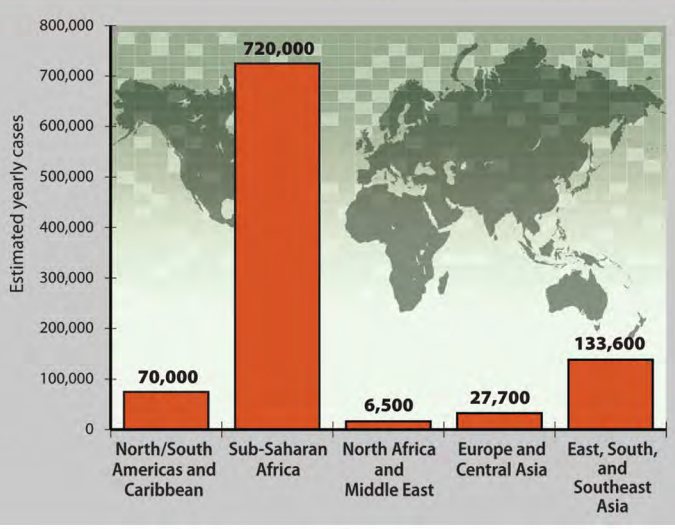
CRYPTOCOCCAL MENINGITIS: A DEADLY FUNGAL DISEASE AMONG PEOPLE LIVING WITH HIV/AIDS

Cryptococcal meningitis (CM) is a life-threatening brain infection caused by the inhalation of *Cryptococcus* spores, a fungus found worldwide in soil. CM primarily affects people with weakened immune systems. CM is the most common cause of meningitis in adults in sub-Saharan Africa,[1] and a leading cause of death among people living with HIV. The disease, which is not transmitted from human to human, accounts for 20-25% of AIDS-related mortality,[1] and occurs mainly in people living with HIV with CD4 T-cell counts below 100 cells/µL.[6,7] While no vaccine currently exists, important new tools enable earlier detection, more effective treatment and drastic reductions in morbidity and mortality due to CM.

"In our clinics, diagnostic tests for cryptococcal meningitis are unavailable; even if we suspect someone is infected, most of the medicines needed to treat the disease are not available anyway. We urgently need to see diagnostic tests rolled out by countries, and treatment needs to be affordable and better adapted to field contexts."

Dr Claudios Muserere ; MSF doctor, Nyanga district -Zimbabwe



Global Disease Burden: Worldwide, an estimated one million new cases of CM occur annually. The majority of cases occur in sub-Saharan Africa, with substantial numbers of cases in Asia and South America as well. In some areas, between 6-20% of new HIV/AIDS patients present with CM.[8,9] Most cases occur among adults, with children infrequently affected. Despite the expansion of antiretroviral therapy (ART), CM continues to be a highly lethal infection, causing an estimated 625,000 deaths per year.[1] Patients are at risk of developing CM both prior to initiation of ART, when their immune system remains depressed, and in the immediate post-ART period due to cryptococcal immune reconstitution inflammatory syndrome (IRIS)

Figure 1: Estimates of the global disease burden of CM.[1,2]

New WHO Guidelines: An important step toward reducing the burden of cryptococcal disease

In 2011, the World Health Organization released *Rapid Advice on Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children*.[5] The guidelines, based on the latest research, recommend screening at risk persons (HIV-positive, with CD4<100) for cryptococcal disease using tests that detect cryptococcal antigen (CrAg), including a novel dipstick assay (see below) with subsequent treatment if early disease is identified. The guidelines also provide valuable updates on diagnosis and treatment of cryptococcal disease. These guidelines are an important step forward in improving the prompt diagnosis and management of cryptococcal disease, providing countries with clear recommendations to adapt and implement (available at: http://www.who.int/hiv/pub/cryptococcal_disease2011/en/).[5] Comprehensive guidelines are expected to be released by early 2014.

