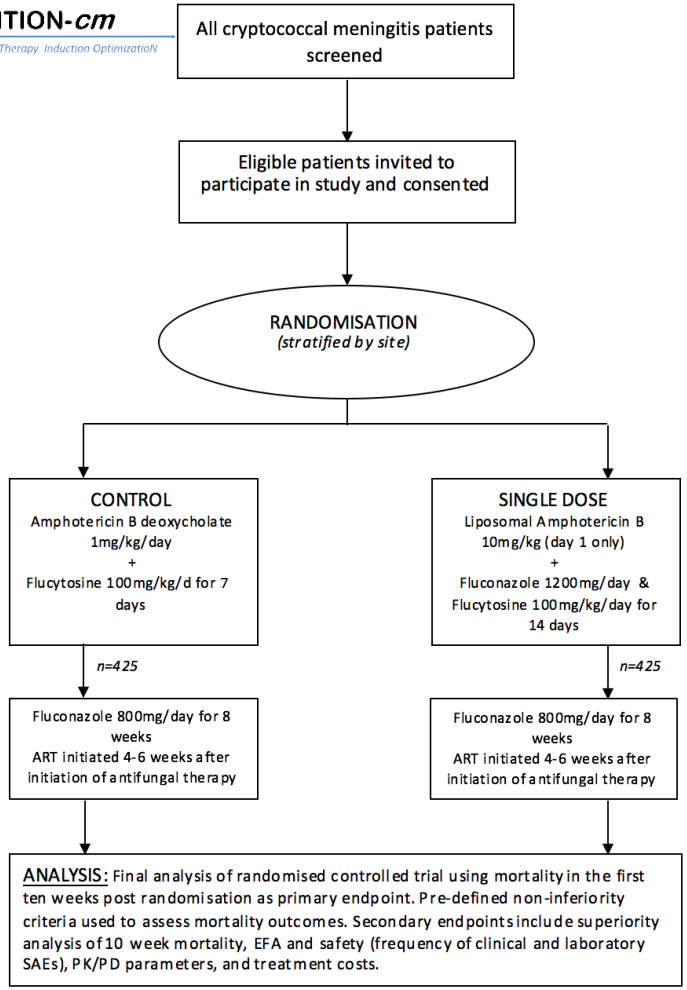

AMBITION Phase-III study – clinical endpoint non-inferiority trial

L-AmB 10 mg/kg day 1 (single dose)

vs

Amphotericin B deoxycholate 1.0 mg/kg/d 7 days (*"control arm"*)

Hypothesis: Short-course high-dose L-AmB given with high dose fluconazole and flucytosine will be non-inferior to standard daily-dosed amphotericin B deoxycholate with flucytosine induction therapy for the treatment of HIV-associated cryptococcal meningitis in averting all-cause mortality.

Endpoints:

Primary: All-cause mortality within the first 10 weeks

Secondary: Early Fungicidal Activity (EFA); 2-week mortality; tolerability and adverse events; cost-effectiveness

850 patients total (425 per arm) (10% NI margin)

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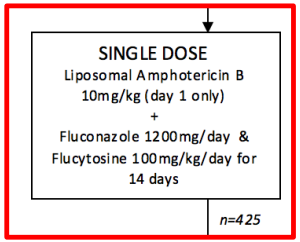

We are studying a form triple therapy chosen as best possible challenger to the new standard of care established by ACTA, on the basis that:

1. AMBITION phase II: single high dose is best way to deliver Ambisome

2. ACTA data showing 5FC essential component and best partner drug with AmB

3. Concern if ONLY single dose Ambisome + 5FC were used a risk of 5FC monotherapy in second week leading possible 5FC resistance, and no phase 2 data for this approach

4. With oral combination Fluconazole / 5FC backbone: includes the AMBITION phase II combination, phase 3 ACTA supported oral combination (which was just lacking a non toxic EFA kick?), no downside to including fluconazole (cost, availability), and .....some evidence 3 drugs may actually be superior

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AMBIsome Therapy Induction OptimizatioN

Kampala and Mbarara, Uganda
Infectious Diseases Institute

Lilongwe, Malawi
UNC Project

Blantyre, Malawi
Malawi-Liverpool Wellcome Trust Clinical Research Programme

Harare, Zimbabwe
University of Zimbabwe

Gaborone, Botswana
Botswana-Harvard Partnership and University of Botswana

Cape Town, South Africa
University of Cape Town

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EDCTP
European & Developing Countries Clinical Trials Partnership

