Ending Cryptococcal Meningitis Deaths by 2030

A Strategic Framework

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

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GAFFI Global Action Fund for Fungal Infections

St George's University of London

ITPC International Treatment Preparedness Coalition

CDC Foundation Together our impact is greater

DNDi Drugs for Neglected Diseases *initiative*

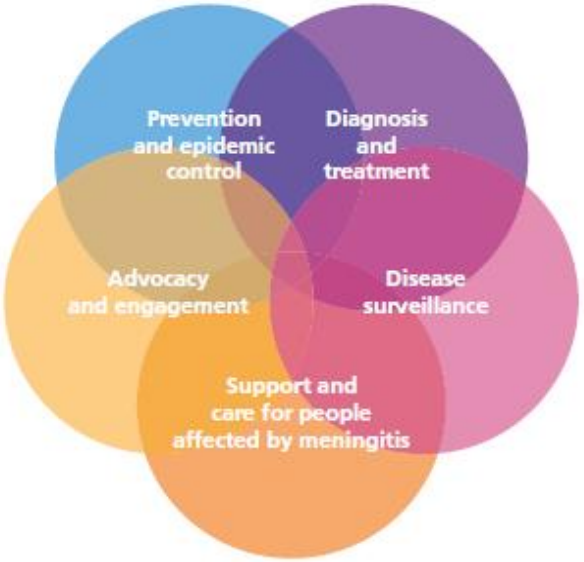
Médecins Sans Frontières

Conflicts of interest

Current research grants from the National Institutes of Health, Centers for Disease Control and Prevention, UK Medical Research Council, Gates Foundation, National Health Laboratory Service Research Trust

