Advanced HIV Disease: Issue Brief

Unchecked deaths: protecting people living with HIV from cryptococcal meningitis

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1. Introduction

Cryptococcal meningitis (CM) is the second largest killer of people living with HIV (PLHIV) and is one of the most painful ways to die. It was responsible for an estimated 19% of AIDS-related mortality and 112,000 deaths among PLHIV in 2021. (1) Caused by Cryptococcus fungi, a fungus ubiquitous in nature, CM specifically attacks people with suppressed immune systems. Symptoms of CM include the classic symptoms of meningitis: fever, altered mental status, and neck stiffness. People may also present with severe headache, nausea and vomiting, and vision difficulties.

Despite scientific advancements in preventing, diagnosing, and curing CM, it largely goes unchecked, causing a fifth of all AIDS-related deaths over the last decade. (2) CM remains underrecognized, undercounted, under-diagnosed, and under-treated and has failed to receive the programmatic and political commitments that are needed at the national and global levels to reduce its deadly toll.

Inequities in health outcomes

In recent years, the decline in AIDS-related deaths has plateaued despite the consistent scale-up of HIV testing and antiretroviral treatment (ART). This stagnation can be attributed to a variety of factors, including a lack of adequate effort to address advanced HIV disease (AHD) and CM. (3) Civil society-led action has led to growing attention to the urgent need to translate scientific advances and political ambitions into meaningful outcomes for PLHIV. This requires sustained political will and prioritization of CM and AHD to realize the target of reducing annual AIDS-related deaths to under 250,000 by 2025. (4) See Figures 1 and 2.

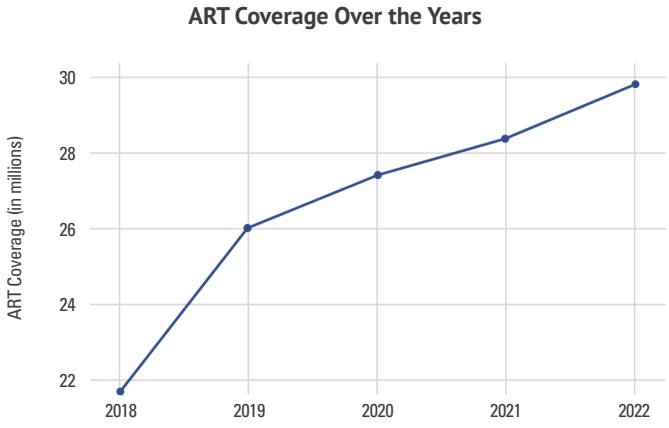


Figure 1

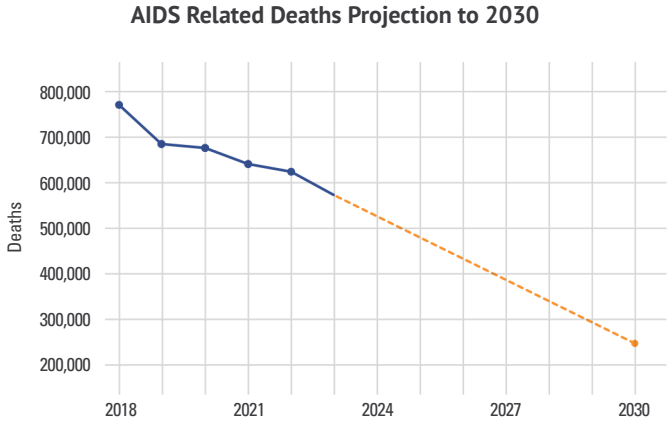


Figure 2

According to a modeling analysis, there were an estimated 152,000 cases of CM in 2022. The mortality rate for CM is approximately 70%, resulting in the loss of 112,000 lives every year. 63% of the deaths due to CM occur in Sub-Saharan Africa. (1) This loss of life persists

despite the scale-up of ARVs, showcasing that more must be done to reduce mortality and morbidity for PLHIV. In fact, evidence suggests that there is no association between ART coverage and mortality from AHD and CM. However, there is a correlation between lower national income and CM-related mortality. (5)