Sida

UKaid
from the British people

MRC Medical Research Council

wellcome

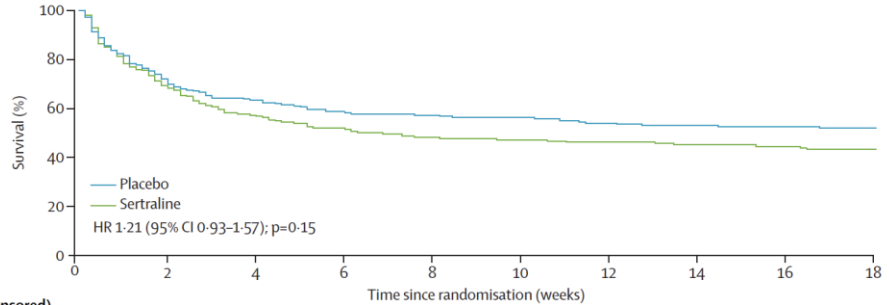
Can we lower mortality with adjunct therapies?

Can we lower mortality with adjunct therapies?

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

*Joshua Rhein, Kathy Huppler Hullsiek, Lillian Tugume, Edwin Nuwagira, Edward Mpoza, Emily E Evans, Reuben Kiggundu, Katelyn A Pastick, Kenneth Ssebambulidde, Andrew Akampurira, Darlisha A Williams, Ananta S Bangdiwala, Mahsa Abassi, Abdu K Musubire, Melanie R Nicol, Conrad Muzoora, David B Meya, David R Boulware, on behalf of ASTRO-CM team**

***Lancet Infect Dis* 2019;**
19: 843–51



Number at risk (number censored)

Placebo	231 (0)	170 (61)	151 (80)	141 (90)	138 (93)	135 (96)	130 (101)	128 (103)	123 (108)	122 (109)
Sertraline	229 (0)	159 (70)	134 (95)	123 (106)	115 (114)	113 (116)	110 (119)	108 (121)	105 (124)	103 (126)

No mortality benefit of adding sertraline to amphotericin B and fluconazole

52% 18-week mortality in the sertraline group,
vs
46% in the control group.

Can we lower mortality with adjunct therapies?

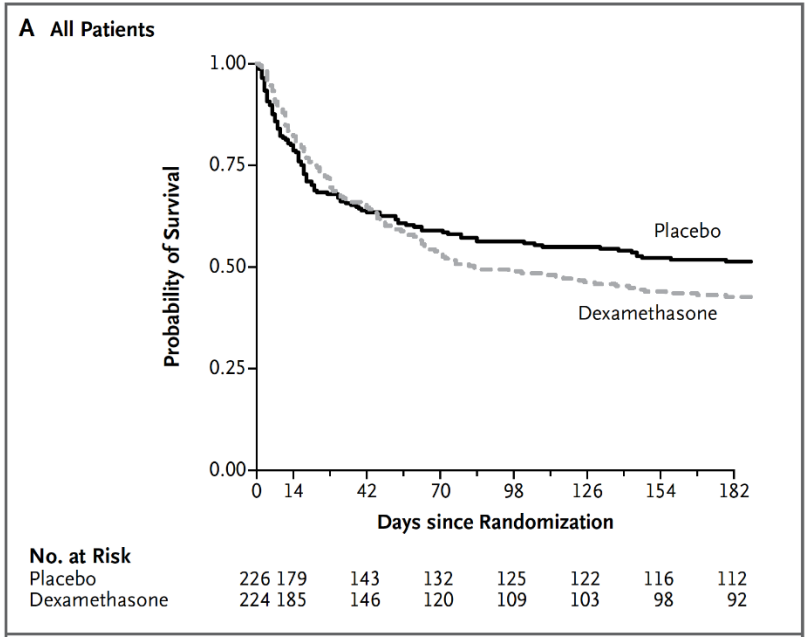
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

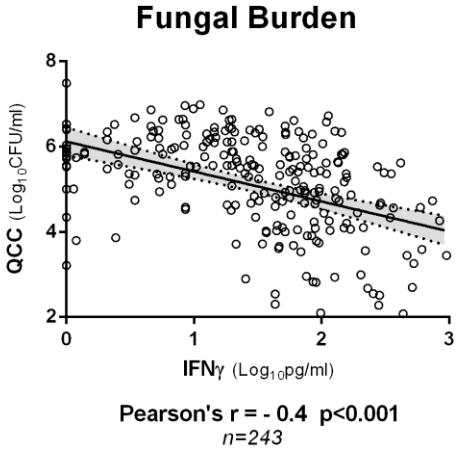
J. Beardsley, M. Wolbers, F.M. Kibengo, A.-B.M. Ggayi, A. Kamali, N.T.K. Cuc,

