



ENDING CRYPTOCOCCAL MENINGITIS DEATHS BY 2030

Strategic Framework



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.

Ending Cryptococcal Meningitis Deaths by 2030 – Strategic Framework

This report can be found at <https://samumf.org/en/resources/hiv/advanced-hiv-disease>, <https://www.gaffi.org/special-webinar-announcement-ending-cryptococcal-meningitis-deaths-by-2030-a-new-global-initiative/> and /or <https://hsc.unm.edu/echo/institute-programs/covid-19-response/international-covid19/cdc-hiv/>

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EXECUTIVE SUMMARY

Cryptococcal meningitis (CM) is one of the main causes of death of people living with HIV (PLHIV). While diagnostic tests and medicines for prevention and treatment exist, access in resource-limited settings is extremely limited. Treatment with fluconazole alone, most commonly used in low-income settings, results in around 20% survival.

This Strategic Framework sets out the case for a re-invigorated global drive to end CM deaths by 2030, as part of a broader drive to end all HIV-related deaths. Following the call for a strategy to end CM deaths to be set by 2030 (Shroufi et al, 2020), we now call for high-level targets and lay out strategic building blocks to help countries develop their own strategies to minimise deaths from CM. Earlier diagnosis and optimised treatment with flucytosine and amphotericin B, as recommended by the World Health Organisation (WHO), could improve survival to around 70%.



This Strategic Framework outlines the key reasons why a global strategy to address CM deaths is needed and what essential programmatic elements are required to make this a reality.

KEY RECOMMENDATIONS

WHO and UNAIDS

WHO and UNAIDS should **commit to monitoring** the following **high-level indicators**:

- To reduce CM deaths by **50% by 2025** from 2020 baseline
- To reduce CM deaths by **90% by 2030** from 2020 baseline

Detailed programme indicators are outlined on page 15.

Donors

Donors should **commit to fund** and **support a roadmap** for ending CM deaths, **investing proportionately in improving disease screening, pre-emptive therapy, diagnosis and treatment**.

Countries

Countries should develop **national guidelines**, an **implementation plan** and a **country-level dashboard for screening, diagnosis, pre-emptive therapy and treatment of CM** according to WHO recommendations. Countries should also ensure that the **items outlined in the country-level dashboard** (shown in Appendix 2) are **present on the ground**. In particular, countries should ensure **access to screening, Cryptococcal Antigen testing (CrAg), pre-emptive therapy** and ensure availability of **fluconazole, flucytosine and amphotericin B** for all people with CM.

Implementing Partners

Implementing Partners should **support national HIV programmes** and provide the **tools and technical assistance** to ensure **screening, pre-emptive therapy and treatment of CM** is available to **all**.

Civil Society Organisations

Civil Society Organisations should ensure **PLHIV are aware of what screening, prevention and treatment** should be **provided** and **advocate to government, donors and international agencies** to ensure the **package of tools** needed is **available**.

Industry and Product Development Partners

There is a need for **collaboration with industry** to support additional research and development (R&D) into more effective treatments for cryptococcal meningitis. Liposomal amphotericin B is currently unaffordable, and work is needed to accelerate access to this medicine.

DEFINITION OF KEY TERMS

(where available, WHO definitions are used)

Advanced HIV Disease (AHD)	For adults, adolescents and children five years or older, advanced HIV disease is defined as a CD4 cell count <200 cells/mm ³ or a WHO clinical stage 3 or 4 event at presentation for care. All children younger than five years old with HIV should be considered as having advanced disease at presentation.
CD4 counts	In this document, all CD4 counts are in units of cells/mm ³ (x10 ⁶ /L).
Cryptococcal disease	Disease caused by <i>Cryptococcus</i> species with abnormal clinical symptoms or signs, such as meningeal, skin, pulmonary or disseminated disease.
Cryptococcal meningitis (CM)	Inflammation of the meninges due to infection with <i>Cryptococcus</i> species. Without treatment, the disease is fatal.
Induction treatment	The initial phase of treatment for CM.
Consolidation and maintenance treatment	Longer-term phase of treatment, with fluconazole (for dosages and duration of each stage of therapy see WHO guidelines). Note: Maintenance treatment is also referred to as secondary prophylaxis.
Cryptococcal antigen positivity in blood (CrAg antigenaemia)	Positive serum, plasma, or whole blood cryptococcal antigen test. Note: A positive cerebrospinal fluid antigen test indicates cryptococcal meningitis (CM).
Cryptococcal antigen lateral flow assay (CrAg LFA)	A point-of-care (POC) test that rapidly detects cryptococcal antigen in clinical specimens and can be performed on cerebrospinal fluid, venous or finger-prick blood samples.
Cryptococcal antigen screening	Testing people at high risk of CM with a CrAg assay.
Fluconazole primary prophylaxis	The provision of fluconazole to people at high risk to prevent cryptococcal disease, when cryptococcal antigen screening is not available.
Pre-emptive therapy	The provision of antifungal treatment with fluconazole in an attempt to prevent <i>Cryptococcus</i> in the blood from causing CM.

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SECTION 1:

THE CASE FOR A STRATEGY TO END CRYPTOCOCCAL MENINGITIS (CM) DEATHS BY 2030

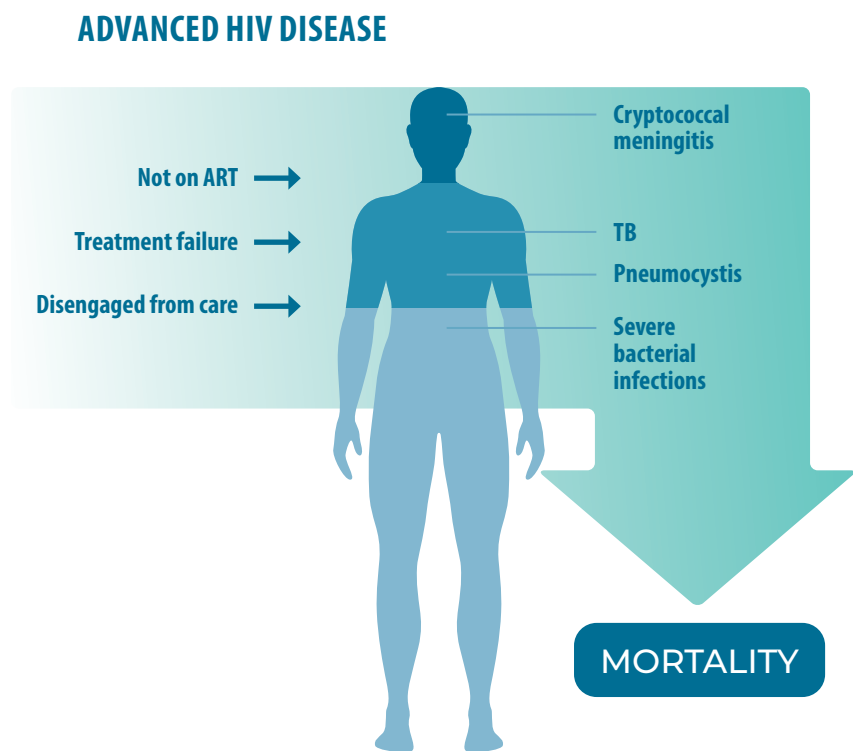
REDUCING HIV-RELATED MORTALITY

In 2019 690,000 people lost their lives to AIDS-related causes. The UNAIDS target to reduce AIDS deaths below 500,000 by 2020 will not be met. In many countries, 30% or more of new HIV patients still present with advanced HIV disease (AHD).