No other conflicts of interest

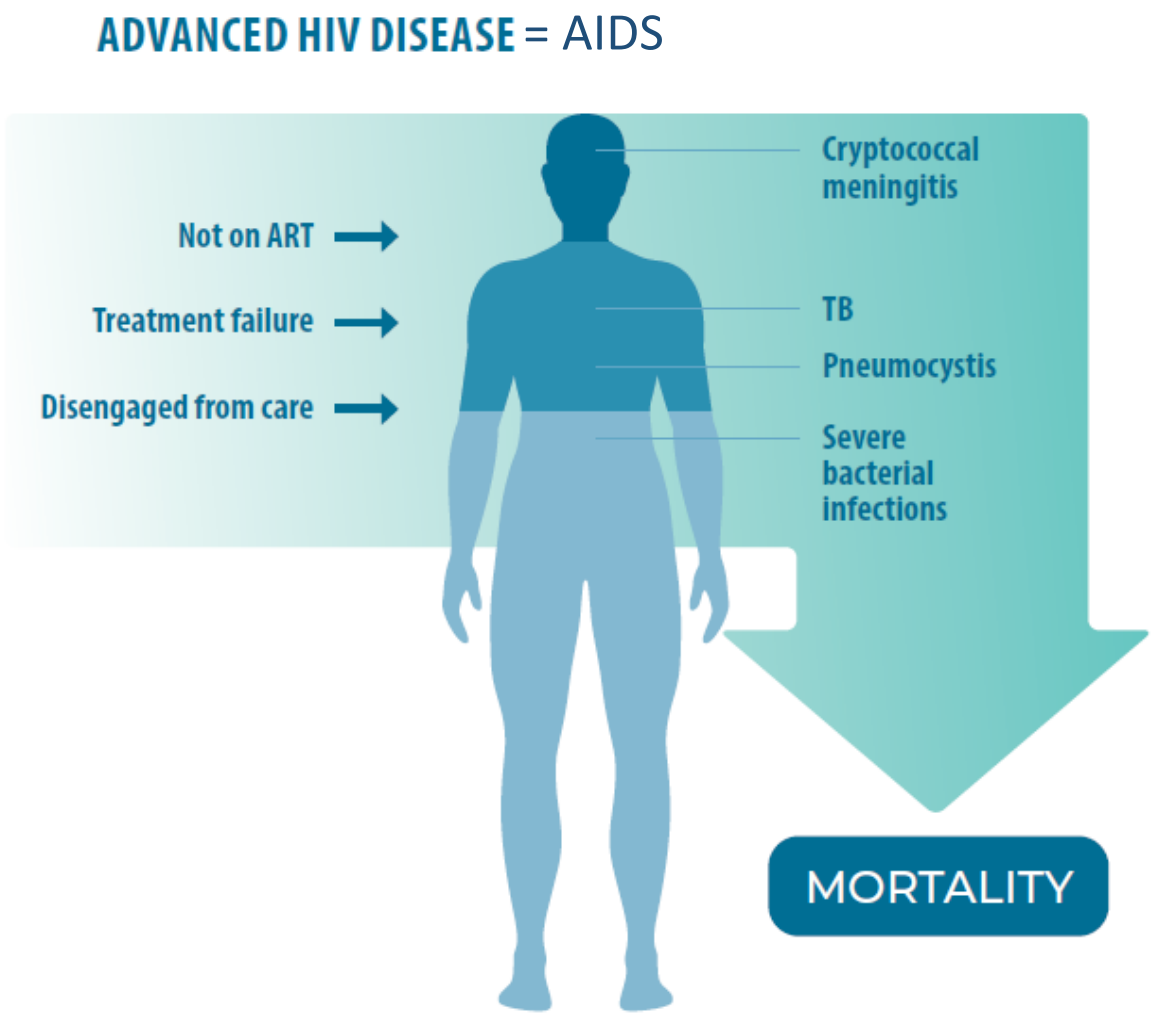
Connection to other global initiatives



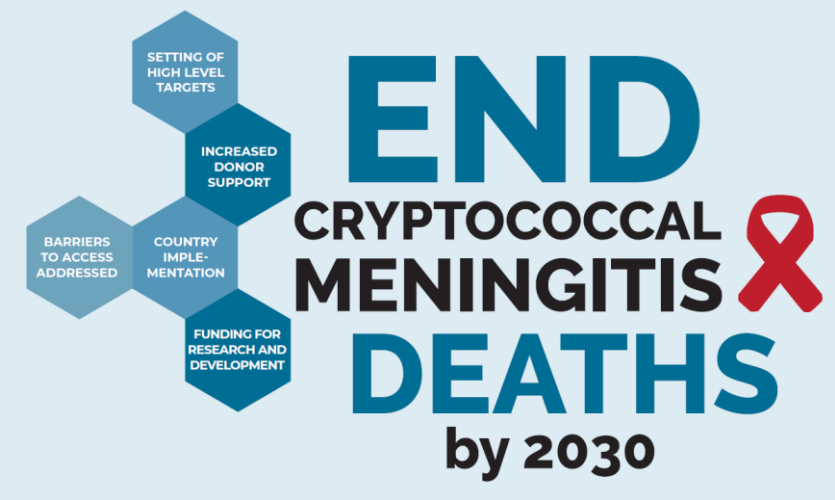
DEFEATING MENINGITIS BY 2030

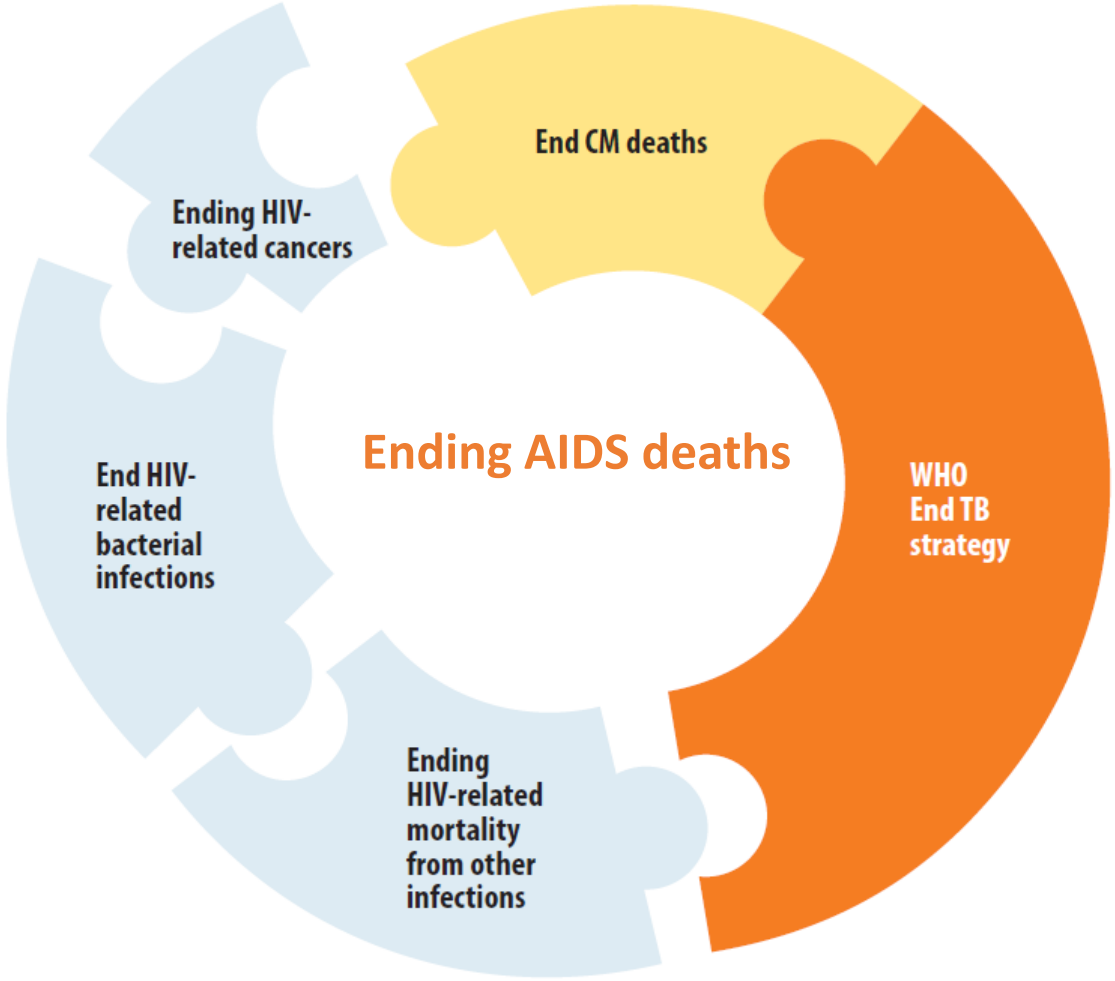
A GLOBAL ROAD MAP

The main infectious causes of AIDS deaths



Connection to other global initiatives





Cryptococcal meningitis (CM)

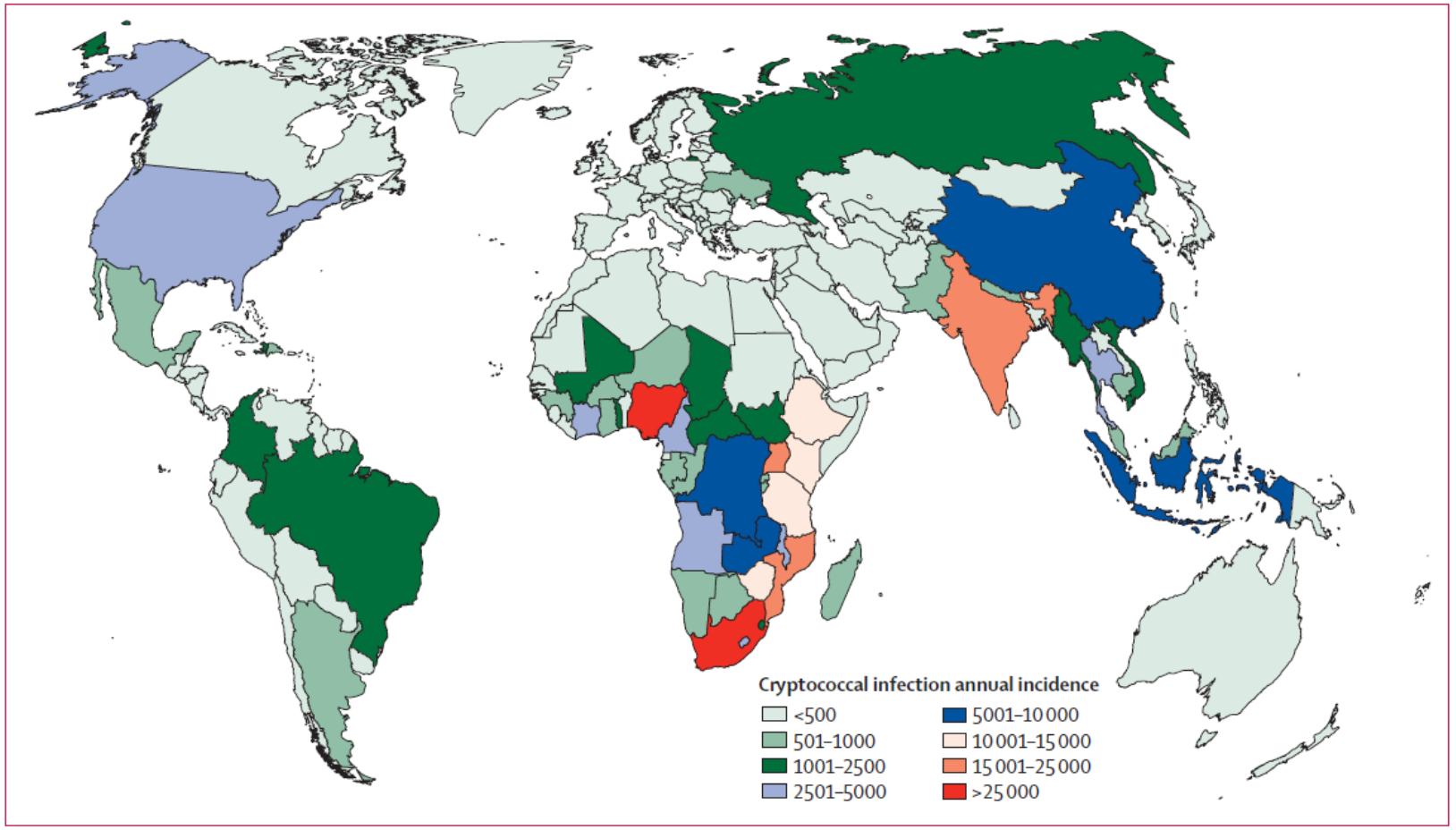


Figure 2: Annual incidence of cryptococcal infection by country
The annual number of people positive with cryptococcal antigenaemia estimated at 278 000 (95% CI 195 500–340 600) globally in 2014. We estimated 223 100 annual incident cases of cryptococcal meningitis in 2014..