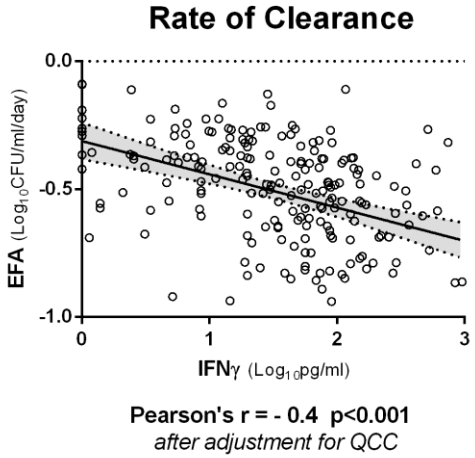
N ENGL J MED 374;6 NEJM.ORG FEBRUARY 11, 2016

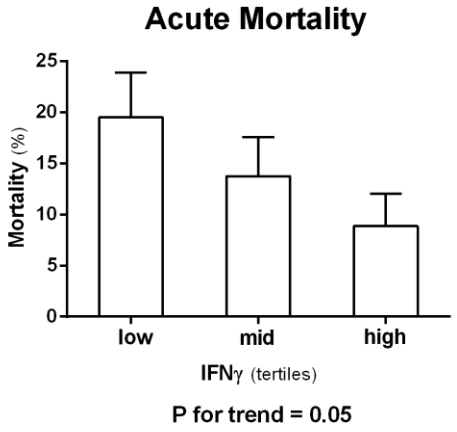


Can we lower mortality with adjunct therapies?

Interferon-γ (IFNγ) plays a key role in host defense



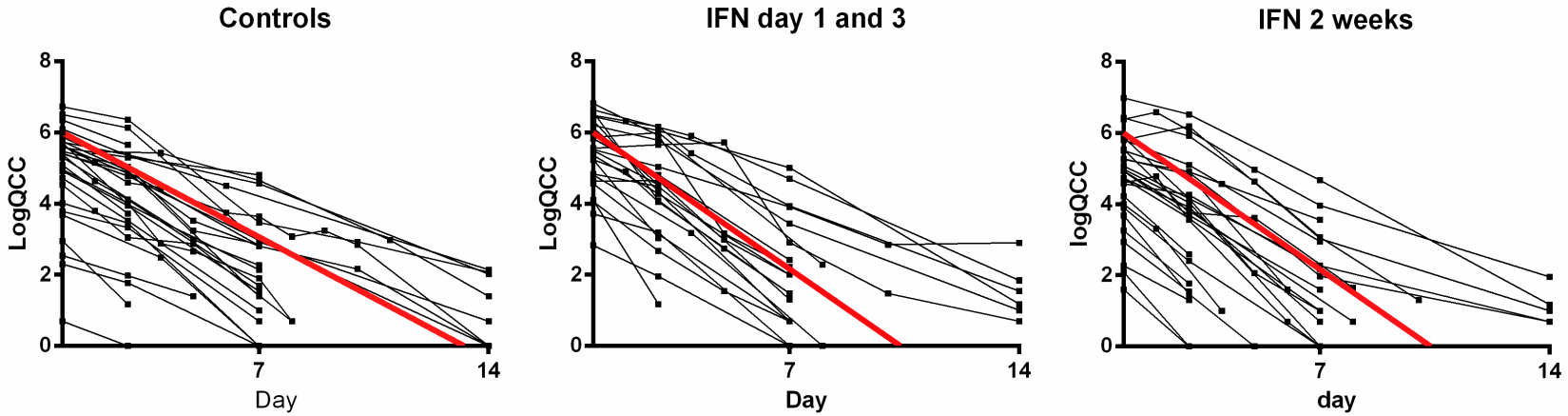




Clinical Infectious Diseases. 2014 Mar;58(5):736-45.

Can we lower mortality with adjunct therapies?

IFNγ therapy led to significantly increased rates of clearance of cryptococcal infection from the CSF



***AIDS*.** 2012 June 1; 26(9):1105-1113.

Novel drugs for cryptococcal meningitis

Novel azole type drugs – (Mycovia) VT-1598.

Lockhart SR, Fothergill AW, Iqbal N, et al. The investigational fungal Cyp51 inhibitor VT-1129 demonstrates potent in vitro activity against Cryptococcus neoformans and Cryptococcus gattii. *Antimicrob Agents Chemother* 2016;60: 2528–31.

