Ending Cryptococcal Meningitis Deaths by 2030
A Strategic Framework

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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

ADVANCED HIV DISEASE = AIDS

- Not on ART
- Treatment failure
- Disengaged from care

- Cryptococcal meningitis
- TB
- Pneumocystis
- Severe bacterial infections

MORTALITY
Connection to other global initiatives

END CRYPTOCOCCAL MENINGITIS DEATHS by 2030

Ending AIDS deaths
- Ending HIV-related cancers
- End HIV-related bacterial infections
- Ending HIV-related mortality from other infections

End CM deaths

WHO End TB strategy

Setting of high level targets
Increased donor support
Barriers to access addressed
Country implementation
Funding for research and development
Cryptococcal meningitis (CM)

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

The global scale of AIDS deaths

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

### Global HIV data

<table>
<thead>
<tr>
<th>Year</th>
<th>People living with HIV</th>
<th>AIDS-related deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>25.5 million [20.5 million–30.7 million]</td>
<td>1.5 million [1.1 million–2.2 million]</td>
</tr>
<tr>
<td>2005</td>
<td>28.6 million [23.0 million–34.3 million]</td>
<td>1.9 million [1.3 million–2.7 million]</td>
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<tr>
<td>2010</td>
<td>31.1 million [25.0 million–37.3 million]</td>
<td>1.3 million [910 000–1.9 million]</td>
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<tr>
<td>2015</td>
<td>34.6 million [27.7 million–41.4 million]</td>
<td>900 000 [640 000–1.3 million]</td>
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<tr>
<td>2016</td>
<td>35.3 million [28.3 million–42.2 million]</td>
<td>850 000 [600 000–1.2 million]</td>
</tr>
<tr>
<td>2017</td>
<td>35.9 million [28.8 million–43.0 million]</td>
<td>800 000 [570 000–1.2 million]</td>
</tr>
<tr>
<td>2018</td>
<td>36.6 million [29.3 million–43.8 million]</td>
<td>750 000 [530 000–1.1 million]</td>
</tr>
<tr>
<td>2019</td>
<td>37.2 million [29.8 million–44.5 million]</td>
<td>720 000 [510 000–1.1 million]</td>
</tr>
<tr>
<td>2020</td>
<td>37.7 million [30.2 million–45.1 million]</td>
<td>680 000 [480 000–1.0 million]</td>
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</tbody>
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https://www.unaids.org/en/resources/fact-sheet
Cryptococcal meningitis


- Global: 182,000 cases
  - CrAg+: 121,000
  - Cryptococcal meningitis: 93,000
  - CrAg+/meningitis deaths: 49,000

- Eastern & Southern Africa: 74,000 cases
  - CrAg+: 44,000
  - Cryptococcal meningitis: 23,000
  - CrAg+/meningitis deaths: 15,000

- Western and Central Africa: 36,000 cases
  - CrAg+: 23,000
  - Cryptococcal meningitis: 13,000
  - CrAg+/meningitis deaths: 10,000

- Asia & Pacific: 54,000 cases
  - CrAg+: 36,000
  - Cryptococcal meningitis: 23,000
  - CrAg+/meningitis deaths: 13,000

- Central and South America: 54,000 cases
  - CrAg+: 14,000
  - Cryptococcal meningitis: 9,000
  - CrAg+/meningitis deaths: 5,000

- Eastern Europe & Central Asia: 12,000 cases
  - CrAg+: 8,000
  - Cryptococcal meningitis: 5,000
  - CrAg+/meningitis deaths: 3,000

- West Central Europe & North America: 2,000 cases
  - CrAg+: 1,000
  - Cryptococcal meningitis: 2,000
  - CrAg+/meningitis deaths: 1,000
Treatment of cryptococcal meningitis

ACTA trial

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)
Critical antifungal agents for meningitis
A feasible and effective screen-and-treat intervention for cryptococcal disease is now being implemented globally.
1. Cryptococcal antigen can be found in the bloodstream weeks before 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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- CD4 tests
- Cryptococcal antigen tests for screening and meningitis diagnosis
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CrAg test availability in Africa

- **No data**
- **Not publicly available**
- **Publicly available; used rarely**
- **Publicly available; used occasionally**
- **Publicly available; used often**
Amphotericin B registration in Africa
Flucytosine registration in Africa

No data
No supply
Some supply in country but unable to determine level of access
Some limited patient access supported by non government agencies
Some national programme usage, with up to 35% patients having access
Access for >35-80% those in need
Access for >80% those in need

In no African country can we find evidence that even one third of those in need receive flucytosine
Missed opportunities in CrAg screening & treatment

Pre-emptive urgent therapy with fluconazole

Positive serum CrAg test, asymptomatic and negative CrAg on LP

Pre-emptive therapy with fluconazole is often delayed or unavailable

WHAT SHOULD HAPPEN?
- CD4 count to diagnose AID
- Comprehensive management according to WHO AID package of care
- Serum CrAg testing if CD4 < 200

WHAT HAPPENS IN PRACTICE?
- Patient with new HIV diagnosis, returning to care or failing ART
- CD4 < 200
- AID package of care is uninsured and incompletely implemented
- Access to CD4 testing is not universally available

Impact on mortality
- No routine data available on community support, but likely very poor
- Community limited impact on mortality
- Greatly improved survival
- Positive serum CrAg test and positive CrAg on LP
- Laryngoscopy and amphotericin B often not available
- Community support for CrAg positive patients
- No routine data available on community support, but likely very poor
- Community limited impact on mortality
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- Positive serum CrAg test and positive CrAg on LP
- Laryngoscopy and amphotericin B often not available
- Community support for CrAg positive patients
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- Community limited impact on mortality
Aiming for zero cryptococcal meningitis deaths

Undiagnosed, cryptococcal meningitis is always fatal.

Diagnosis with fluconazole monotherapy improves survival marginally.

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

Adding flucytosine to a fluconazole induction regimen improves survival even more.

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

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

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%)
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

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
<table>
<thead>
<tr>
<th>Indicator</th>
<th>2025 Target</th>
<th>2030 Target</th>
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<tbody>
<tr>
<td>Number and proportion of eligible adults with CD4 result</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>Number and proportion of adults with advanced HIV disease with a CrAg result</td>
<td>80%</td>
<td>90%</td>
</tr>
</tbody>
</table>

## Treatment Indicators
- Number and proportion of adults with cryptococcal antigenaemia (no meningitis) commenced on pre-emptive fluconazole therapy: 80% to 90%
- Number and proportion of adults with CM treated with a flucytosine-containing induction treatment regimen: 80% to 90%

## Outcome Indicator
- Number and proportion of in-hospital deaths among adults with CM: <20% to <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