Globally, cryptococcal meningitis was responsible for 15% of AIDS-related deaths (95% CI 10–19)

Rajasingham R, et al. Lancet Infect Dis 2017

The global scale of AIDS deaths

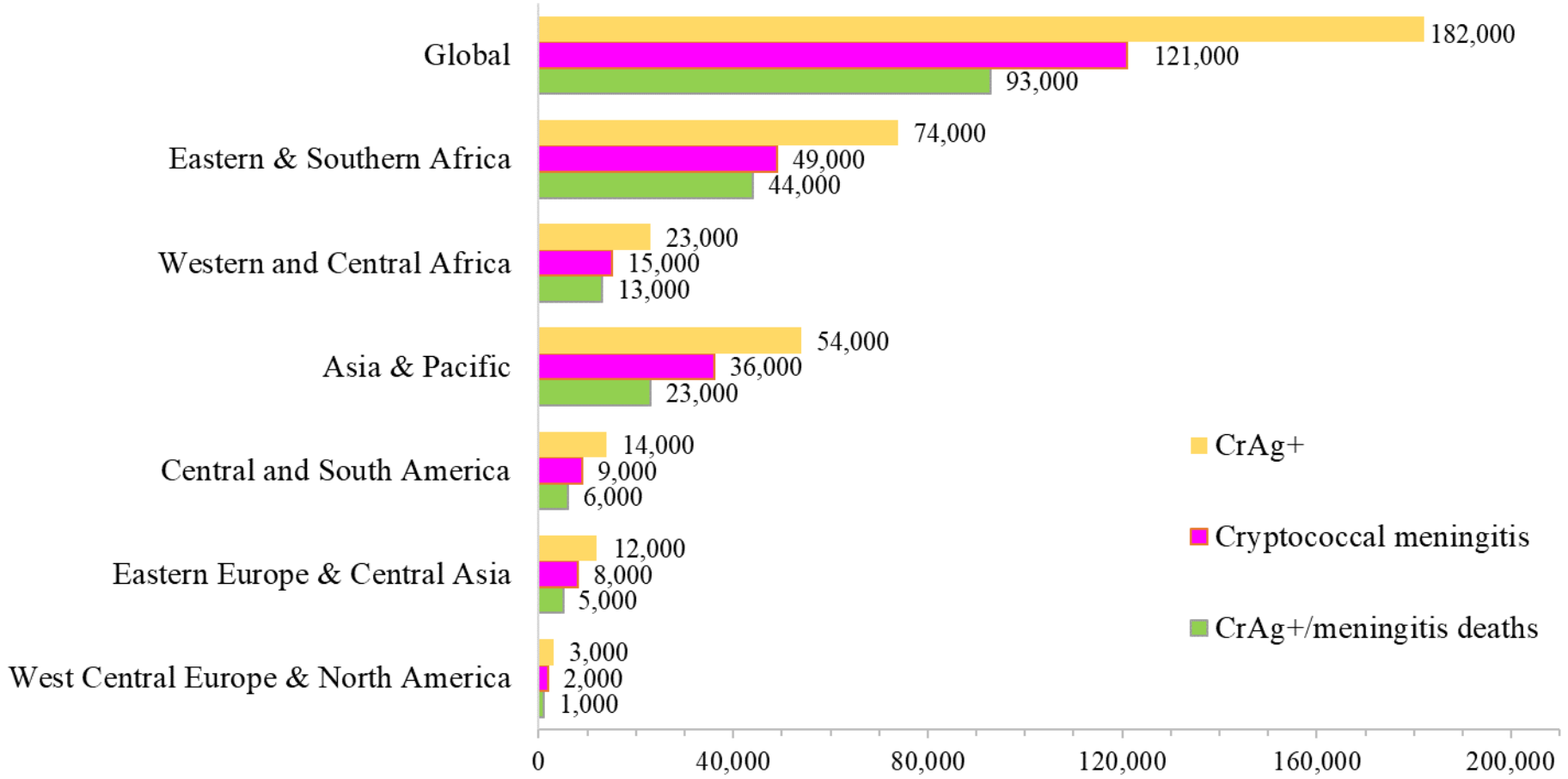
Global HIV data

	2000	2005	2010	2015	2016	2017	2018	2019	2020
People living with HIV	25.5 million [20.5 million–30.7 million]	28.6 million [23.0 million–34.3 million]	31.1 million [25.0 million–37.3 million]	34.6 million [27.7 million–41.4 million]	35.3 million [28.3 million–42.2 million]	35.9 million [28.8 million–43.0 million]	36.6 million [29.3 million–43.8 million]	37.2 million [29.8 million–44.5 million]	37.7 million [30.2 million–45.1 million]
AIDS-related deaths	1.5 million [1.1 million–2.2 million]	1.9 million [1.3 million–2.7 million]	1.3 million [910 000–1.9 million]	900 000 [640 000–1.3 million]	850 000 [600 000–1.2 million]	800 000 [570 000–1.2 million]	750 000 [530 000–1.1 million]	720 000 [510 000–1.1 million]	680 000 [480 000–1.0 million]

AIDS-related deaths have been reduced by 64% since the peak in 2004 and by 47% since 2010