Health outcomes for CM vary widely based on geography according to 1-year mortality rates for those in care: 20-30% in high-income countries (HICs), 40% in middle-income countries (MICs), and 70% in low-income countries (LICs). For those out of care, 1-year mortality is 30%, 60%, and 100% for HIC, MICs, and LICs, respectively. The disparities in health outcomes stem primarily from lack of accessibility, availability, and affordability of optimal interventions for CM. (6)

The World Health Organization (WHO) defines health equity as "the absence of unfair and avoidable or remediable differences in health among social groups". (7) To achieve the goal of health equity, in line with the 2021 UNAIDS report on inequalities, there must be "[e]qual access to rights, [e]qual access to services, [e]qual access to science, [e]qual access to resources" for CM. (8) . Therefore, the WHO developed a public health approach to manage AHD and CM. The guidelines, focused on low- and middle-income countries (LMICs) and resource-limited settings, outline a standardized 'package of care' for people with AHD and CM.

To watch Zikhona's story, scan here:

Zikhona Mboto, New Crossroads, Cape Town, South Africa

"*It was so painful, I thought I was going to die,*" is how Zikhona Mboto described her condition when she went to the hospital in 2019 with a severe headache, neck stiffness, and near blindness. She was diagnosed with CM and was started on an optimal treatment regimen. She recalls the feeling of happiness when she realized that the medication was working and attests to the fact that "*treatment can save your life*". Zikhona made a full recovery following her treatment for CM.

2. Life-saving policies and interventions for CM

"*The path that ends AIDS is not a mystery – it is a policy choice.*" — **Winnie Byanyima**, Executive Director, UNAIDS

2.1 Evidence-based interventions for CM

In 2022, WHO released updated evidence-based recommendations in its "Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV." The guidelines recommend a package of care for optimal diagnosis, treatment, and prevention of CM. (9)

Diagnosing advanced HIV disease

An estimated 30-40% of PLHIV starting ART in LMICs have AHD. AHD is defined by a CD4 count <200 cell/mm3 or a clinical stage 3 or 4 based on symptoms or AIDS-defining illness. (10) However, evidence suggests that clinical staging or symptomatic screening alone has very low sensitivity – meaning they miss too many people who have AHD. (11) Therefore, WHO recommends administering a CD4 count test for all people living with HIV who are entering or reentering HIV care to ensure timely diagnosis of AHD and prompt provision of the AHD package of care. This package of care includes screening, treatment, and prophylaxis for opportunistic infections, including tuberculosis, CM, histoplasmosis, and other bacterial infections.

Screening and preventing CM

The cryptococcal antibody is the body's response to a cryptococcal fungal infection and can be detected with point-of-care tests up to 22 days before symptoms of CM appear. (12)

This gives enough time to screen and intervene for optimal prevention:

- **CM screening:** WHO recommends screening people living with HIV/AIDS using the cryptococcal antigen (CrAg) test. This point-of-care rapid test helps detect cryptococcal antigenemia, indicating a potential infection even in the absence of visible symptoms.
- **Pre-emptive therapy:** WHO recommends pre-emptive fluconazole therapy (800–1200 mg/day for adults and 12 mg/kg per day for adolescents for two weeks) to prevent the development of CM disease for PLHIV who test CrAg positive.
- **Prophylaxis:** Where CrAg testing is not available, WHO recommends that fluconazole prophylaxis should be given to PLHIV until the CD4 cell count rises above 100 cells/mm3. While CrAg screening followed by pre-emptive therapy is preferred, providing fluconazole primary prophylaxis can still help to save lives.

Diagnosing CM

WHO guidelines attribute the gap in health outcomes between high- and low-income countries primarily to a lack of appropriate diagnostics. (10) WHO recommends that people with a positive CrAg test be checked for symptoms of meningitis. If symptoms are present, a lumbar puncture is recommended. When possible, even those without symptoms should consider a lumbar puncture, along with a cerebrospinal fluid examination and a CrAg test (or India ink if the CrAg test is not available) to rule out cryptococcal meningitis.