When people with HIV present late, discontinue treatment and/or are unable to access effective antiretroviral therapy (ART), they may develop AHD. People with AHD are at high risk for opportunistic infections (OI) such as TB, as well as other diseases.

Figure 1: The main infectious causes of HIV-related deaths

Increasing access to ART and CD4 cell count is critically important. People who are diagnosed with HIV should receive a baseline CD4 cell count to identify those with AHD so that they can receive the WHO-recommended package of care that will reduce HIV related deaths. To reduce the number of those who develop AHD, people need information about and access to HIV testing. People diagnosed with HIV then need to be linked to care and treatment services rapidly. For those who are newly diagnosed, are returning to care, or have failed ART, it is important that services incorporate systematic prevention, screening and treatment for opportunistic infections.



WHERE DOES THE REDUCTION OF MORTALITY FROM CRYPTOCOCCAL MENINGITIS FIT IN?

Strategic frameworks are useful for priority setting, resource allocation and planning. The End TB Strategy provides a framework for addressing all TB-related deaths, including among PLHIV (see Appendix 1). However, there

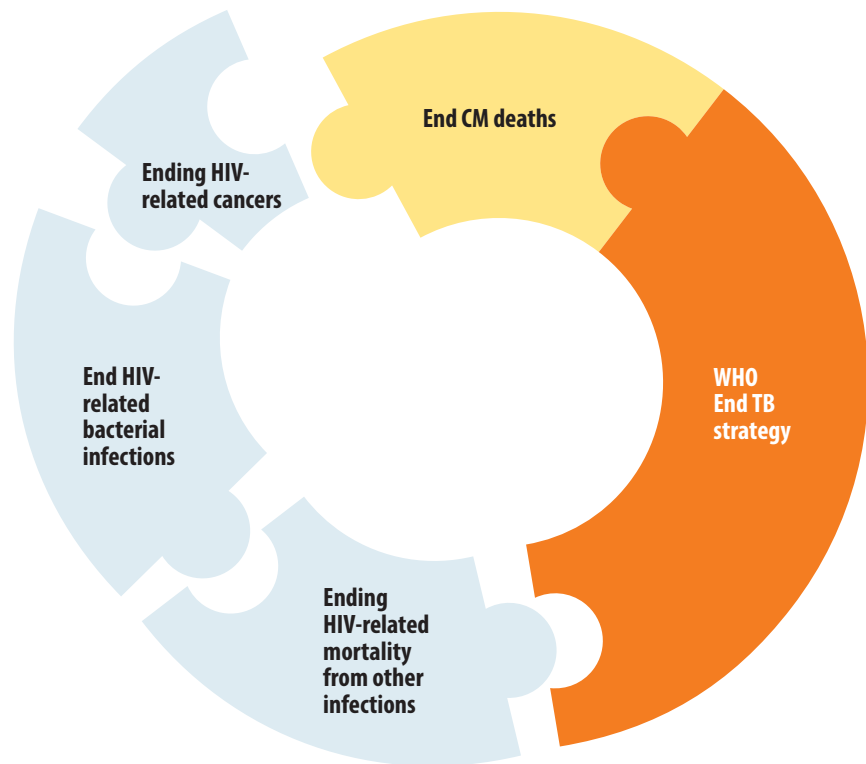
are no other strategic frameworks for addressing the major causes of death among PLHIV. This leaves a gap and may create uncertainty for donors, governments and implementing partners regarding which areas are

of greatest priority for investment. A strategy to end CM deaths by 2030 can help focus attention on the steps needed to end CM deaths and who should be responsible for addressing those steps.

Figure 2: Developing a strategic approach to ending HIV related deaths – the missing pieces of the jigsaw

Current high-level strategies addressing HIV-related deaths (orange), where this proposal fits (yellow), and gaps that could be addressed by others (white). Other key non-bacterial infections include *Pneumocystis pneumonia*, toxoplasmosis (usually in the brain), disseminated histoplasmosis, cytomegalovirus disease and invasive aspergillosis.

The UNAIDS 90-90-90 targets have helped to focus attention on HIV diagnosis, ART scale-up, retention in care and viral load monitoring. Mortality reduction targets, however, have received less attention. Access to diagnostics and medicines to prevent and treat the major opportunistic infections and cancers remains very poor. We need strategies and global targets to address the main causes of AIDS-related deaths.



CRYPTOCOCCAL MENINGITIS: BACKGROUND INFORMATION

CM is a severe opportunistic infection mainly occurring in those with AHD. *Cryptococcus neoformans* or *Cryptococcus gattii*, the causative agents, are present in the environment worldwide. In those people with severely weakened immune systems, these pathogens cause severe disease, typically presenting with CM. Without treatment, CM is almost universally fatal.

Before CM develops, it is possible to detect a component of the *Cryptococcus* capsule (known as an antigen) in the blood, using a simple POC test called the cryptococcal antigen lateral flow assay (CrAg LFA). Providing pre-emptive therapy

with fluconazole to those with a positive serum CrAg early enough can prevent the development of CM.

CM is estimated to have been responsible for 181,100 deaths in 2014. Most of these deaths were preventable. In low- and middle-income countries (LMICs), where management is largely suboptimal, about 70-80% of people with CM die. In high-income countries, where appropriate treatments are more widely used, mortality is around 20-30%. With effective treatment and timely antiretroviral therapy the prognosis of CM is much better (Rajasingham et al, 2017).

See Appendix 1 for a link to WHO guidelines on screening and preventing CM

Screening and pre-emptive therapy for cryptococcal infection

Most countries do not currently implement programmes to screen for and pre-emptively treat those with cryptococcal antigenaemia (see figure 3). Hence the opportunity to identify people with cryptococcal disease early and prevent CM is missed. Before meningitis sets in, there is a short window to prevent it by detecting antigen in blood and preventing progression of disease with fluconazole (French et al, 2002).

Those provided with pre-emptive fluconazole should also receive weekly home visits by lay workers or a similar cadre for the first four weeks on ART, because some will develop meningitis anyway. This group remains at risk of other OIs and may also need help with remaining adherent. Community support of this sort has been found to contribute significantly to mortality reduction (Mfinanga et al, 2015).

Treating CM

The WHO recommends a combination of intravenous amphotericin B and oral flucytosine for one week, followed by one week of high dose oral fluconazole, as induction therapy for the treatment of CM. Where amphotericin B is unavailable or cannot be safely monitored, the alternative WHO-recommended treatment is two weeks of fluconazole and flucytosine.