https://www.unaids.org/en/resources/fact-sheet

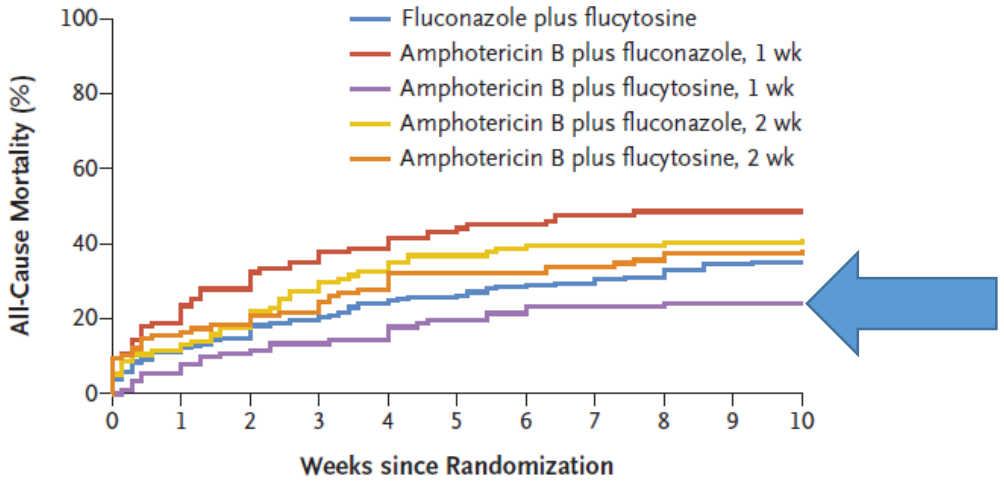
Cryptococcal meningitis



Rajasingham R, et al. Unpublished estimates for 2020

Treatment of cryptococcal meningitis

ACTA trial



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

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

Treatment of cryptococcal meningitis

Induction

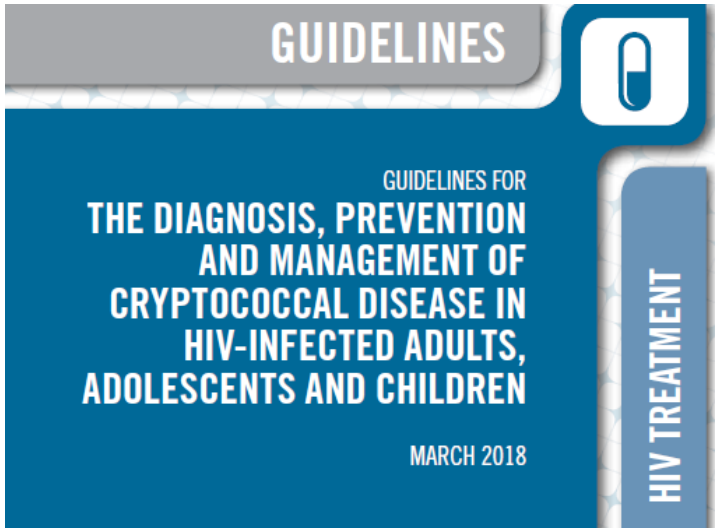
- **1 week: AmB + 5-FC, then 1 week high-dose fluconazole**
- *(2 weeks: fluconazole + 5-FC)*

Consolidation

- 8 weeks: fluconazole

Maintenance

- Minimum 12 months: fluconazole



World Health Organization, March 2018
http://apps.who.int/

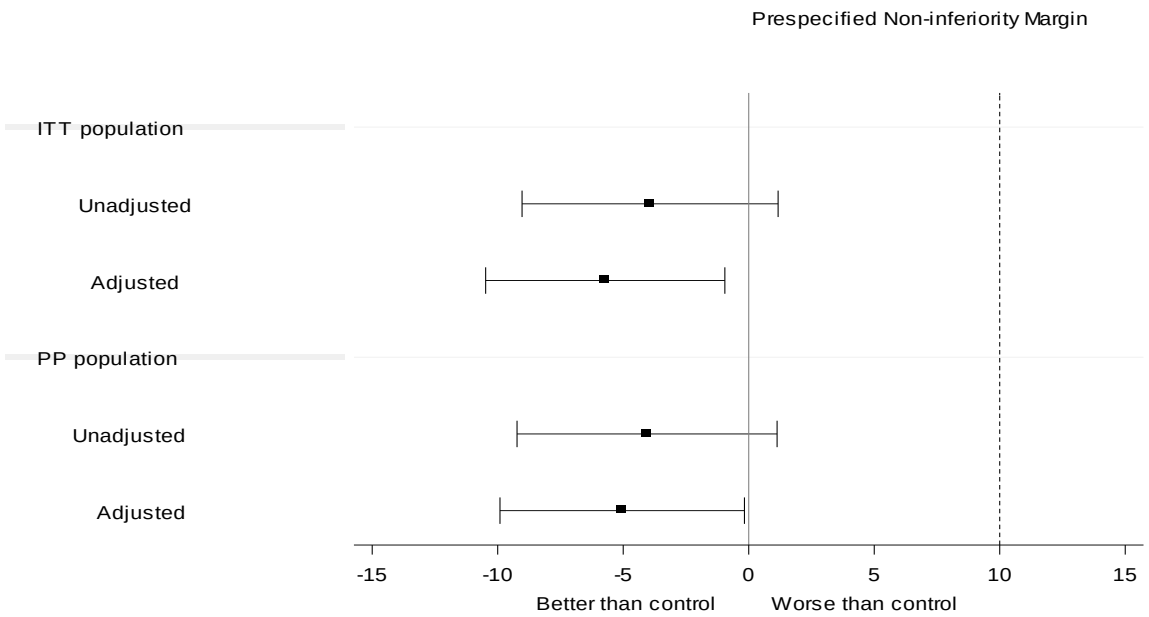
Treatment of cryptococcal meningitis

AmBisome arm

10 mg/kg LAmB single dose
AND
5FC 100 mg/kg/day for 14 days
AND
FLU 1200 mg/day for 14 days

Control arm (WHO standard)

1 mg/kg AmB for 7 days
AND
5FC 100 mg/kg/day for 7 days
THEN
FLU 1200 mg/day for 7 days



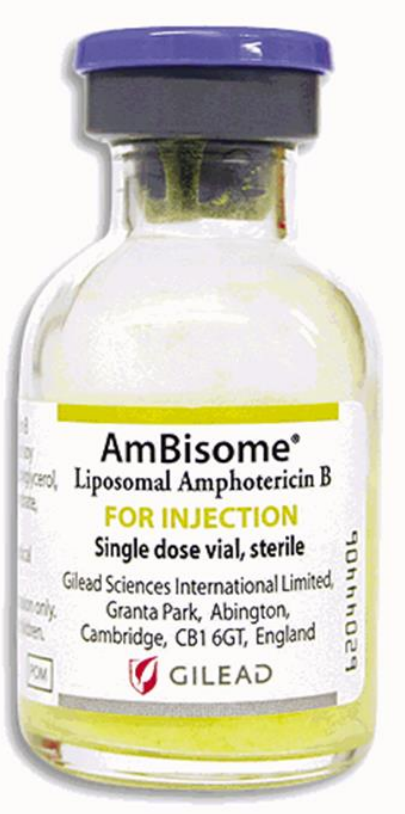
Primary outcome: All-cause mortality at 10 weeks (non-inferiority)

