



# The impact of HIV-associated cryptococcal meningitis on health

Why is cryptococcal meningitis important to study?

## Training module structure



- ▶ This training module is organised into 7 sections which can be accessed individually.
- ▶ This is section 1: **The impact of HIV-associated cryptococcal meningitis on health**
- ▶ It is recommended to complete all sections and access them sequentially from 1 to 7.
- ▶ All references and acknowledgments can be found in the notes section of each slide as well as more information and external links to resources.

*It is a real tragedy that more than 100,000 persons living with HIV are still losing their lives every year from meningitis. Widespread roll out of proven and improved treatments could mean tens of thousands more survivors, who could then go on to a long life thanks to antiretroviral therapy.*

”

# 940,000

deaths from AIDS-related illnesses worldwide in 2017<sup>1</sup>

# 15–20%

AIDS-related deaths globally due to CCM<sup>2</sup>

# 135,900

Annual deaths due to CCM in sub-Saharan Africa<sup>2</sup>

1. UNAIDS Global 2017 HIV Factsheet - July 2018

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

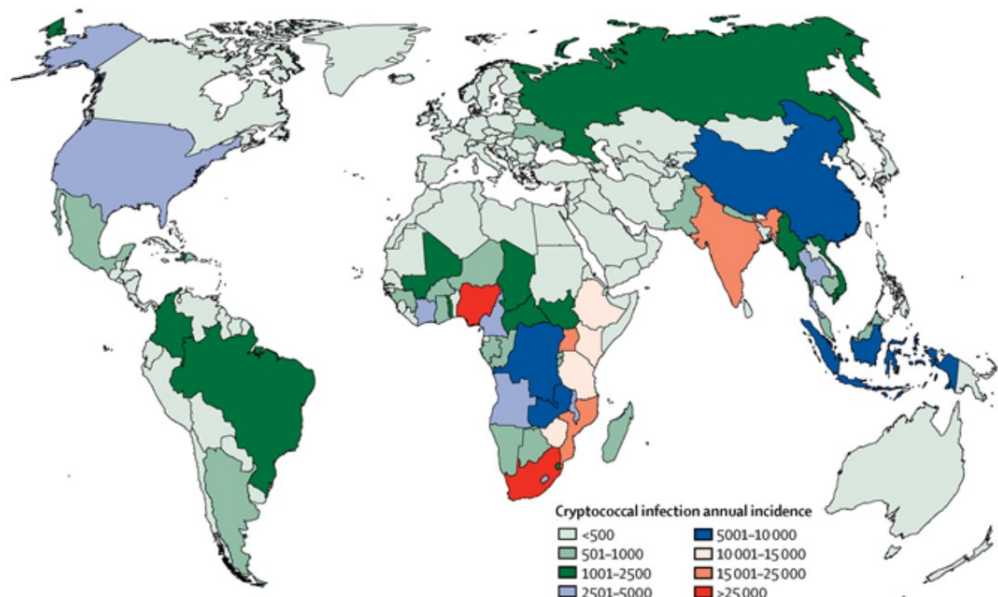


## Burden and mortality

- ▶ Cryptococcal meningitis is one of the leading causes of meningitis in PLHIV in many LMIC settings.
- ▶ Cryptococcal disease is associated with an estimated 135,900 deaths per year in Africa.
- ▶ 40% mortality for patients treated with Amphotericin B in clinical trial settings at 10 weeks.
- ▶ Estimated 3-month mortality is 70% in routine care settings with more available but inadequate fluconazole monotherapy.

## Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis

Radha Rajasingham, Rachel M Smith, Benjamin J Park, Joseph N Jarvis, Nelesh P Govender, Tom M Chiller, David W Denning, Angela Loyse, David R Boulware



Estimated an average global cryptococcal antigenaemia prevalence of 6.0% (95% CI 5.8–6.2) among people with a CD4 cell count of less than 100 cells per  $\mu\text{L}$ .

Figure used with permission from: Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *The Lancet Infectious diseases*. 2017;17(8):873-881. doi:10.1016/S1473-3099(17)30243-8

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	Total cryptococcal antigenaemia positive (uncertainty interval)	Annual burden of cryptococcal meningitis (uncertainty interval)	Deaths from cryptococcal meningitis (uncertainty interval)
Sub-Saharan Africa	204 300 (148 400–237 800)	162 500 (113 600–193 900)	135 900 (93 900–163 900)
Asia and Pacific	52 300 (32 900–74 100)	43 200 (25 300–64 700)	39 700 (20 600–59 700)
Caribbean	1800 (1300–2200)	1400 (1000–1800)	700 (500–900)
Latin America	7000 (3600–11 100)	5300 (2600–8900)	2400 (1100–4400)
North America	3700 (3000–4600)	3000 (2300–3700)	700 (500–1000)
North Africa and Middle East	3600 (2600–5000)	3300 (2400–4500)	1900 (1300–2700)
Europe	5200 (4000–6500)	4400 (3400–5600)	1800 (1300–2400)
Global	278 000 (195 500–341 000)	223 100 (150 600–282 400)	181 100 (119 400–234 300)

278 000 (95% CI 195 500–340 600) people positive for cryptococcal antigen globally and 223 100 (95% CI 150 600–282 400) incident cases of cryptococcal meningitis globally in 2014. Estimated 70% persons positive for cryptococcal antigenaemia will develop CCM.