Treating CM

WHO recommends the following three options for CM treatment, each divided into three phases: induction, consolidation, and maintenance. The regimens, in order of preference, are:

- Single high dose (10 mg/kg) of liposomal amphotericin B (LAmB) with 14 days of flucytosine (100 mg/kg per day, divided into four doses per day) and fluconazole (1200 mg daily for adults). The consolidation and maintenance phase includes fluconazole at 800 mg/day for eight weeks. The regimen is most preferred as it is better tolerated, has fewer adverse effects, and shortens hospital stays.
- Where LAmB is not available, a 7-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day) followed by seven days of fluconazole (1200 mg daily). The consolidation and maintenance phase includes fluconazole at 800 mg/day for eight weeks.
- Where amphotericin B is not available, a flucytosine and fluconazole-based regimen should be initiated.

2.2 From evidence to action

For scientific evidence to impact health outcomes, tools in the WHO-recommended package of care must be optimally scaled up. This requires that countries adopt new guidelines, adapt national policies, and scale up optimal tools and interventions. As policies are vital enablers for bringing optimal interventions to scale, tracking progress across countries and drawing attention to the degree to which governments are aligned with global policy recommendations should help to reduce the time between generation of scientific evidence, revision of WHO recommendations, and policy adoption by national health authorities.

Built in collaboration between the Drugs for Neglected Diseases initiative (DNDi) and HIV Policy Lab, **the AHD Dashboard** tracks, visualizes, and compares policy adoption for CM across the care continuum and alignment with international norms. It draws information from legal documents, government reports, and independent analyses.

The AHD dashboard:

- Tracks the incorporation/adoption of evidence-based and optimal interventions for CM across the care continuum into national policies as a way to measure policy progress;
- Visualizes policies as maps and dashboards by policy, country, and region to identify gaps and make comparisons more accessible; and
- Provides users – including duty bearers, civil society organizations, and other stakeholders – with compelling policy data and allows them to make comparisons across countries.

Currently, the dashboard consists of the dataset, a reference library, and visualizations of policies in eastern and southern Africa and western and central Africa for CM. Going further, the dashboard will be updated on a yearly basis, capturing year-on-

year longitudinal developments and highlighting the impact of policy uptake. Simultaneously, the dashboard will be expanded to include a broader geographical scope and additional conditions associated with AHD.

Please see **Annex 1** for an overview of HIV Policy Lab methodology.

3. State of national policies in sub-Saharan Africa

The HIV Policy Lab mapped CM-related policies in 46 countries in sub-Saharan Africa, including 21 countries in Eastern and Southern Africa (ESA) and 25 in Western and Central Africa (WCA). Relevant documents were found for 35 countries. Overall, we found that policy alignment was better in ESA than in WCA.