Amplyx APX001. First in a new class of broad-spectrum antifungal agents that inhibit Gwt1, an enzyme which is required for cell wall localization of glycosylphosphatidylinositol (GPI)-anchored mannoproteins in fungi.

FDA grants orphan drug designation to Amplyx Pharmaceuticals for APX001 for treatment of cryptococcosis. https://amplyx.com/fdagrants-orphan-drug-designation-to-amplyx-pharmaceuticals-for-apx001-for-treatment-of-cryptococcosis/ (accessed March 31, 2019).

Oral formulations of Amphotericin B.

Lu R, Hollingsworth C, Qiu J, et al. Efficacy of Oral Encochleated Amphotericin B in a Mouse Model of Cryptococcal Meningoencephalitis. *MBio*. 2019 May 28;10(3). pii: e00724-19.

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FDA grants o[illegible] armaceuticals for APX001 for treatment of cryptococcosis. https://ampl[illegible] designation-to-amplyx-pharmaceuticals-for-apx001-for-treatment-of-cryptococc[illegible], 2019).

Soon to start phase II trials

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Diagnosis

Lumbar puncture and India ink staining +/- culture

Immunodiagnosis (CRAG)

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Lumbar puncture and India ink staining +/- culture

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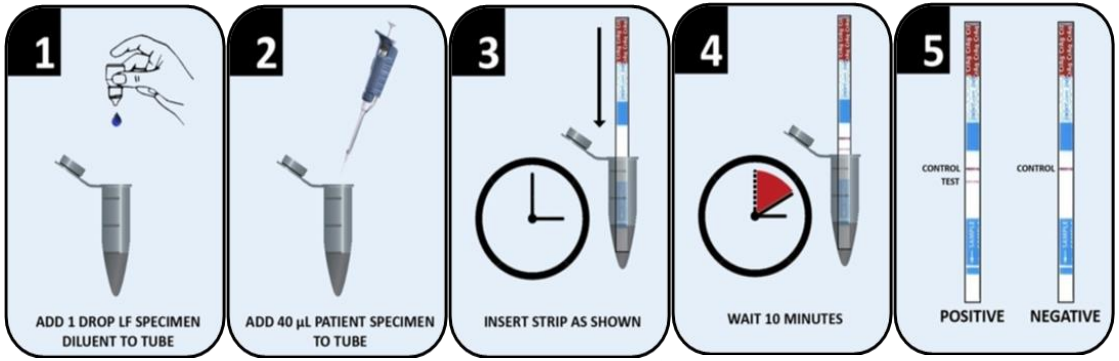
A point of care test?

Earlier diagnosis

Antigen screening

Serum, Plasma, and fingerprick

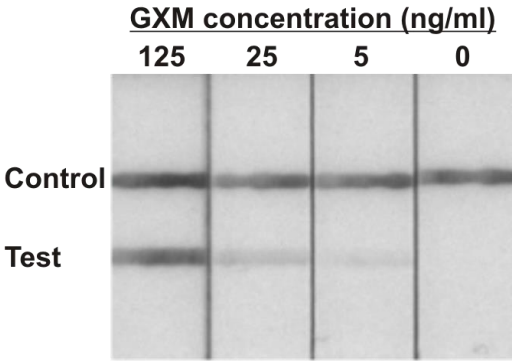


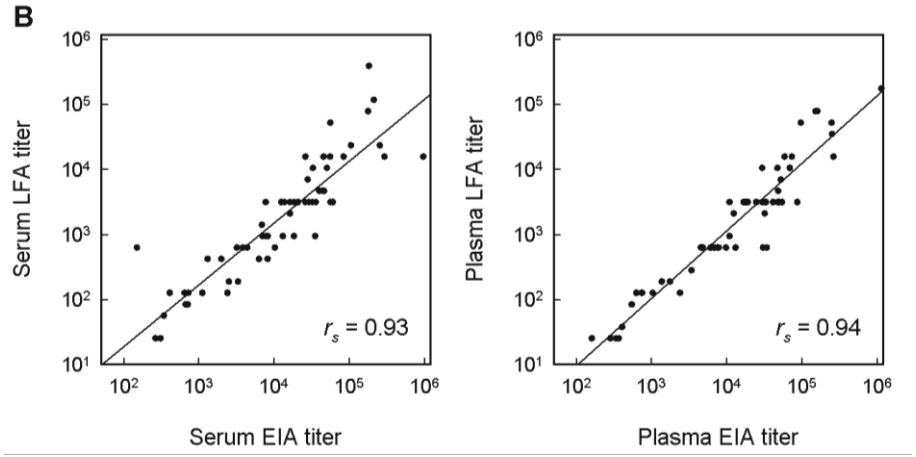
IMMY CrAg LFA

Clin Infect Dis. 2011 Nov; 53(10):1019-23.