In LMICs many of those who die are not diagnosed and have no opportunity to receive treatment. Those who are diagnosed most often receive suboptimal treatment – most not gaining access to flucytosine (see figure 4). Although CM is fatal without treatment, access to the current best diagnostics and antifungal drugs can reduce mortality to around 30% (Molloy et al, 2018). In the future, with more effective and less toxic treatment, even more CM deaths could be avoided. (See Appendix 1 for a link to WHO guidelines on treating CM.)



SECTION 2:

MISSED OPPORTUNITIES

While HIV viral load testing in Africa is widespread, CD4 counts are patchy in distribution, especially in locations outside cities. Several different technologies are used, including in a small number of centres the relatively new lateral flow assay (Visitech) which has a <200 cutoff.

COUNTRIES COMPLETELY LACKING ROUTINE ACCESS TO CD4:

According to either **UNAIDS (1 <https://aidsinfo.unaids.org>)** or **GAFFI (2)** or both, patients in the following countries in Africa have no or almost no access to routine CD4 counts:

- Comoros¹
- D.R. Congo¹
- Ghana¹
- Guinea¹
- Madagascar¹
- Malawi²
- Mauritania¹
- Mauritius¹
- Mozambique²
- Niger¹
- Sudan²
- Tunisia¹

Access in many other African countries is likely to be low, but precise data are hard to ascertain, partly because there is so much variation within countries and many gaps in service in remote areas.

In order to improve our understanding of the situation across the continent, we are encouraging countries and labs to collect details of the number of CD4 counts performed annually, and send to info@GAFFI.org, so that we can in future provide a comprehensive picture of current access to CD4 testing in Africa.

Figure 3: Map of provision of CrAg test access across Africa in 2020

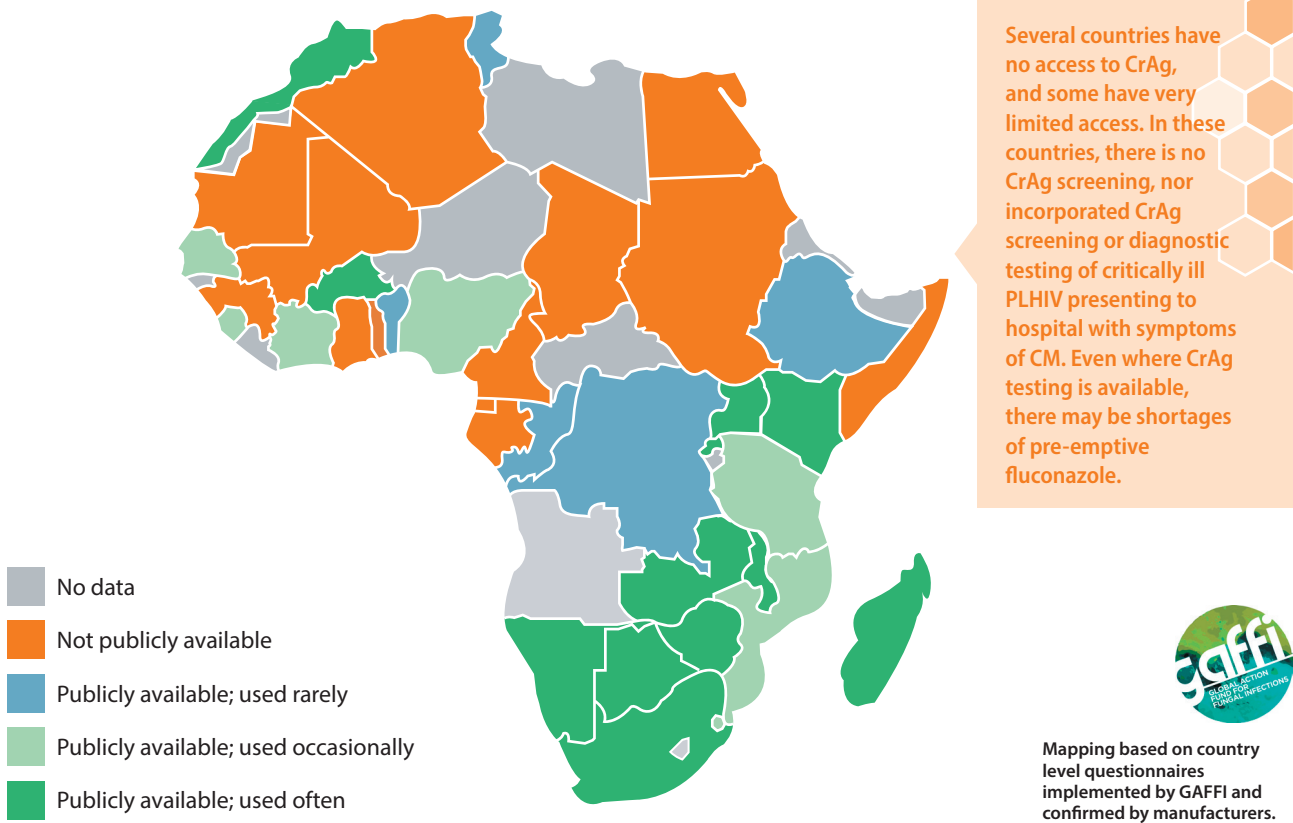


Figure 4: Map of current access to flucytosine for the treatment of CM in Africa March 2021

Flucytosine is registered in very few countries in Africa, although applications have been made in South Africa and several other countries and supplied to Eswatini. Special importation licences are being used on an ad-hoc basis to allow importation in the absence of product registration.