Screen and Treat – a new strategy that saves lives

In a targeted screening program, high-risk (CD4<100) people living with HIV are tested for CrAg before starting ART. CrAg is detectable in blood weeks to months[3] before symptomatic meningitis develops, allowing for early disease detection through screening. CrAg-positive patients are then treated with high-dose oral fluconazole to prevent the infection from progressing to meningitis. Treatment continues until their immune system recovers with ART and is able to control the disease. This approach is now recommended by WHO in areas of high disease burden[5], and can help save lives.

Rapid and accurate cryptococcal diagnosis

Tools for diagnosis of cryptococcal disease are not available in many resource-limited countries or are limited to less sensitive methods of detection such as the India Ink test. CrAg testing, which detects unique markers on the capsule of *Cryptococcus*, is a newer diagnostic technique that can be performed in blood and cerebrospinal fluid (CSF). Older CrAg tests, while extremely sensitive and specific are expensive, and require extensive laboratory infrastructure and training.

LFA in South Africa

South Africa is leading the way in providing care for CM in resource-limited settings, and has implemented screening for cryptococcal disease among people living with HIV with CD4<100. Blood samples with CD4<100 are automatically tested for cryptococcal antigen using the LFA.[2,4]

A new rapid "dipstick" antigen test, the lateral flow assay (LFA), is available in resource-limited settings and offers important improvements over current tools. The LFA is more sensitive than traditional methods, inexpensive ($2 to $4 per test)[12,13], easy to use, provides results in less than ten minutes, and can be stored at room temperature. The LFA is licensed for use in serum and CSF, but validation is being performed on whole blood and urine, which may facilitate the use of the LFA as a point of care test.

The LFA has the potential to dramatically improve access to cryptococcal diagnosis in resource-limited settings, and improve outcomes through targeted screening for early infection in high-risk individuals. Screening for CrAg using the LFA, with subsequent antifungal treatment in persons with a positive LFA test, provides the opportunity to treat cryptococcal disease before its deadly progression to the brain. This approach has been shown to be a cost effective intervention that save lives.[10]

Treatment of CM: new evidence and new guidance

Treatment of CM involves three phases: induction, consolidation and maintenance.

- **Induction** clears the organism quickly from the body and usually lasts 2 weeks
- **Consolidation** fully suppresses the disease and typically lasts 8 weeks
- **Maintenance** (or secondary prophylaxis) prevents recurrence of the disease until a person's immune system recovers and treatment is no longer needed.

Treatment covering all three phases can last a year or more, depending on the rapidity of immune system recovery (as measured by CD4 count). WHO guidelines recommend amphotericin B and flucytosine as the preferred induction treatment regimen. Where flucytosine is not available, such as is the case in many resource-limited settings, fluconazole may be used in conjunction with amphotericin B for induction. Fluconazole at varying doses is the recommended antifungal treatment for consolidation and maintenance therapy (see overview of treatments below).

Symptoms of CM

Headache ✓
Fever ✓
Neck pain ✓
Nausea and vomiting ✓
Sensitivity to light ✓
Confusion or coma ✓

Amphotericin B deoxycholate is an intravenous medication that has been used since the 1950s for the treatment of many invasive fungal infections. It can also be obtained in lipid-based formulations which include: liposomal amphotericin B, amphotericin B lipid complex (ABLC), and amphotericin B colloidal dispersion (ABCD).

Flucytosine is an antifungal drug, originally developed in 1957 and is available in both oral and intravenous forms. Flucytosine should not be administered alone for induction therapy due to the development of drug resistance.

Fluconazole is an antifungal drug that was US FDA approved in 2000. Fluconazole is available in both oral and intravenous forms.

Efficacy

Survival is greatest when patients with CM are treated with amphotericin B and flucytosine in the induction phase. All current cryptococcal meningitis guidelines recommend amphotericin B-based antifungal regimens as first line induction therapy due to the associated survival benefit (see **Figure 2**), followed by fluconazole only as consolidation and maintenance therapy.[5] Fluconazole monotherapy is sub-optimal for treatment of patients with CM in the induction phase, and should only be used in settings where amphotericin B is not available.