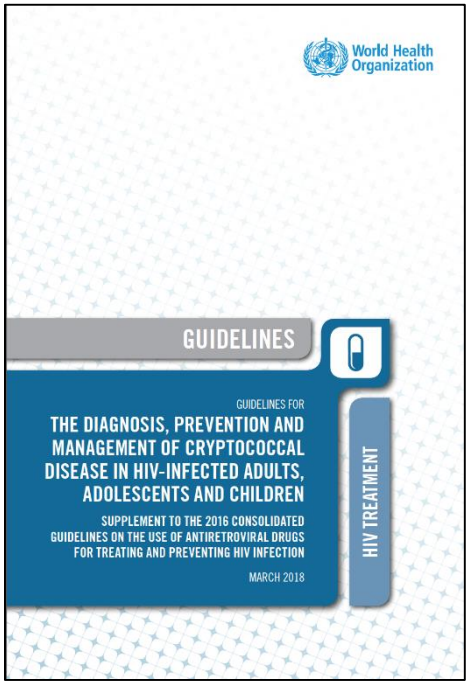
Sensitivity 99.3%, Specificity 99.1%

Emerg Infect Dis. 2014 Jan;20(1):45-53.





Cryptococcal antigen screening

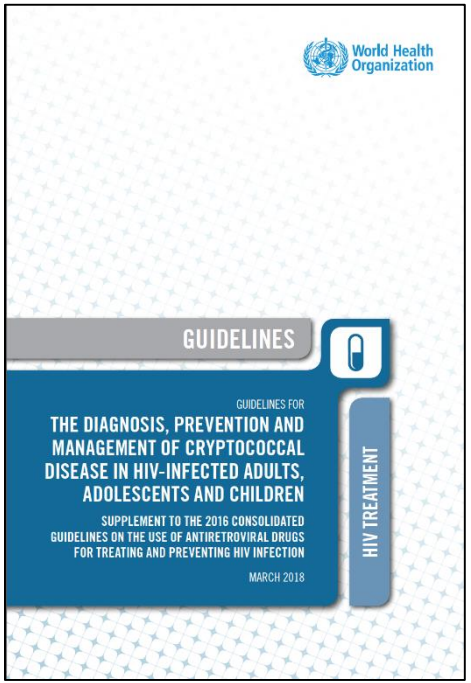


"Screening for cryptococcal antigen is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying risk of progression to disease when managing people presenting with advanced HIV disease."

Recommendations

- Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3 (strong recommendation; moderate-certainty evidence) and may be considered at a higher CD4 cell count threshold of <200 cells/mm3 (conditional recommendation; moderate-certainty evidence).

Cryptococcal antigen screening



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TOP 5 POSTER session later today:

Cryptococcal Meningitis is a Cause of Death Among HIV-Infected Adults Despite Cryptococcal Antigen Screening and Pre-emptive Fluconazole Treatment

Dr Rachel Wake, St George's University of London

A novel semi-quantitative CrAg dipstick may enable stratified treatment

220 CrAg+ plasma samples from patients in Botswana

Kwana Lechiile et al
Evaluating the IMMY semi-quantitative CRAG LFA in HIV-positive patients in Botswana. Unpublished.

To be presented at CROI 2020
Boston, MA, USA

Challenges and opportunities

Challenges
Flucytosine access
Liposomal amphotericin B pricing and availability

Progress
WHO prequalification of liposomal amphotericin B (AmBisome) in June, 2018;

Addition of cryptococcal meningitis to the US Food and Drug Administration's priority review voucher scheme in August, 2018;

Expansion of Gilead's preferential AmBisome pricing programme for visceral leishmaniasis to include cryptococcal meningitis in September, 2018;

Announcement of substantial UNITAID funding for cryptococcal meningitis treatment in high-burden African countries in January, 2019

Summary

Cryptococcal meningitis remains the commonest cause of adult meningitis in east, central, and southern Africa despite expanded access to ART

Mortality rates are unacceptably high with current treatments, which are toxic and difficult to administer in low-resource settings

A novel short-course highly effective and safer L-AmB treatment regimen for CM could transform the management of late-stage HIV and markedly improve outcomes in HIV programmes in Africa.

Screening HIV-positive individuals with low CD4 counts for sub-clinical cryptococcal infection using CrAg tests and giving early treatment is recommended to reduce the burden of cryptococcal meningitis

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