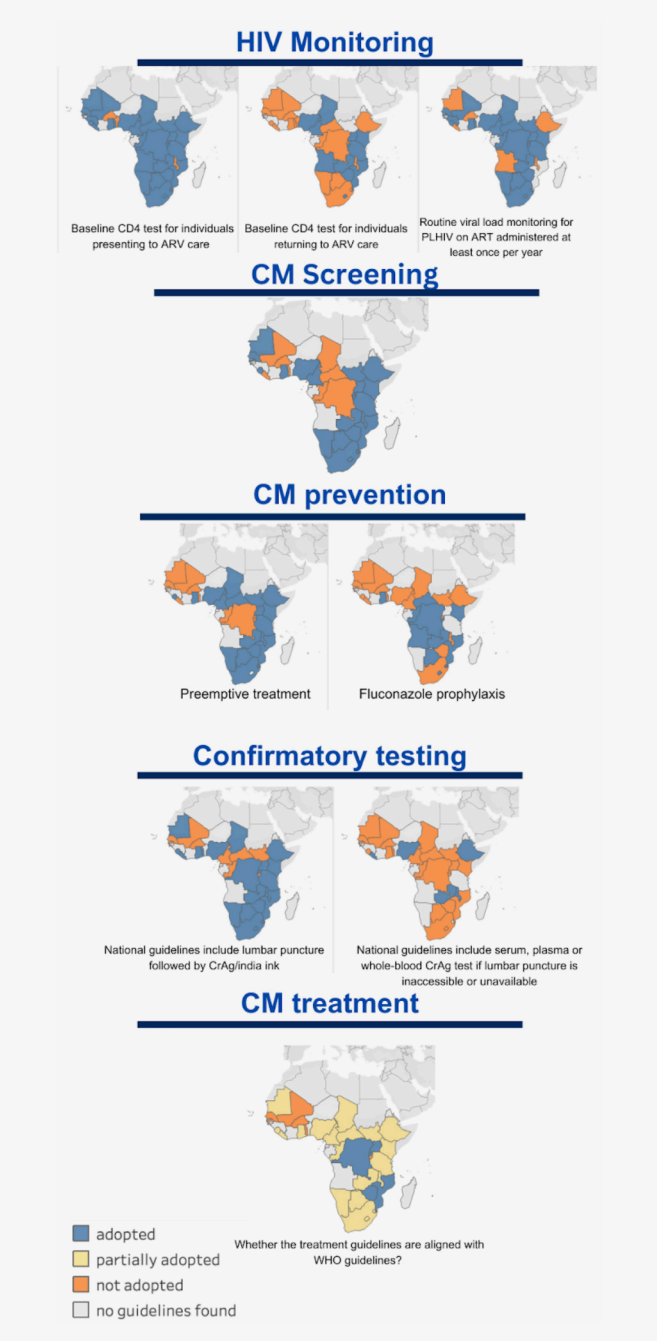
Eastern and Southern Africa

In ESA, relevant guidelines were found for 17 of 21 countries. Of these, Zambia, Mozambique, and Kenya adopted 11 of 13 policies, while South Africa, Rwanda, and Malawi adopted only 7 policies. 16 countries require baseline CD4 testing, in keeping with WHO guidelines, but five lack guidelines on CD4 testing for people reentering HIV care. All countries in ESA have adopted the CrAg test as a screening tool, acknowledging its cruciality.

Despite the 2022 WHO guidelines strongly recommending a single high dose of LAmB as part of the preferred induction regimen for the treatment of CM for PLHIV, only 4 countries adopted it; 7 adopted amphotericin B-based therapy, and 2 continue to recommend fluconazole-based monotherapy only. Regarding medicines included in countries' national essential medicines list (EML), LAmB is the least adopted of the medicines needed for optimal treatment, with only Mozambique including it in its EML for CM.

Western and Central Africa

The policy scenario in WCA is quite different. Overall policy adoption for CM and AHD remains low. In WSA, relevant guidelines were found for 18 of 25 countries. Out of the 18 countries, 15 have adopted baseline CD4 testing for people entering care; 13 countries are aligned with regular viral load testing, but only 3 countries explicitly require CD4 testing for people reentering HIV care. CrAg screening for all PLWA is adopted by only 7 countries. Pre-emptive and prophylactic fluconazole therapy is adopted by only 6 and 5 countries, respectively. 8 countries have adopted lumbar puncture followed by CrAg/India ink testing for confirmatory diagnosis of CM, but only 2 countries provide guidance for scenarios where lumbar puncture is not available. Lastly, for treatment of CM, only the Democratic Republic of Congo has adopted the WHO-preferred LAmB induction therapy; 9 have adopted amphotericin B-based therapy.



Challenges:

1. **We need to raise awareness:** Civil society, clinicians, global health actors, and allies in government must continue to raise awareness of the scale of needless pain and suffering caused by CM and hold governments and global health actors accountable to end the invisibility of CM and AHD-related deaths.