AMBITION-*cm*

AMBIsome Therapy Induction OptimizatioN

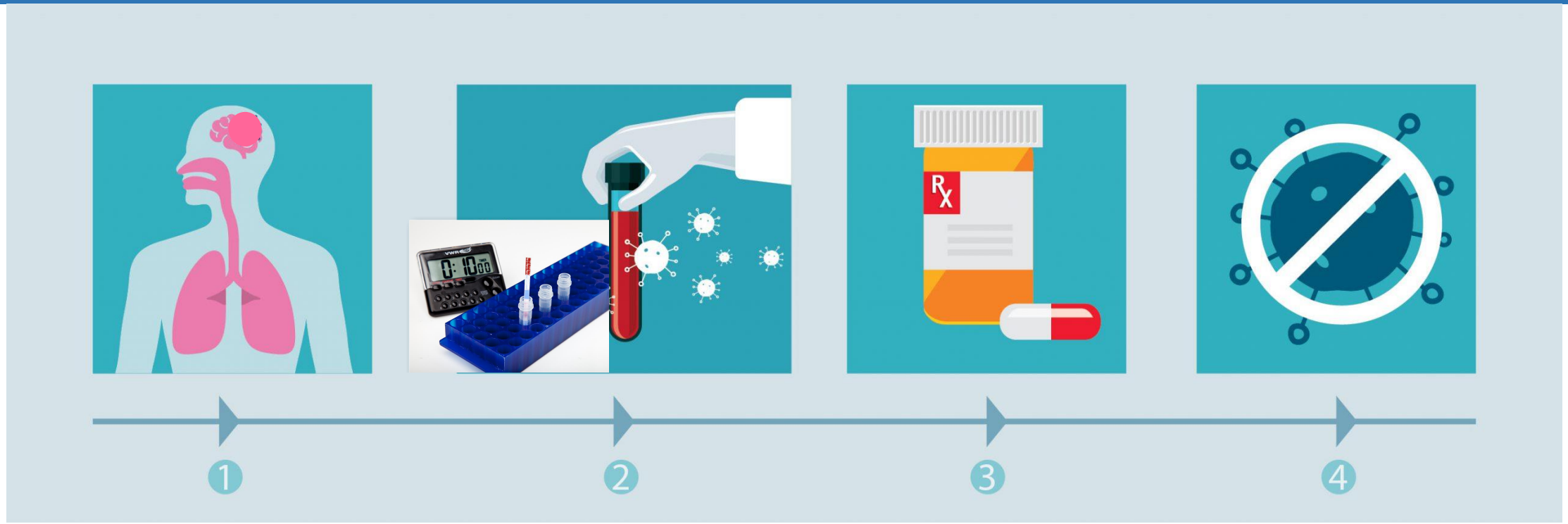
Lawrence D, et al. IAS July 2021

Critical antifungal agents for meningitis



A feasible and effective screen-and-treat intervention for cryptococcal disease is now being implemented globally

Screening for cryptococcal antigen in blood



1. Cryptococcal antigen can be found in the bloodstream weeks <u>before</u> symptoms of meningitis
2. People with advanced HIV are tested early for cryptococcal disease
3. Patients who test positive for blood cryptococcal antigen are screened for meningitis (LP) and prescribed appropriate antifungal medicines
4. Antifungal medicines treats meningitis in those who have it, and can prevent meningitis in those who do not

What are the main gaps?