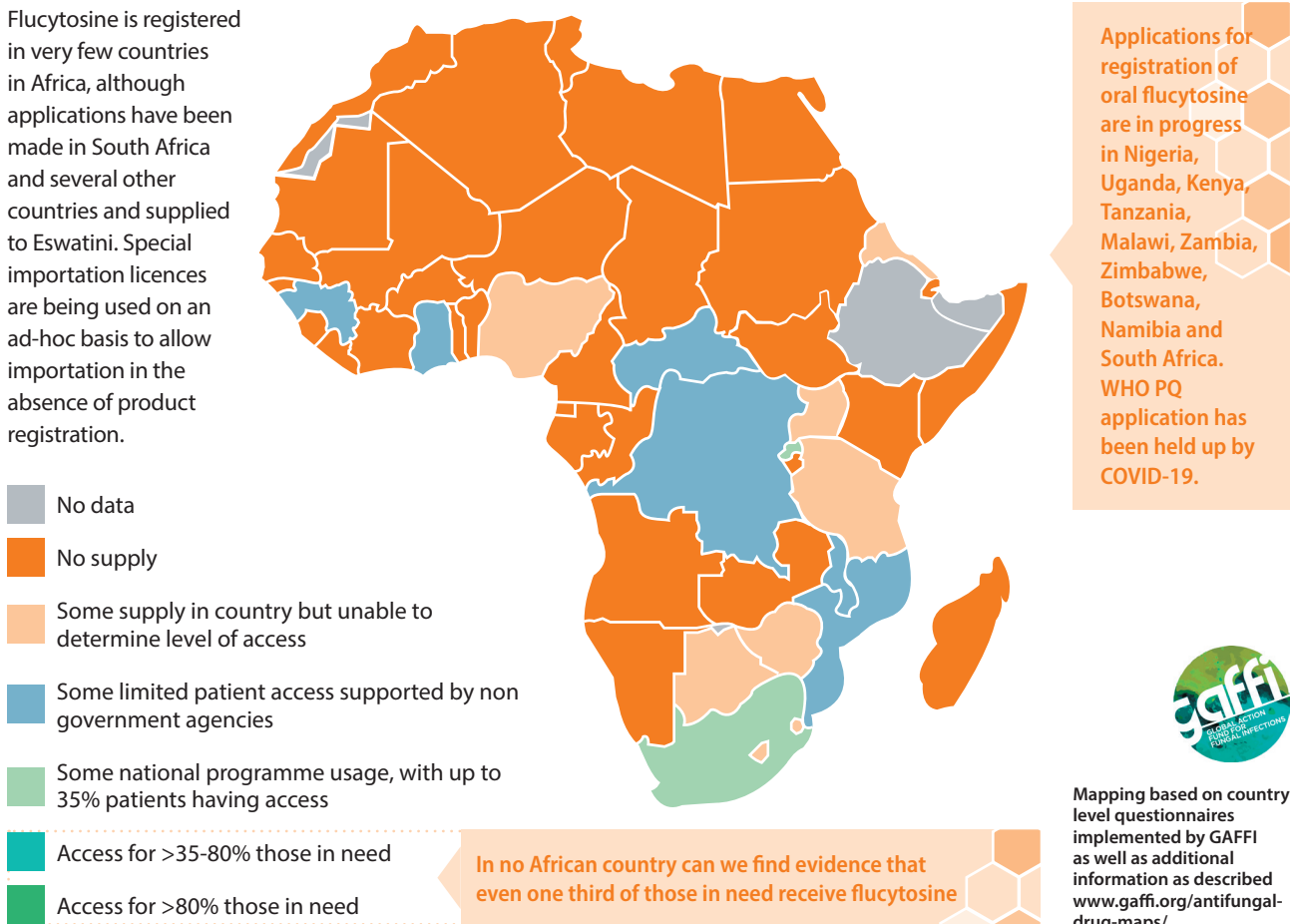


Figure 5: Map of country registration of amphotericin B deoxycholate in Africa in 2020



Liposomal amphotericin B is only available in a small number of African countries, although as Unitaid/ CHAI AHD initiative begins to deliver liposomal amphotericin B to nine countries, it is hoped that patient access will increase in the near future.

These maps can be found at www.gaffi.org/antifungal-drug-maps/ and will be updated on a six monthly basis. If information for your setting or the setting you work in is not shown or not updated please submit an email indicating current status of implementation to info@GAFFI.org



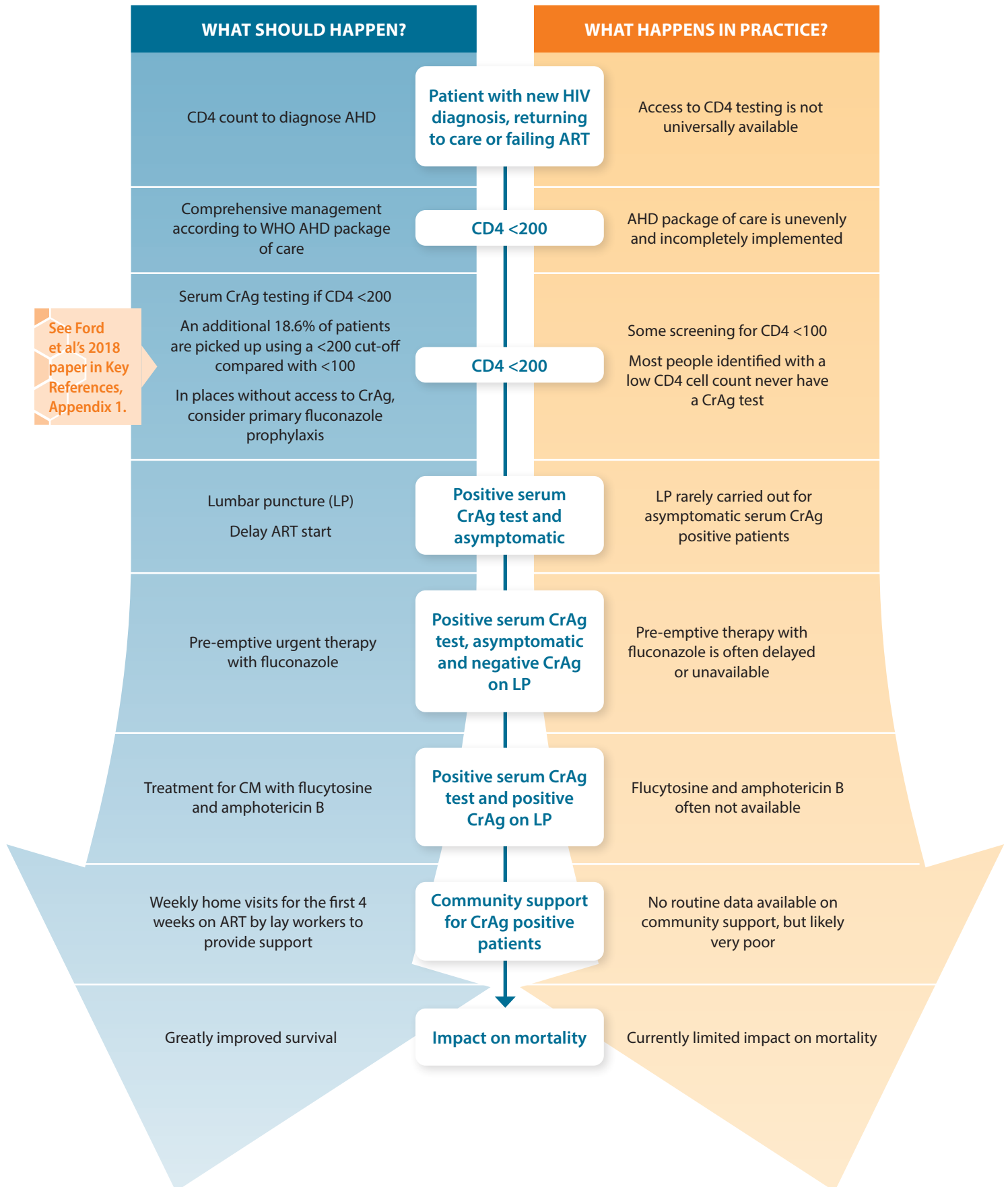
Mapping based on country level questionnaires implemented by GAFFI as well as additional information as described www.gaffi.org/antifungal-drug-maps/

NGO donations and access for limited populations is present in a few countries, notably via Médecins Sans Frontières (MSF). We have, therefore, mapped access according to latest intelligence in the first quarter of 2021.

Amphotericin B deoxycholate is available in the majority of African countries, although supply is intermittent in many. Even if available, it is used routinely for CM in a few locations and often must be paid for out of pocket by the patient.