Sub-Saharan Africa accounted for 73% of the estimated cryptococcal meningitis cases in 2014 (162 500 cases [95% CI 113 600–193 900]).

Figure used with permission from: Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *The Lancet Infectious diseases*. 2017;17(8):873-881. doi:10.1016/S1473-3099(17)30243-8

Countries with the highest incidence of CCM

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	Annual incidence of cryptococcal meningitis	Number at risk (CD4 <100 cells per µL)	Cost of screening all at risk (US\$)*	HIV budget to screen all at risk (%) <sup>57</sup>
Nigeria	27 100	325 900	\$1 303 437	0·23%
South Africa	21 400	382 400	\$1 529 685	0·09%
Mozambique	18 600	184 300	\$737 228	0·28%
India	18 300	209 900	\$839 502	0·06%
Uganda	12 200	110 500	\$441 933	0·08%
Ethiopia	9600	60 600	\$242 561	0·06%
Kenya	9000	84 700	\$329 138	0·08%
Tanzania	8400	117 200	\$468 959	0·15%
DR Congo	8400	51 200	\$204 889	0·24%
Zimbabwe	8100	92 400	\$369 621	..
Indonesia	6600	58 900	\$235 564	0·27%
Zambia	5000	66 200	\$264 611	0·10%

Based on presumed cost of cryptococcal antigenaemia lateral flow assay test of US\$3 per test delivered price for resource-limited areas, with an additional \$0·50 added for laboratory labour, and \$0·50 for profit and overhead costs. Although not every person at risk will present to care, this gives an estimate of the magnitude of budgetary resources necessary to start screening.

Figure used with permission from: Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. The Lancet Infectious diseases. 2017;17(8):873-881. doi:10.1016/S1473-3099(17)30243-8

## DREAMM: Driving Reduced AIDS-associated Meningo-encephalitis Mortality



- DREAMM - Integrating the diagnosis and management of HIV-associated central nervous system (CNS) infections into routine health services in low and middle income countries (LMICs). DREAMM: Driving Reduced AIDS-associated Meningo-encephalitis Mortality
- Funded by EDCTP and ANRS (Cameroon site) and sponsored by St George's University of London and ANRS (Cameroon site). Clinicaltrials.gov record number - NCT03226379
- The DREAMM project is ongoing in 5 representative and geographically distinct African sites in: Dar Es Salaam, **Tanzania**, Yaoundé, **Cameroon** and Lilongwe, **Malawi**
- DREAMM has 3 phases: 1) Observation, 2) Training and 3) Implementation. The DREAMM education programme is used during the training phase.
- Optimised and sustainable patient and laboratory pathways within an algorithmic approach to the diagnosis and treatment of HIV-associated meningo-encephalitis involving bedside point of care diagnostic testing are implemented in the last phase of DREAMM.

**Project Triad**

\* African research leadership \*

\* Clinical lead counterparts \*

\* Local Ministry of Health leaders \*



## The DREAMM Project

The DREAMM Project is an implementation project structured into 3 phases:

### ► Observation

The observation phase will determine current HIV-associated meningo-encephalitis mortality rates and availability of diagnostic tests and essential medicines in routine care.

### ► Training (laboratory and clinical)

Key clinical and laboratory personnel will be trained on the latest point of care diagnostic tests and safe administration of essential medicines for HIV-associated meningo-encephalitis such as amphotericin B deoxycholate. They will disseminate this knowledge to their hospital counterparts.

### ► Implementation

Optimised laboratory and patient pathways and a diagnostic and treatment algorithm are implemented in order to reduce the time from patient presentation to diagnostic testing and administration of effective, microbiologically-driven treatment.

## Annual incidence/incidence range of CCM cases by DREAMM Site – Tanzania, Malawi, Cameroon



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

110

patients enrolled into Observation phase of DREAMM  
(75 Tanzania, 35 Malawi)

75%

Were ART experienced

82%

Had abnormal mental status\*

77%

Overall mortality rate at 10 weeks follow-up in Tanzania\*\*

\*A patient was defined as having an abnormal mental status if the Glasgow Coma Score (GCS) <15 (including confusion and drowsiness), the patient had had a recent seizure resulting in drowsiness/confusion, or displayed abnormal behaviour such as aggression or delusional beliefs.