CD4 tests

Cryptococcal antigen tests for screening and meningitis diagnosis

Lumbar puncture availability, consumables

Critical antifungal medicines for meningitis

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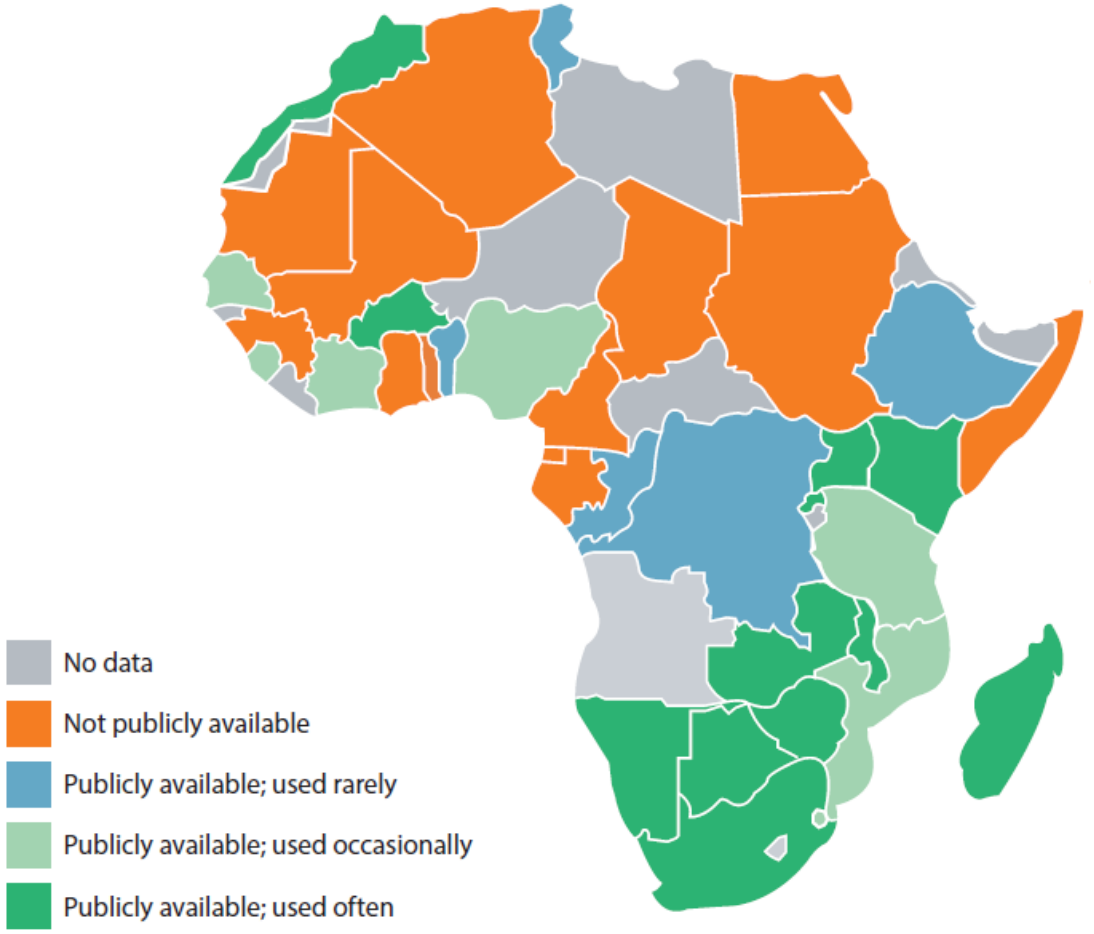
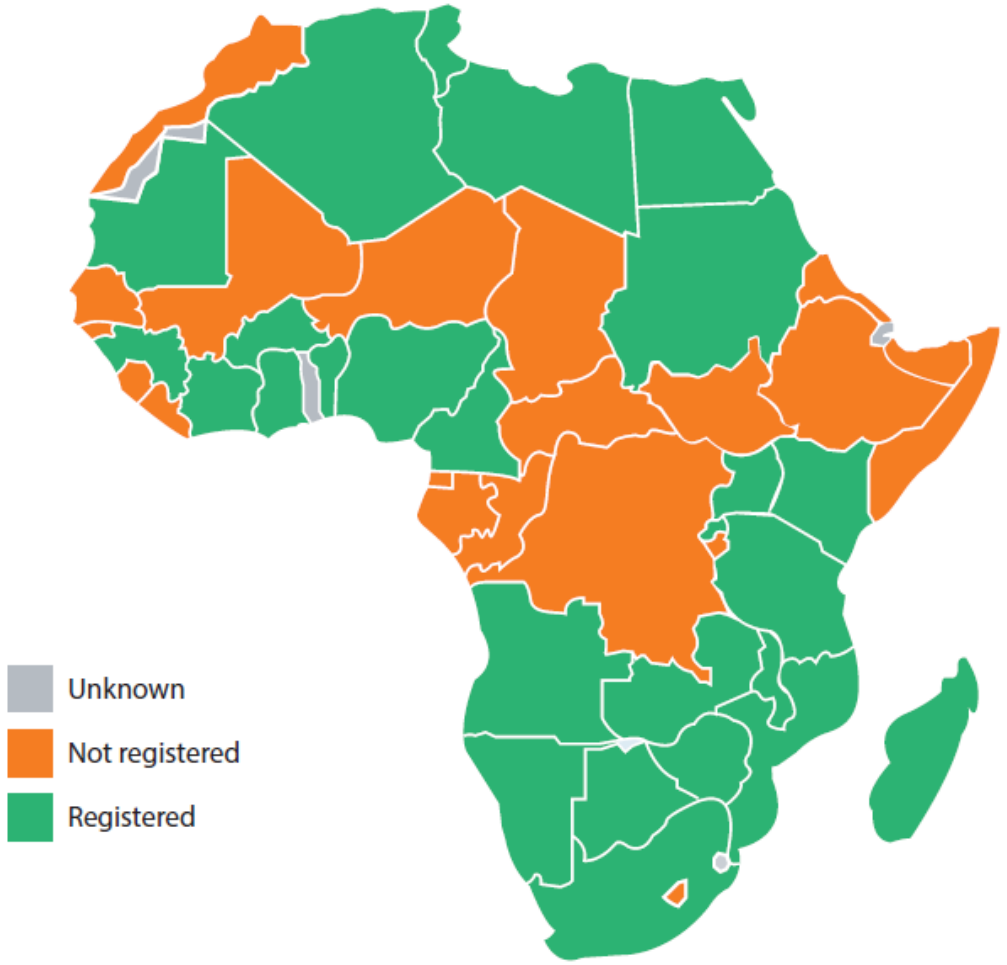
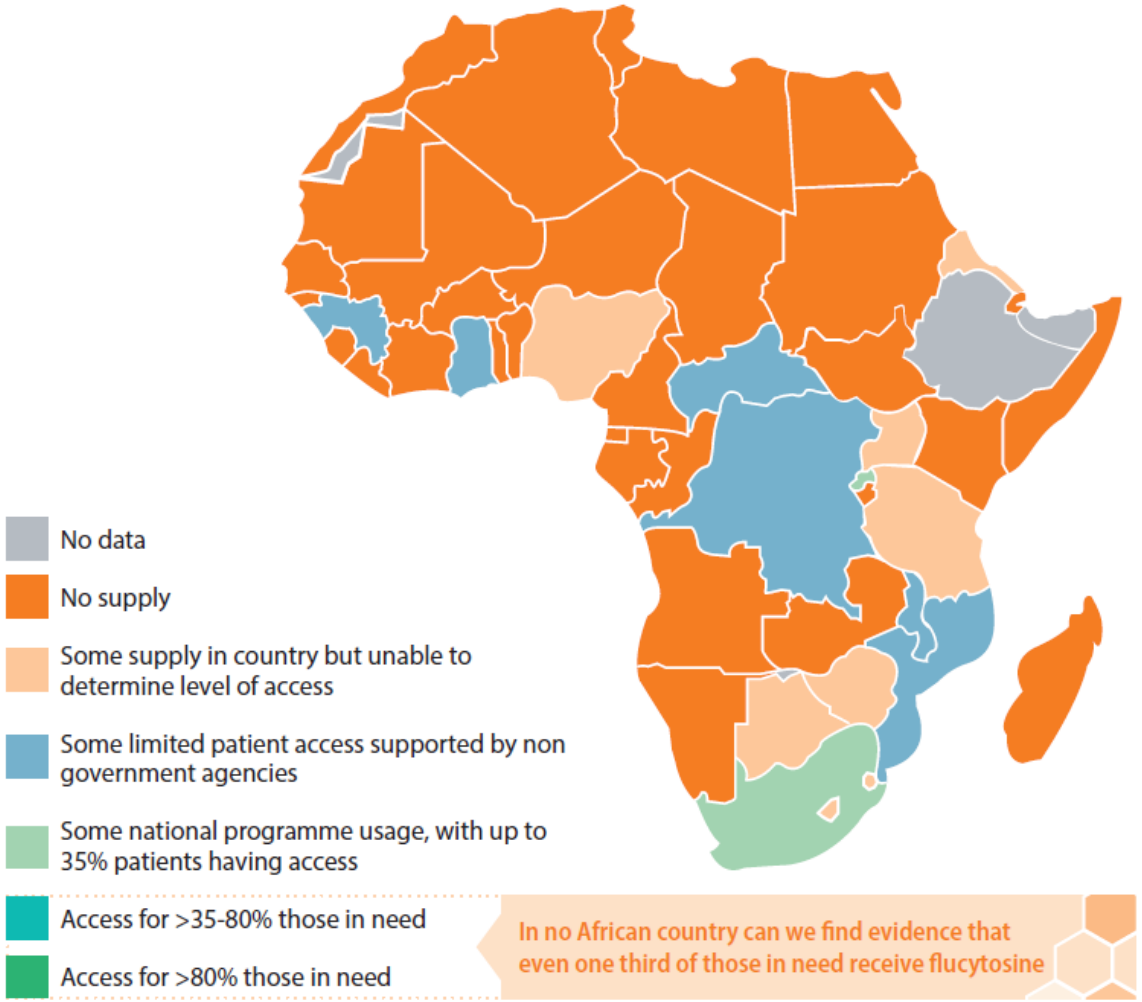
CrAg test availability in Africa