MISSED OPPORTUNITIES IN THE SCREENING AND PRE-EMPTIVE THERAPY FOR CM IN PEOPLE WITH AHD

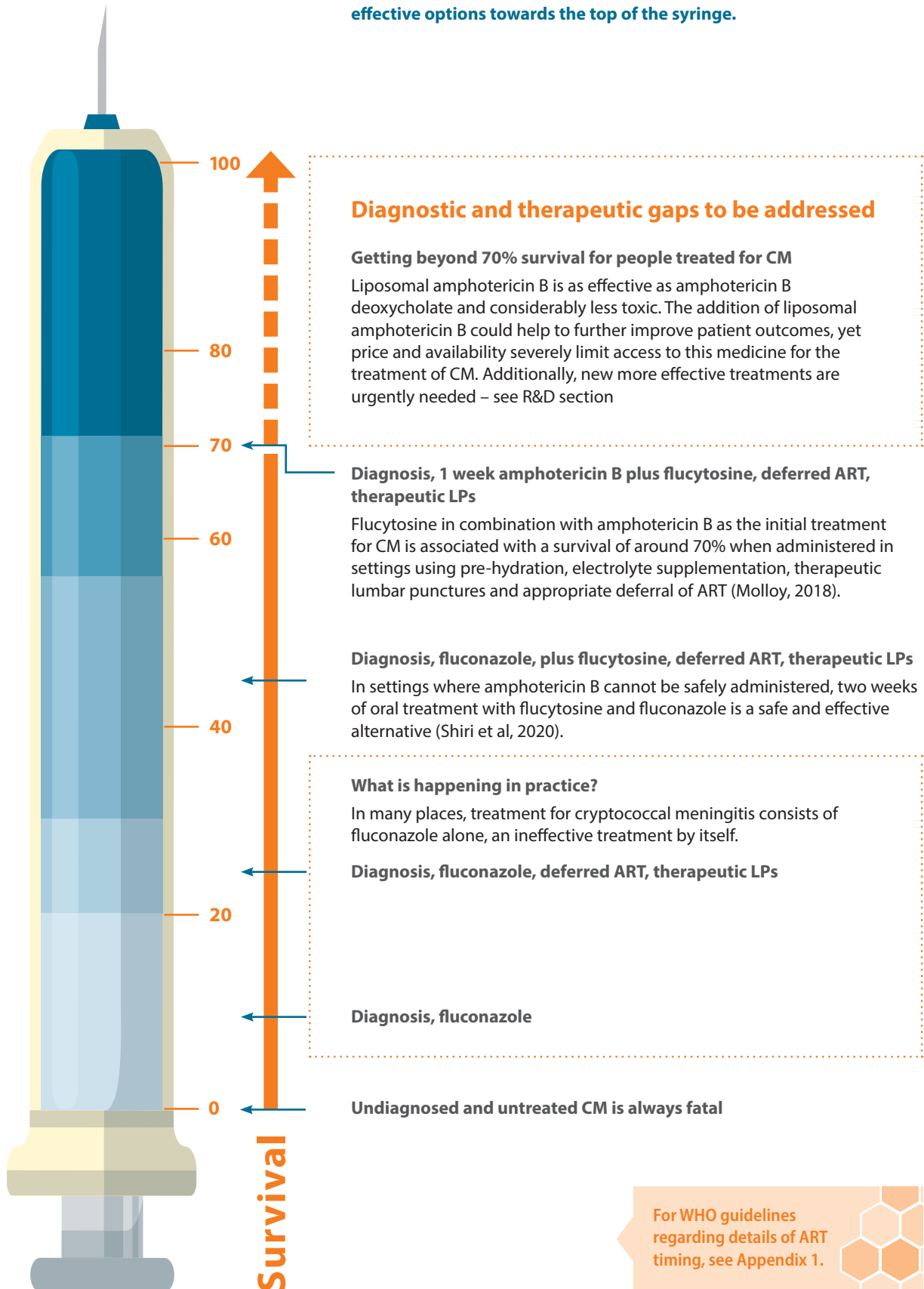
CrAg screening followed by pre-emptive therapy has the potential to prevent a great deal of CM enveloping and in doing so avert many deaths. In reality however this potential is not being realised for the reasons below.



TREATING PEOPLE WITH CRYPTOCOCCAL MENINGITIS: THE IMPLICATIONS OF SUB-OPTIMAL TREATMENTS

Figure 6: CM deaths: aiming for zero

The tools to drastically reduce mortality from CM exist, but they are seldom used. The figure below illustrates this with progressively more effective options towards the top of the syringe.



ADDRESSING THE GAPS

ADDRESSING THE GAPS AT COUNTRY LEVEL NOW

Increase access to CrAg screening:

WHO recommends cryptococcal antigen screening with the CrAg LFA for all PLHIV with a CD4 count <100 and it should be strongly considered for PLHIV with a CD4 count <200.

Screening should also be considered for:

- All PLHIV admitted to hospital (regardless of CD4 count)
- All patients seen in primary care clinics with features of AHD or symptomatic HIV disease

Increase access to CrAg diagnostic testing for CM:

Diagnostic testing for CM consists of a lumbar puncture (LP) and a CrAg test on cerebrospinal fluid. CM can be subtle in its presentation, therefore, CrAg diagnostic testing should be done for all PLHIV with:

- A positive serum CrAg
- Symptoms of meningitis or unexplained headache, especially if CD4 count <200

Address gaps in access to key medicines:

Ensure adequate availability of fluconazole.

When flucytosine is not available, fluconazole is recommended with amphotericin B for induction therapy. Fluconazole is also necessary for consolidation and maintenance treatment for meningitis, as well as for pre-emptive therapy for antigenaemia. Despite having a number of generic manufacturers providing this medication at low cost, it is still frequently unavailable at country-level due to stockouts, supply and budgeting issues.

Register and procure sufficient flucytosine to treat all cases of CM.

Induction therapy with flucytosine and amphotericin B can improve survival by around 40%, compared to fluconazole monotherapy. However, quality-assured flucytosine is registered in very few countries in Africa (although some import waivers have been obtained).

The South African access programme (Shroufi et al, 2020) demonstrates that market failure can be overcome by ensuring communication between and alignment of interests among clients, clinicians, governments and manufacturers. Awareness and medical education will be required to ensure uniform access in every country and district.

Manage CrAg positive individuals who do not have CM:

Pre-emptive therapy often does not occur at all and, when implemented, it is often delayed. It is important that when pre-emptive therapy is used, it is started immediately after a positive serum CrAg is identified, or as soon as possible thereafter.

It is also important to ensure that those treated with pre-emptive therapy in the community also receive regular community follow up (Mfinanga et al, 2015).

For countries to check that all necessary elements for the identification and management of CM are in place, a country-level dashboard is included in Appendix 2.

Amphotericin B deoxycholate must be affordable and accessible.

Amphotericin B deoxycholate, the backbone of WHO-recommended induction therapy (WHO Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children), is frequently not available due to cost (often out-of-pocket), stockouts and limited supply in countries where it is most needed.

Liposomal amphotericin B needs to be readily accessible at an affordable price (\$16.25/vial access price or lower) in those settings where it is most needed.