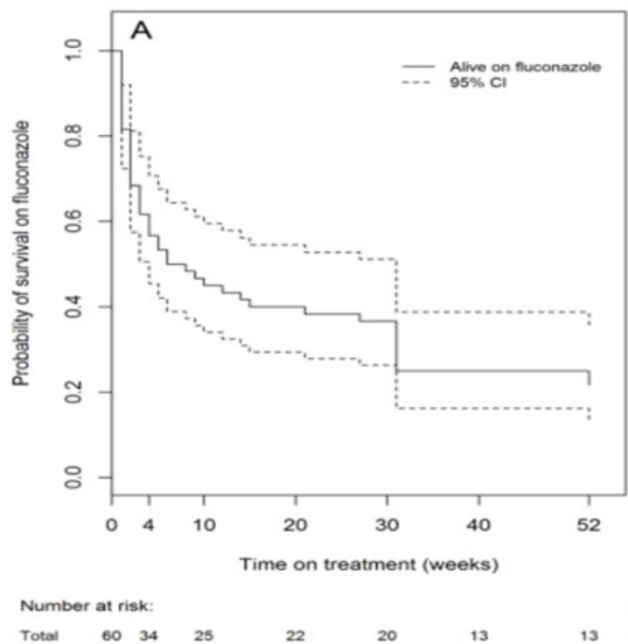
Figures are taken from preliminary analysis of DREAMM Project Observation phase data in Tanzania and Malawi.

\*\* Assumed those lost to follow up died.

A Prospective Longitudinal Study of the Clinical Outcomes from Cryptococcal Meningitis following Treatment Induction with 800 mg Oral Fluconazole in Blantyre, Malawi

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Unacceptably high mortality with inadequate and ineffective fluconazole monotherapy

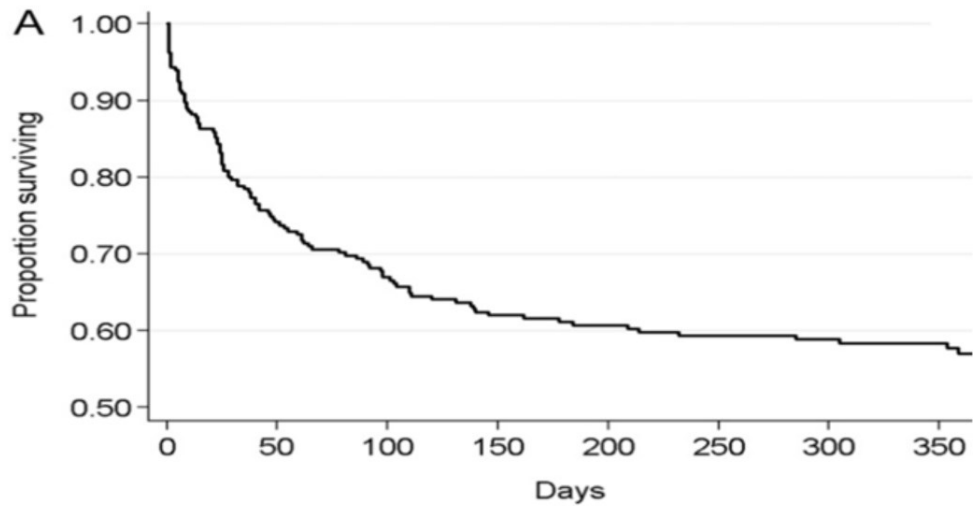


Rothe C, Sloan DJ, Goodson P, Chikafa J, Mukaka M, et al. (2013) PLOS ONE 8(6): e67311

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## Determinants of Mortality in a Combined Cohort of 501 Patients With HIV-Associated Cryptococcal Meningitis: Implications for Improving Outcomes

Survival curve flattens after the 3 month time period to 40% for AmB treated patients



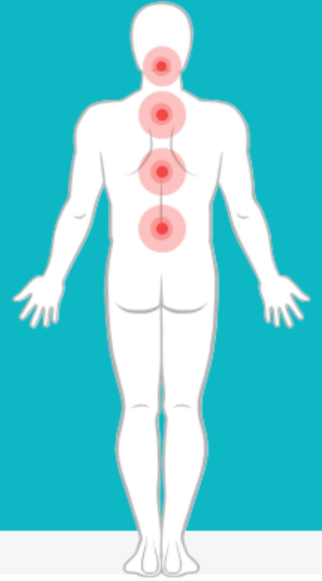
The prognosis after aggressive antifungal therapy with amphotericin-based combination antifungal therapy and timely ART (after 4-6 weeks) is good.

*J Jarvis et al Clin Infect Dis. 2014 Mar 1; 58(5): 736–745*

Figure used with permission from *J Jarvis et al Clin Infect Dis. 2014 Mar 1; 58(5): 736–745*

# DREAMM Clinical Training

**HIV-associated cryptococcal meningitis**





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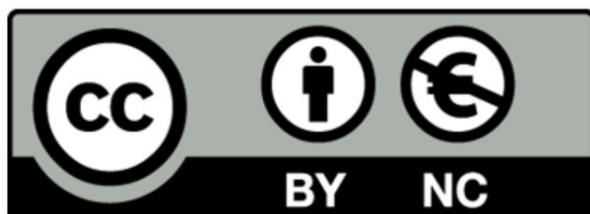
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## Education programme topics

- ▷ General meningo-encephalitis patient management
- ▷ **Cryptococcal meningitis - CCM**
- ▷ Tuberculous meningitis – TBM
- ▷ Bacterial meningitis – BM
- ▷ Toxoplasmic encephalitis - Toxo
- ▷ Neurosyphilis – NS