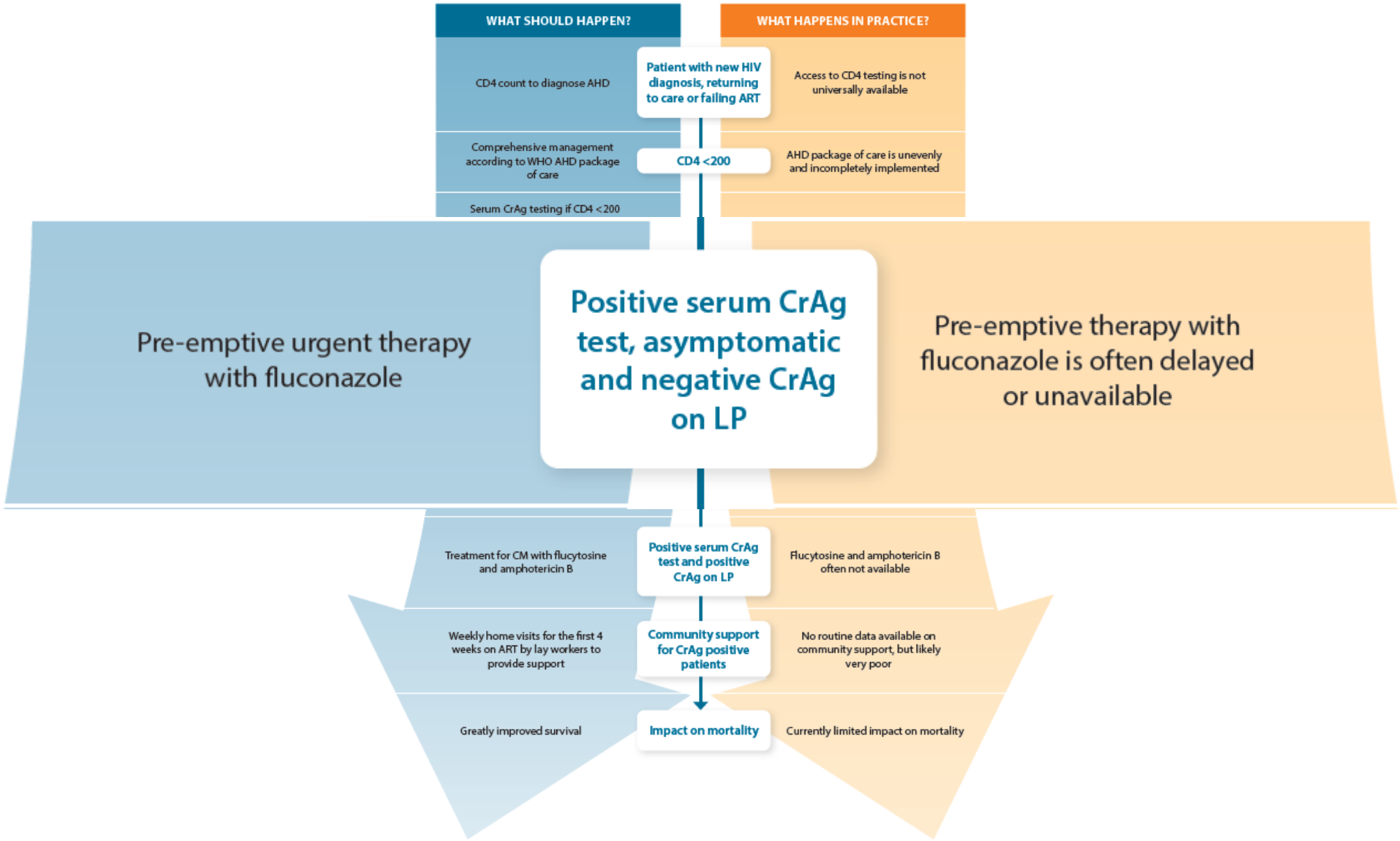
Amphotericin B registration in Africa



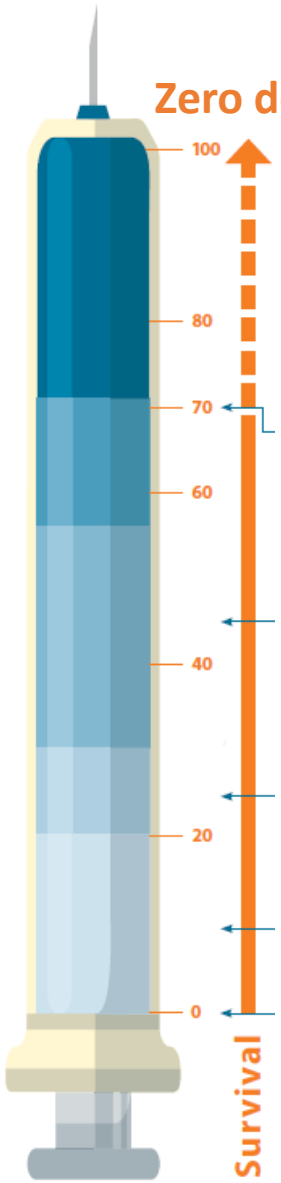
Flucytosine registration in Africa



Missed opportunities in CrAg screening & treatment



Aiming for zero cryptococcal meningitis deaths



Liposomal AmB-based induction regimen non-inferior to WHO standard and less toxic

WHO standard of amphotericin B + flucytosine improves survival to 70%

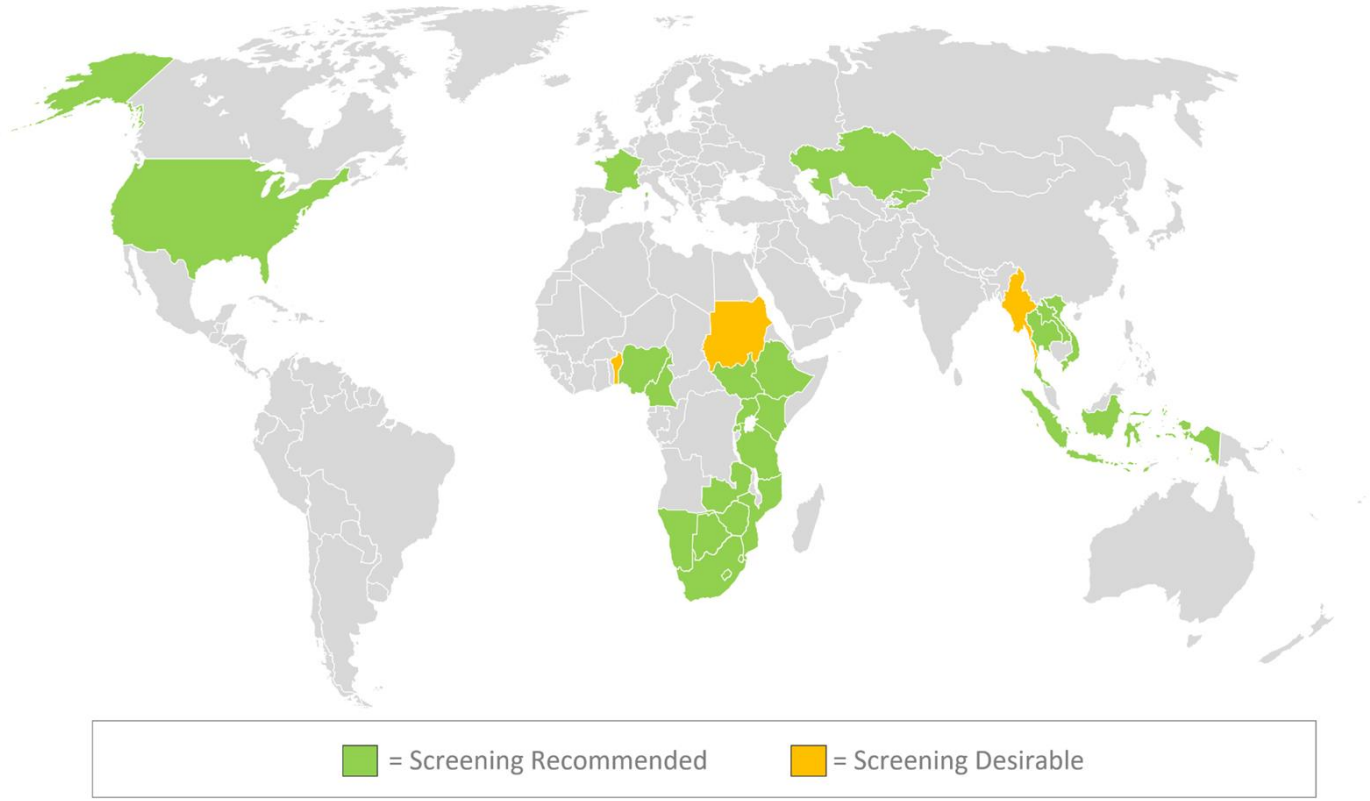
Adding flucytosine to a fluconazole induction regimen improves survival even more