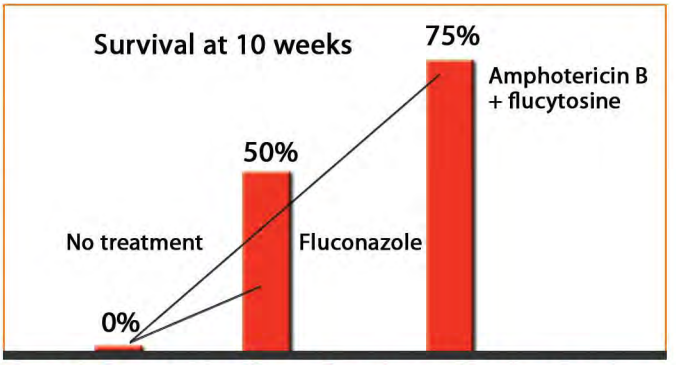


Figure 2: Comparative efficacy of cryptococcal treatment regimens

Safety

Monitoring of patients undergoing antifungal treatment for CM is essential, especially during the induction phase. Proper clinical training and awareness of common side effects of antifungal medications used in the treatment of CM is the first step (see **Table 1**).

CM treatments and associated side effects

During induction with amphotericin B, the risk of renal toxicity and electrolyte imbalances can be minimized with a regimen of intravenous hydration with potassium containing solution. Alternatively tablets of potassium can be given orally. Monitoring of renal function (creatinine), potassium levels, and hemoglobin levels should be done at regular intervals and results should inform clinical care during induction.

Both flucytosine and fluconazole can cause liver damage and care should be taken to monitor patients on these medications for liver toxicity (abdominal pain, jaundice, nausea), especially among patients on other drugs that can cause liver damage (e.g. INH for TB) or in persons with pre-existing liver damage (e.g. cirrhosis). If symptoms of liver toxicity are present, hepatic function tests should be evaluated. Fluconazole has multiple drug interactions, including with TB medications such as rifampin. Evaluation of persons with TB/CM co-infection in order to minimize drug-drug interactions is critical. Fluconazole is contraindicated in the first trimester of pregnancy due to concerns about birth defects.

Barriers to reducing burden of cryptococcal disease

Although important new tools are available to effectively detect and treat early disease in high-risk populations and efficacious drugs exist to treat life-threatening meningitis, these are often unavailable or not used where they are needed most.

Considerable barriers to access exist for the drugs used to treat CM, including limited or single source manufacturing, high prices and lack of registration and availability in countries with the highest disease burden.[11] **Table 1** (see below) illustrates the prices of antifungal drugs in selected countries. Not only are there great variations in pricing, in many cases, the drugs are not registered and not readily available at country level.

Table 1 In-country prices paid for anti-fungal drugs (reported in US$ and unit price)**

Drug and Dosage	*Iran*	*Namibia*	*Russia*	*Tanzania*	*UAE*	*Uganda*	*Vietnam*	*South Africa*
AmB 50 mg vial	$4.20	N/A	$0.52- $14.79	N/A	N/A	$7.97-$8.76	$13.76	$2.60
5FC 250 mg vial	N/A	N/A	$14.65	N/A	N/A	N/A	N/A	N/A
5FC 500 mg capsule	$0.56	N/A	N/A	N/A	$62.62	N/A	N/A	N/A
Fluconazole 50 mg capsule	N/A	N/A	$1.00- $ 4.16	N/A	N/A	N/A	N/A	N/A
Fluconazole 100 mg capsule	$0.06	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fluconazole 150 mg capsule	N/A	$1.80	$2.04-$ 14.40	$0.38-$0.56	$5.58-$11.84	N/A	$0.26-$0.43	N/A
Fluconazole 200 mg capsule	N/A	N/A	N/A	N/A	$24.10-$42.34	$0.40-$3.19	N/A	$1.16-$6.98

**All pricing data for Table 1 has been provided by Global Action Fund for Fungal Infections (GAFFI), www.gaffi.org, and National Institute for Communicable Diseases (NICD) in South Africa. Price range of specific drugs were provided when a range was available, with the lowest price usually reflecting that of generic formulations. The prices listed are reported from supplier level in those countries, they do not reflect procurement prices; these products are not necessarily quality-assured.