2. **We need data:** There is a dearth of data on AHD/AIDS-related morbidity and death. Work to win government and health actors' commitments to increase coverage with optimal CM treatment, for example, or to reduce deaths from CM, is hindered by the fact that WHO, countries, and programs do not regularly include associated indicators in programmatic monitoring, evaluation, and reporting at the individual, program, national, regional, and global levels.

3. **We need to implement the science:** The AHD/AIDS landscape is changing very rapidly: several new research initiatives have shown how to improve health outcomes. The AMBITION trial led to the roll-out of the LAmB based regimen for treatment of CM, which is better tolerated, has fewer adverse effects, and shortens hospital stays.

4. **We need to diagnose AHD:** CD4 testing remains critical for diagnosing AHD/AIDS, which is essential for linking individuals to the life-saving AHD package of care in a timely manner. Clinical staging and symptom screening are not enough, and miss too many people with AHD. (13)

Call to Action

Translating scientific advances and political ambitions into meaningful health outcomes for PLHIV and realizing the target of reducing annual AIDS-related deaths to under 250,000 by 2025 requires sustained political will and prioritization of CM and AHD. This requires multi-stakeholder cooperation.

We call all stakeholders to come together and get the word out: CM and AHD need not be a death sentence if we:

1. **Scale up interventions, including through policy change, to ensure access to the optimal continuum of care and save lives.**
2. **Monitor implementation to ensure that adopted policies are implemented and made available at the point of care.**
3. **Ensure access to care and advocate for accessible and affordable products.**

About us:

The Drugs for Neglected Diseases initiative (DNDi) is an international not-for-profit medical research organization that discovers, develops, and delivers safe, effective, and affordable treatments for neglected people. DNDi's cryptococcal meningitis program aims to develop an improved formulation of flucytosine and remove barriers to access for the two key medicines for CM in LMICs.

The HIV Policy Lab (www.hivpolicylab.org) is a collaboration between Georgetown University, UNAIDS, the Global Network of People Living and others, which systematically gathers, monitors and tracks the adoption status of 33 globally recommended laws and policies for 194 countries. The aim is to improve uptake of evidence-based policies by providing a better picture of which countries are rapid adopters of such policies, as well as which are lagging and why. It uses the data to evaluate not only the status of adoption of international norms in national policies but also the correlation between such national policies and HIV outcomes. It is a tool for accountability in support of uptake of evidence-based policies.

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Please find the AHD Dashboard on advancedhiv.org

Citations:

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Annex 1: The HIV Policy Lab Methodology

Developing Indicators: we have identified and developed 8 indicators, with sub-indicators, based on the WHO guidelines, to track the policy progress in CM. The indicators track the adoption of evidence-based interventions across the continuum of care and are grouped under six categories: HIV monitoring, screening, pre-emptive treatment, diagnostics, treatment, and AHD and CM-related medical products on the national essential medicines list. The indicators are included in the Appendix 1.

The AHD Dashboard focuses on countries in sub-Saharan Africa due to the high burden of CM in the region. We compile national policy data by aggregating information from a wide range of primary sources, including national HIV treatment and testing policy documents, AHD policies and essential medicines lists. The data will be updated on a yearly basis and our repository will ensure that the data is publicly available.

Each policy is benchmarked against the WHO guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV, to interpret and code based on whether a policy is adopted, partially adopted, or not adopted. For all indicators for which there are data, the total of adopted [1] and partially adopted [0.5] is divided by the total number of indicators scored. This scoring metric assigns a quantitative score to convey the degree to which countries' policies are aligned with WHO guidelines.

The database is supported by a set of visualization tools– a web page with a summary on CM, a dynamic map that allows for visualizations of the indicators across countries, a table with multi-colored dots that represent the adoption status for countries – targeted towards advocates, governments, donor agencies, and so on.

Annex 2: Indicators and coding rules

Eight indicators were developed to track the uptake of medical tools required for optimal management of CM. The indicators and the coding rules are listed below.