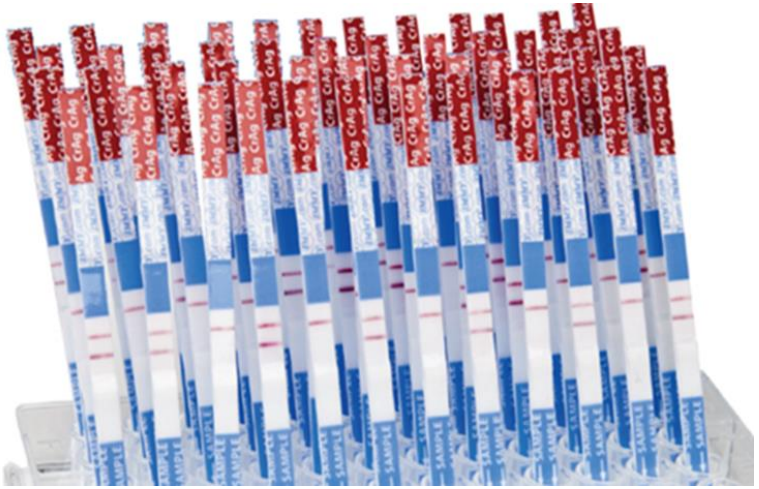
Deferring ART to the appropriate time and therapeutic LPs improves survival further

Diagnosis with fluconazole monotherapy improves survival marginally

Undiagnosed, cryptococcal meningitis is always fatal

Address the gaps in CrAg screening





South Africa's National Reflex CrAg Screening Programme

Feb '17 – Sep'21

CrAg reflex tests run:	1 238 237 (98.9%)
Positive reflex CrAg tests:	76 085 (6.1%)
Eligible patients screened:	1 012 493 (99.1%)
CrAg+ patients identified:	64 310 (6.0%)

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Address the gaps in diagnosis of meningitis

Increase access to lumbar puncture and *CSF* CrAg testing for people with a positive screening blood CrAg test and those with symptoms of meningitis

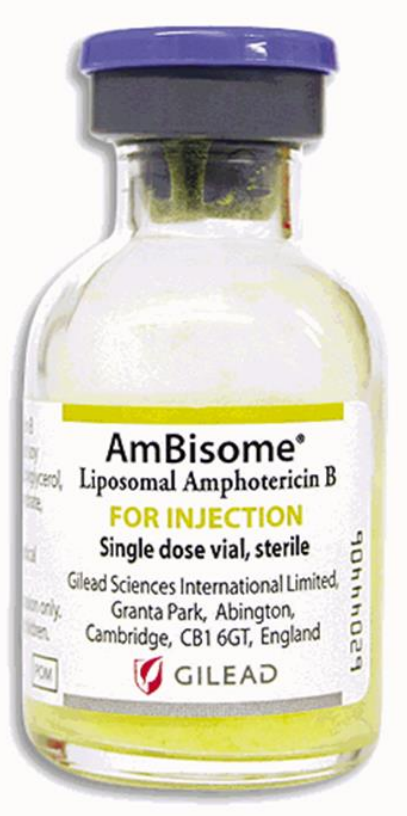
Address the gaps in access to key medicines

Ensure availability

Register and procure

Ensure availability

Reduce costs



Research and development

- Diagnostic needs
  - POC diagnostics for multiple OIs in people with AHD ✗✓
  - POC diagnostics to reliably establish cryptococcal meningitis cure ✗
  - CrAg diagnostics to predict progression of disease ✓
- Treatment needs
  - Test more effective pre-emptive antifungal regimen for antigenaemia in trials ✓
  - Test less toxic and/or oral formulations of amphotericin B in trials ✓
  - Develop a modified slow-release flucytosine for less frequent dosing ✓
  - Bring novel antifungals into phase I, II and III clinical trials ✓

High-level targets

MORTALITY REDUCTION TARGETS		
To reduce CM deaths by **50%** by 2025 from 2020 baseline*		
To reduce CM deaths by **90%** by 2030 from 2020 baseline*		
SCREENING INDICATORS	**2025 TARGET**	**2030 TARGET**
Number and proportion of eligible adults with CD4 result	**90%**	**95%**
Number and proportion of adults with advanced HIV disease with a CrAg result	**80%**	**90%**
TREATMENT INDICATORS		
Number and proportion of adults with cryptococcal antigenaemia (no meningitis) commenced on pre-emptive fluconazole therapy	**80%**	**90%**
Number and proportion of adults with CM treated with a flucytosine-containing induction treatment regimen	**80%**	**90%**
OUTCOME INDICATOR		
Number and proportion of in-hospital deaths among adults with CM	**<20%**	**<10%**

SUMMARY OF
KEY ADVOCACY MESSAGES

To WHO and UNAIDS

National and global Cryptococcal Meningitis (CM) mortality reduction targets for 2025 and 2030 should be set. A CM mortality indicator should be monitored at country level.

A clear strategy and roadmap for countries to address CM deaths by 2030 should be developed.

To Donors

A roadmap for ending CM deaths should be costed, and donors should commit to supporting public sector screening and treatment, at no cost to patients.

Donors should invest proportionately in improving disease screening, pre-emptive management and treatment to help end CM deaths.

Countries must be supported to ensure that all people with CM are identified quickly and treated with the WHO-preferred regimen of flucytosine and amphotericin B.

To Country-Level Programmers

Countries should ensure that the items outlined in the country-level dashboard (Appendix 2) are present on the ground. In particular, countries need to ensure that access to Cryptococcal Antigen-based diagnosis is routine, screening is implemented with pre-emptive therapy, and treatment is with flucytosine and amphotericin B for all people with CM.

To Industry

The pharmaceutical industry must fund additional research and development into new, more effective treatments for CM.

Liposomal amphotericin B must be made accessible at an affordable price in order to accelerate access to this medicine.

Acknowledgements