Liposomal amphotericin B is less toxic than amphotericin B deoxycholate and equivalent in efficacy. However, price and supply challenges limit its use. Moreover, those with renal dysfunction have particular needs for liposomal amphotericin B. Guidelines should define the place for liposomal amphotericin B, and support should be given to help countries set targets for its use. Treatment of CM with a single, high dose of liposomal amphotericin B is a promising option for the future. Results of the AMBITION trial are expected in 2021 (Molefi et al, 2015, see Key References in Appendix 1).

SCREENING COSTS

CrAg screening and pre-emptive therapy with fluconazole for CrAg-positive individuals without meningitis has been found to be

cost-effective across a number of settings (Ramachandran et al, 2017). For the 12 countries with the highest burden of cryptococcal disease, the

cost of implementing this approach for those at highest risk (CD4 count of <100) has been estimated at around **US \$7 million** (Rajasingham et al, 2017).

TREATMENT COSTS

The main drivers of costs are hospital stay and staff costs. Flucytosine containing treatments may reduce duration of hospitalisation. By bringing down hospital stay and staff costs, overall treatment costs come down.

In Figure 8 we show the cost per 1,000 treated patients of four alternative induction therapy options for the treatment of CM in South Africa and Uganda, as examples. The top bar

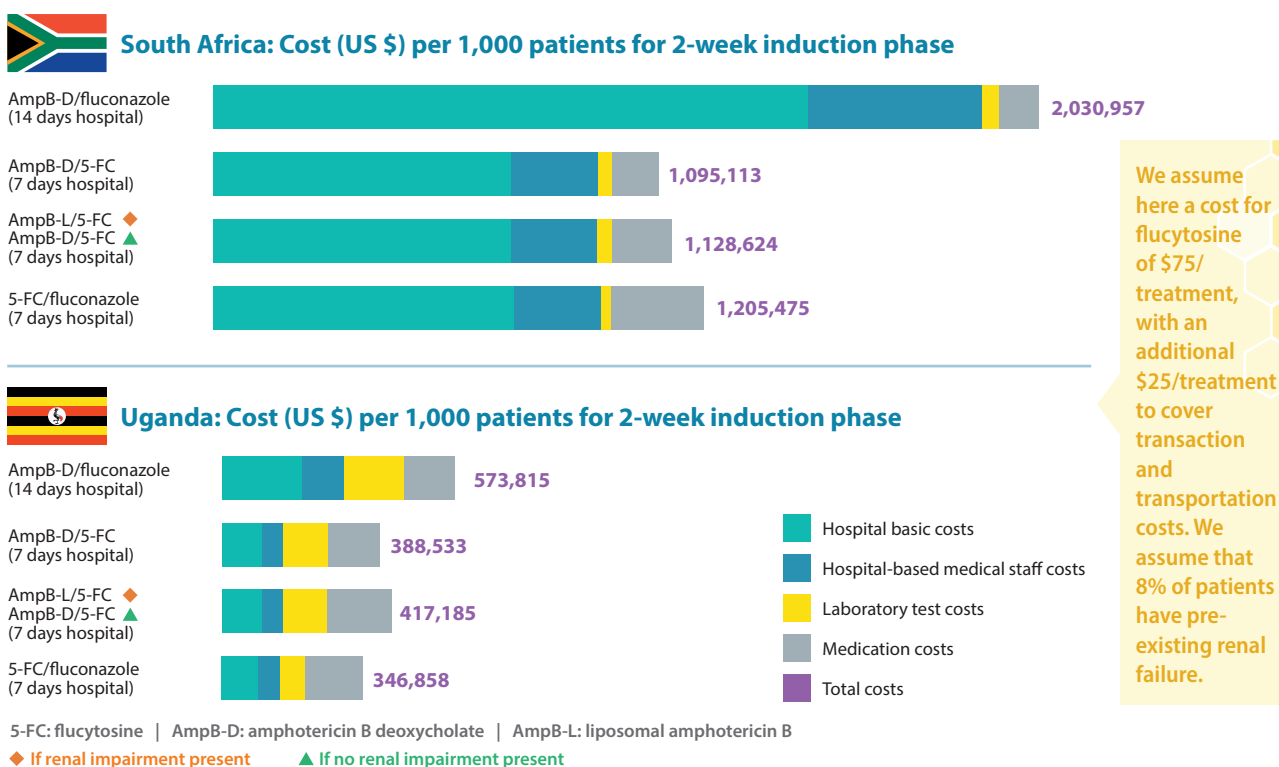
illustrates costs using amphotericin B deoxycholate and fluconazole for 14 days. This is the WHO recommended treatment option in the absence of flucytosine. Hospital basic and medical staff costs (shown in green and blue) are much higher for the 14-day fluconazole-based regimen than for 7-day flucytosine regimens.

Note that treatment with liposomal amphotericin B for those with pre-

existing renal impairment could also be delivered at lower cost than amphotericin B deoxycholate and fluconazole, if it is used in combination with flucytosine.

An open access file and user guide to allow for similar calculations to be developed for any country can be accessed at <https://open.bu.edu/handle/2144/41876>

Figure 8: Cost per thousand treated patients for alternative induction treatments for CM in South Africa and Uganda



Daily costs of medicines that can be used to improve CM management

Drug cost for a day of treatment with flucytosine: \$9.38 (dose of 100mg/kg/day, 10 pills of 500mg/day for a 50kg patient), at a price of \$75.00 per pack (each containing 100 x 500mg pills), assuming an additional 25% on top of medicine costs for customs, insurance and transport costs.




Drug costs for a day of treatment with liposomal amphotericin B: \$60.95 (dose of 3mg/kg/day, 3 vials per day for a 50kg patient), at a price of \$16.25 per vial, assuming an additional 25% on top of medicine costs for customs, insurance and transport costs.

National-level costs of flucytosine for treatment

Across the 12 countries with the highest burden of CM, the combined cost of including flucytosine for CM treatment would be approximately US \$15.27 million.

NECESSARY PROGRAMMATIC APPROACHES ACROSS THE CASCADE OF CARE

Table 1: Delivering screening, prevention and treatment for CM across the health system.

	 COMMUNITY	 PRIMARY CARE	 HOSPITAL
ACTIVITIES			
Community support for asymptomatic CrAg positive patients, some of whom may develop meningitis and need referral, as well as for patients discharged to the community following induction therapy in hospital	Community support provided to CrAg positive patients	Be aware of importance of community support, and ensure that community support is in place for those being managed with pre-emptive therapy	Be aware of importance of community support, and ensure that community support is in place on discharge after treatment for CM
CD4 testing	✓	✓	✓
CrAg screening and pre-emptive therapy	✓	✓	✓
Lumbar puncture (LP) for serum CrAg-positive people	✗	If appropriately trained staff available	✓
CM treatment	✗	Not currently recommended	✓
Integration of package of care for AHD	✓	✓	✓
COMMODITIES			
CrAg supply. Important to have timely and reliable FBC and renal function testing for safe antifungal medicine administration	✗	✓	✓
LP needles	✗	✓/✗	✓
Fluconazole	✗	✓	✓
Flucytosine and amphotericin B, intravenous fluids, potassium supplements, magnesium supplements and manometers	✗	✗	✓
TRAINING			
How to support those managed with pre-emptive therapy	Yes, so community support can be provided	Yes, so that facilities ensure those treated with pre-emptive therapy are referred for community support	Yes, so that facilities ensure those treated with pre-emptive therapy are referred for community support
How to perform a LP*	✗	✓/✗	✓
How to diagnose CM	Yes, able to identify and refer CM cases swiftly	Yes, use of CrAg and symptom screen to identify and refer CM cases swiftly	✓
How to treat CM	✗	Yes, train HCWs in basics of management in case of instances where referral is not possible	Yes, train providers to identify and treat CM cases promptly and safely

Everyone newly diagnosed with HIV and those returning to care after having discontinued ART.