CATEGORY	INDICATOR	CODING RULE
1. HIV monitoring	Do national guidelines require a baseline CD4 test, followed by a routine schedule of follow-up testing, for all newly diagnosed PLHIV?	*Adopted* (1): National guidelines require newly diagnosed PLHIV to be offered a CD4 test, followed by repeat testing at 6 months and then yearly. *Not Adopted* (0): National guidelines do not require a CD4 test for newly diagnosed PLHIV.
	Is a baseline CD4 test offered to all PLHIV who are returning to care?	*Adopted* (1): National guidelines require all PLHIV returning to care to be offered a CD4 test. *Not Adopted* (0): National guidelines do not explicitly state that all PLHIV returning to care be offered CD4 test.
	Do national guidelines recommend conducting viral load monitoring at least annually for PLHIV on ART?	*Adopted* (1): National guidelines require viral load monitoring for all PLHIV with viral suppression at least once a year. *Not adopted* (0): National guidelines do not require routine viral load monitoring or recommend less frequent routine viral load monitoring.
2. CM Screening	Do the national guidelines offer CrAg screening for all PLWA (CD4<200 mm3?	*Adopted* (1): National guidelines recommend the screening of all PLWA* for CrAg prior to initiating or reinitiating ART. *Not Adopted* (0): National guidelines do not require all PLWA be screened for cryptococcal antigen before ART initiation or reinitiation. [*WHO guidelines provide that all people with CD4 count below <100/mm3 should be screened while those with CD4 count <200 cells/mm3 may also be considered for CrAg screening]
3. CM pre-emptive treatment	3.1 Pre-emptive treatment: the national guidelines support initiating pre-emptive fluconazole therapy* for CrAg+ individuals? 3.2 Prophylaxis: the national guidelines support fluconazole primary prophylaxis for all with CD4<100 mm3?	*Adopted* (1): National guidelines recommend preemptive antifungal therapy (fluconazole 800–1200 mg/day for adults and 12 mg/kg per day for adolescents for two weeks), followed by consolidation and maintenance fluconazole therapy for all PLWA* or with a positive CrAg be given. *Not Adopted* (0): National guidelines do not require all PLWA* or those who test positive for CrAg be given preemptive antifungal therapy. [*WHO guidelines provide that all people with CD4 count below <100/mm3 should be screened while those with CD4 count <200 cells/mm3 may also be considered for CrAg screening.]
4. Testing	4.1 Confirmatory test: Does the national guidelines include the definitive test for CM – lumbar puncture followed by CrAg/india ink? 4.2 Confirmatory test: If lumbar puncture is inaccessible or unavailable-serum, plasma or whole-blood CrAg test.	*Adopted* (1): National guidelines recommend lumbar puncture with rapid CSF CrAg assay or India Ink test, unless contraindicated, as the preferred diagnostic approach. *Not Adopted* (0): National guidelines do not offer any recommendations regarding confirmatory tests for CM.
5. Treatment	Do the preferred regimens for CM included in national guidelines align with WHO recommendations?	*Adopted* (1): The national guidelines recommend a single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) as the preferred induction regimen for treating people with cryptococcal meningitis. *Partially adopted* (.5): The national guidelines require a seven-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by seven days of fluconazole (1200 mg daily for adults and 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). Or the national guidelines provide for 14 days of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) + flucytosine (100 mg/kg per day, divided into four doses per day). *Not Adopted* (0): The national guidelines do not include any of the WHO-recommended regimens for treatment of CM.
6. Key medical products on the national essential medicines list (NEML)	Does the NEML include the four key products – fluconazole, flucytosine, amphotericin B, and liposomal amphotericin B -for treatment of CM?	*Adopted* (1): The NELM list includes all 4 products – fluconazole, flucytosine, amphotericin B and liposomal amphotericin B – to treat CM. *Partially Adopted* (.5): The NELM includes at least one out of four key products to treat CM. *Not Adopted* (0): The NELM list does not include any of the 4 key products to treat CM.

Abbreviations: CM = cryptococcal meningitis; CrAg = cryptococcal antigen; NEML = national essential medicines list; PLWA = People living with advanced HIV disease; PLHIV = People living with HIV