Table 2 shows the cost of two weeks of induction treatment for CM, per WHO guidelines[5], using four country examples, Iran, Russia, South Africa and Vietnam. All prices are reported in US dollars and the lowest reported in-country price from Table 1 has been used to calculate the price.

Table 2 Cost of two-weeks induction treatment for CM (in US$)

Country	Cost of 14 days AMB[1]	Cost of 14 days of 5FC[2]	Cost of 14 days of Flucaonzole[3]	Total cost of induction
South Africa	$43.52	N/A	$95.76	**$139.28**
Iran	$71.40	$94.08	N/A	**$165.48**
Russia	$8.84	N/A	$224	**$232.84**
Vietnam	$233.92	N/A	$19.50	**$253.42**

[1]AMB dose 1mg/kg/day for 60 kg patient
[2]5FC dose 100mg/kg/day for 60 kg patient
[3]High dose Fluconazole (800mg/day) used when 5FC not available for induction

Current barriers include:

- Limited surveillance data – a lack of systematic data collection on burden of disease limits accurate forecasting for drug demand which is needed for pharmaceutical manufacturers and to ensure enough drugs are available for patients.
- Although there have been recent decreases in price for essential antifungal medicines, prices remain relatively high, particularly flucytosine and amphotericin B, in part due to lack of competition.
- Lack of registration for flucytosine and amphotericin B in regions of the world where disease burden is highest, particularly in Africa and Asia, hindering drug entry into the country.
- Absence of screening for latent cryptococcal disease as recommended by WHO guidelines.
- Poor dissemination of improved diagnostics, such as the LFA.

What needs to be done?

Countries:

- Rapidly adapt new WHO guidelines to local contexts, and integrate into existing national guidelines.
- Implement screening for cryptococcal infection in people living with HIV with CD4 count below 100 cells/μL
- Ensure availability of antifungal medicines and monitoring tools recommended for CM treatment.
- Improve drug forecasting through collection of better data on cryptococcal disease burden in-country.
- Incentivize generic pharmaceutical companies to manufacture antifungal medications used in treatment of CM, particularly for flucytosine and amphotericin B.
- Rapidly validate, register and distribute the LFA for use.

WHO:

- Develop clinical training materials for the management and treatment of cryptococcal disease based on the new WHO guidelines.
- Include in WHO Expression of Interest (EoI) list antifungal medicines to diversify manufacturer base and induce price reductions from competition.

Manufacturers:

- Increase investment in research & development for new products and formulations better adapted to low-resource contexts (e.g. oral formulations).
- Register key cryptococcal medicines widely to facilitate access.
- Consider rapid manufacture and market entry of additional generic versions of flucytosine and amphotericin B.

Funders:

- Support funding for purchase of prompt diagnostics and essential medicines.
- Support countries to implement new CM treatment guidelines.
- Support countries to implement cryptococcal screening and treatment activities
- Prioritize cryptococcal diagnostic, screening and treatment activities.

Non-governmental implementers:

- Support rapid implementation of new WHO guidelines in country.
- Create an international pricing guide to improve transparency of prices reported by manufacturers.

Patient advocacy groups:

- Engage manufacturers and in-country policy makers for access to cheaper antifungal medicines and more effective diagnostics.
- Engage law-makers to help ensure laws allow for increased market entry of generic manufacturers.

"At large South African hospitals, 8 in 10 patients with CM are treated with amphotericin B. Despite this, 1 in 3 die in hospital. To prevent these deaths, we need to diagnose disease earlier (i.e. before meningitis). Screening for the presence of cryptococcal antigenaemia is a cost-effective way to save lives."

Dr. Nelesh Govender, Head of the Mycology Reference Laboratory at South Africa's National Institute for Communicable Diseases (NICD)

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