Open access training materials (such as posters, workshops, etc.) for frontline HCWs and local Ministries of Health can be found within the DREAMM project (www.sgul.ac.uk/about/our-institutes/infection-and-immunity/research-themes/working-internationally/dreamms-of-implementation) and Global AHD toolkit (www.differentiatedservicedelivery.org/Resources/Resource-Library/Global-Advanced-HIV-DiseaseToolkit).

*Implementation research is needed to identify the feasibility and role of LP for people who have a positive CrAg test result (recommended in the latest SA HIV guidelines) but do not have symptoms of meningitis.

RESEARCH AND DEVELOPMENT GAPS

Research and development (R&D) investment is often not proportionate to need. Despite CM being responsible for a huge burden of mortality, investment in bringing new treatments to market has been incredibly low. Industry as well as product development partners should urgently work to address the unmet diagnostic and therapeutic needs outlined below.

Diagnostic needs

- More affordable and accurate POC diagnostics for multiple opportunistic infections are needed.
- POC diagnostics that would be able to reliably establish CM cure.
- CrAg diagnostics that predict likelihood of progression to disease can guide treatment choices.

Treatment needs

- More effective pre-emptive treatment options are needed, given that considerable mortality is seen even where screening and pre-emptive treatments are implemented (Wake et al, 2020).
- Amphotericin B is often toxic and needs to be administered by IV infusion. A more effective, ideally all-orally administered, non-toxic version would improve on this.
- Flucytosine must be administered four times per day, so dosing is challenging. A modified, slow release flucytosine formulation is currently under development.
- New therapeutic options that meet the above criteria are also needed.

Where to focus attention

- The time taken from early drug development to demonstrating efficacy in large numbers of people in comparison to a placebo (phase III) trial success can exceed 10 years.
- To address 2030 targets, we need urgent action to rapidly bring pre-clinical or more advanced treatment candidates to phase III trials.

The ideal diagnostic for use in AHD: An affordable, rapid POC test that can diagnose TB, cryptococcal disease and bacterial infection simultaneously.

The ideal treatment for cryptococcal meningitis: An effective, low toxicity, all-orally administered therapy or combination therapy.

SECTION 4:

HIGH-LEVEL TARGETS AND RECOMMENDATIONS

HIGH-LEVEL TARGETS FOR ENDING CRYPTOCOCCAL MENINGITIS DEATHS

Proposed targets for mortality reduction by 2025 are based on what can be achieved with current tools. To achieve 2030 targets, new diagnostics and therapeutic tools will be needed. Proposals are based upon results of an expert workshop involving co-authors.

A 2020 baseline for CM incidence and mortality by country will be developed by the team responsible for 2014 estimates.

Table 2: Proposed CM 2025 and 2030 mortality targets and programme indicators

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%

*2020 baseline is currently being estimated

To support measurable action in these areas, investment in monitoring and evaluation of these indicators is needed, just as there has been for TB-related indicators.



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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 CrAg-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.

APPENDIX 1: KEY DOCUMENTS SUMMARY

KEY GUIDELINES	
WHO Advanced HIV disease (AHD) Guidelines. 2017.	<p>Outlines the package of care (and supporting evidence base) for managing individuals with AHD. Includes recommendations for cryptococcal antigen (CrAg) screening and pre-emptive treatment with fluconazole.</p> <p>https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/</p>
WHO Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. 2018 supplement.	<p>These are the most recent WHO guidelines addressing CrAg screening and CM management.</p> <p>https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/</p>
Southern African HIV Clinicians Society Guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons. 2019 update.	<p>Provides additional detail on some areas of CM management, such as in the use of liposomal amphotericin B.</p> <p>https://sahivsoc.org/Files/crypto%20guidelines.pdf</p>
WHO Information Note: What's New in Treatment Monitoring: Viral Load and CD4 Testing. 2017.	<p>Emphasises the ongoing importance of CD4 in all patients initiating ART, re-entering care and for unstable patients.</p> <p>https://www.who.int/hiv/pub/arv/treatment-monitoring-info-2017/en/</p>
WHO. "The End TB Strategy". 2015.	<p>Sets out a strategic framework for addressing the TB epidemic, both in people with HIV as well as the HIV uninfected.</p> <p>https://www.who.int/tb/strategy/end-tb/en/</p>
KEY REFERENCES	
Ford, Nathan, et al. "CD4 Cell Count Threshold for Cryptococcal Antigen Screening of HIV-Infected Individuals: A Systematic Review and Meta-analysis." <i>Clin Infect Dis</i> . (2018) Mar 4; 66 (suppl_2): S152-S159.	<p>In this study, 6.5% of people with a CD4 count <100 were found to have CrAg antigenaemia, which the authors highlight supports recommendations to screen this group using CrAg LFA.</p> <p>The authors note that of all cases identified at a CD4 <200, 18.6% of those cases were identified at ≤ a CD4 count of 101-200 cells.</p> <p>https://pubmed.ncbi.nlm.nih.gov/29514236/</p>
French, Neil et al. "Cryptococcal Infection in a Cohort of HIV-1-infected Ugandan Adults." <i>AIDS</i> vol. 16, 7 (2002): 1031-8.	<p>This cohort study conducted in Uganda highlights the importance of cryptococcal disease as a major contributor to AIDS mortality (cryptococcal disease associated with 17% of all deaths in this cohort). Median survival from date of diagnosis was 26 days (range 0–138) in cryptococcal meningitis cases, although only 18% of cases had classical signs of meningitis at diagnosis. In asymptomatic CrAg-positive people, CrAg positivity preceded clinical symptoms by a median of 22 days.</p> <p>https://pubmed.ncbi.nlm.nih.gov/11953469/</p>
Mfinanga, Sayoki et al. "Cryptococcal Meningitis Screening and Community-Based Early Adherence Support in People with Advanced HIV Infection Starting Antiretroviral Therapy in Tanzania and Zambia: An Open-Label, Randomised Controlled Trial." <i>Lancet</i> vol 385, 9983 (2015): 2173-82.	<p>Provides evidence for the benefits of CrAg screening and pre-emptive treatment. Those receiving screening for serum cryptococcal antigen combined with antifungal therapy for patients testing antigen positive as well as weekly home visits for the first four weeks on ART by lay workers had 28% lower mortality than the standard of care group.</p> <p>https://pubmed.ncbi.nlm.nih.gov/25765698/</p>

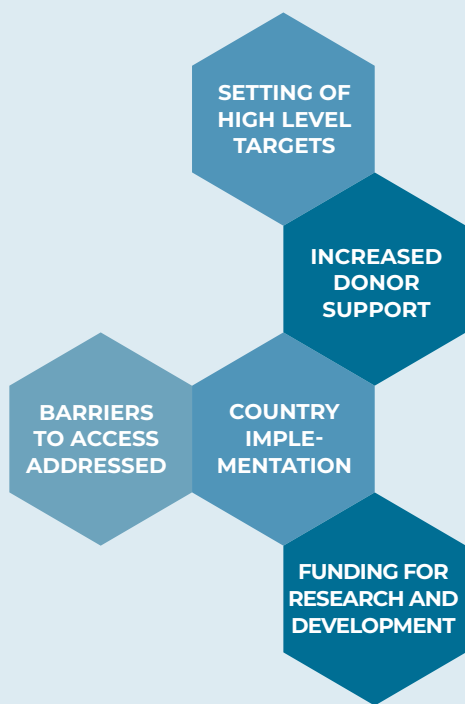
<p>Molefi, Mooketsi et al. "AMBITION-cm: intermittent high dose AmBisome on a high dose fluconazole backbone for cryptococcal meningitis induction therapy in sub-Saharan Africa: study protocol for a randomized controlled trial." <i>Trials</i> vol. 16, 276 (2015).</p>	<p>The AMBITION trial investigates the efficacy, safety and cost-effectiveness of a single high dose of liposomal amphotericin B on a backbone of flucytosine and fluconazole for CM. Data on early fungicidal activity demonstrated non-inferiority; data on mortality are awaited in June 2021.</p> <p>https://pubmed.ncbi.nlm.nih.gov/26081985/</p>
<p>Molloy, Sile F et al. "Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa." <i>The New England Journal of Medicine</i> vol. 378, 11 (2018): 1004-1017.</p>	<p>This landmark trial provides the most robust evidence to date on the optimal treatment of CM and highlights the importance of ensuring that flucytosine is used as part of induction treatment.</p> <p>https://pubmed.ncbi.nlm.nih.gov/29539274/</p>
<p>Rajasingham, Radha et al. "Global Burden of Disease of HIV-associated Cryptococcal Meningitis: An Updated Analysis." <i>Lancet Infectious Diseases</i> vol. 17, 8 (2017): 873-881.</p>	<p>The most robust estimates of the burden of cryptococcal disease currently available. Here it was estimated that there were 223,100 incident cases of CM globally in 2014, with those cases leading to 181,100 deaths, of which 135,900 deaths occurred in sub-Saharan Africa. Analysis is currently being updated.</p> <p>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5818156/</p>
<p>Ramachandran, Anu et al. "Cost-effectiveness of CrAG -LFA Screening for Cryptococcal Meningitis Among People Living with HIV in Uganda." <i>BMC Infectious Diseases</i> vol. 17, 1 225, (2017).</p>	<p>This economic analysis conducted for Uganda found CrAG screening to be highly cost-effective (ICER of \$6.14 per DALY averted compared to no screening). Secondary analysis estimated that 100% screening implementation in Uganda would cost \$651,454 and would avert 1,228 deaths compared to no screening.</p> <p>https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2325-9</p>
<p>Shiri, Tinevimbo et al. "Addition of Flucytosine to Fluconazole for the Treatment of Cryptococcal Meningitis in Africa: A Multi-country Cost-effectiveness Analysis." <i>Clinical Infectious Diseases</i> vol. 70, 1 (2020): 26-29.</p>	<p>Provides the strongest evidence currently available for the mortality reduction that can be achieved by using flucytosine in combination with amphotericin B as induction therapy for CM compared to amphotericin B with fluconazole. Also provides evidence that the use of an all-oral induction regimen of fluconazole and flucytosine may be superior to fluconazole and amphotericin B.</p> <p>https://jhu.pure.elsevier.com/en/publications/addition-of-flucytosine-to-fluconazole-for-the-treatment-of-crypt</p>
<p>Shroufi, Amir et al. "Ending Deaths from HIV-related Cryptococcal Meningitis by 2030." <i>Lancet Infectious Diseases</i> vol. 21 (2021):16-18.</p>	<p>This commentary sets out the basic tenets of reducing deaths from CM in summary form.</p> <p>https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30909-9/fulltext</p>
<p>Shroufi, Amir et al. "Time to Embrace Access Programmes for Medicines: Lessons from the South African Flucytosine Access Programme." <i>International Journal of Infectious Diseases</i> vol. 95 (2020): 459-461.</p>	<p>This paper describes the establishment of the South African flucytosine access programme, which has helped to initiate public sector flucytosine access in South Africa.</p> <p>https://pubmed.ncbi.nlm.nih.gov/32126322/</p>
<p>Wake, Rachel M et al. "Cryptococcal-related Mortality Despite Fluconazole Pre-emptive Treatment in a Cryptococcal Antigen Screen-and-Treat Program." <i>Clinical Infectious Diseases</i> [published correction appears in <i>Clin Infect Dis.</i> (2020) May 23; 70 (11): 2459]. <i>Clin Infect Dis.</i> (2020) 70 (8): 1683-1690.</p>	<p>In this study, comparing outcomes in CrAg positive and negative individuals 17/67 (25%) of CrAg-positive individuals died despite pre-emptive fluconazole treatment, with cryptococcal disease an immediate or contributing cause of death in 12/17 (71%). This work highlights the need for improved treatment options in screen-and-treat strategies.</p> <p>https://pubmed.ncbi.nlm.nih.gov/31179488/</p>

APPENDIX 2: COUNTRY-LEVEL DASHBOARD

Below is a suggested dashboard, to be adapted as needed at the country level, that outlines what should be in place to support adequate CM management in a specified country.

Table A2-1: Suggested core country-level dashboard

	Not achieved	Partially achieved	Fully achieved
SCREENING			
CD4 testing capacity sufficient to test those commencing ART, failing treatment or re-engaging from care			
CrAg tests available and guidelines for use in place			
PRE-EMPTIVE TREATMENT			
Fluconazole for pre-emptive treatment registered and available in sufficient quantity			
TREATMENT			
Flucytosine registered and available in country			
Amphotericin B deoxycholate registered and available in country			
Manometers available for measuring intracranial pressure (ICP)			
Liposomal amphotericin B registered and available in country			
Fluconazole registered and available in sufficient quantity (induction and maintenance, consolidation therapy)			
Adjunctive fluids and oral potassium and magnesium for safe amphotericin B administration registered and available in country			
TRAINING			
Training and mentorship programmes for CM screening and management exist			
MONITORING AND EVALUATION			
Surveillance of CM case fatality in hospitals			
HEALTH SYSTEM STRENGTHENING			
Temperature regulated storage systems in place for Rapid Diagnostic Tests (RDTs) and medicines			
Timely and accurate renal function and full blood count testing available in hospitals delivering CM care			
Cerebrospinal fluid (CSF) biochemistry and fungal culture available in referral centres at minimum			



END CRYPTOCOCCAL MENINGITIS DEATHS by 2030