

# CRYPTOCOCCAL SCREENING

A New Strategy for Saving Lives among People with HIV/AIDS



National Center for Emerging and Zoonotic Infectious Diseases  
Division of Foodborne, Waterborne, and Environmental Diseases

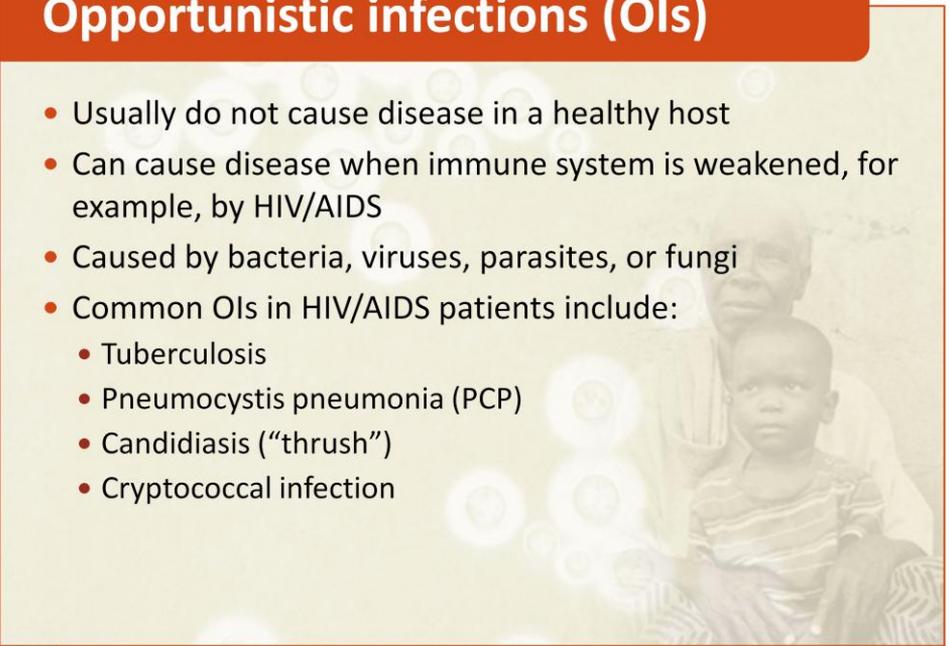


Cryptococcal Screening.

A New Strategy for saving lives among people with HIV/AIDS

## Opportunistic infections (OIs)

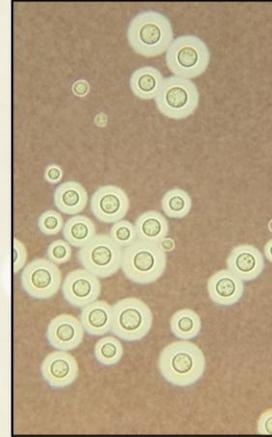
- Usually do not cause disease in a healthy host
- Can cause disease when immune system is weakened, for example, by HIV/AIDS
- Caused by bacteria, viruses, parasites, or fungi
- Common OIs in HIV/AIDS patients include:
  - Tuberculosis
  - Pneumocystis pneumonia (PCP)
  - Candidiasis (“thrush”)
  - Cryptococcal infection

 Cryptococcal Screening Program

Opportunistic infections usually do not cause disease in a healthy host, but can cause disease in people when the immune system is weakened, for example, by HIV/AIDS. These infections can be caused by many different organisms, including bacteria, viruses, parasites, or fungi. Common opportunistic infections in HIV/AIDS patients include tuberculosis, *Pneumocystis pneumonia*, candidiasis, and cryptococcal infection. This presentation will focus on the large public health burden of cryptococcal infection, and a new strategy to prevent death among HIV-infected persons.

## Cryptococcal infection

- Caused by inhalation of spores from the fungus *Cryptococcus*
  - Found in soil, bird droppings
- Incubation period unknown, can be dormant for many years
- Reactivation in immunosuppressed (HIV/AIDS, especially CD4<100)
- No person-to-person transmission

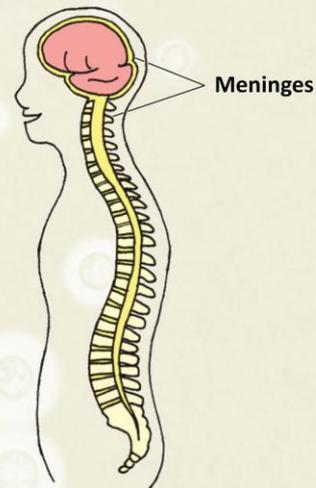


India Ink microscopy of *Cryptococcus*

Cryptococcal infection is caused by inhalation of spores from the fungus *Cryptococcus*, which is found in soil, especially soil contaminated with bird droppings. The incubation period is not known, but it is thought that the infection can remain dormant in the body for many years. In immunosuppressed persons, particularly HIV-infected persons with CD4 counts under 100, the infection can reactivate and spread throughout the body. There is no person-to-person transmission of this infection.

## Cryptococcal meningitis (CM)

- Cryptococcal infection usually presents as meningitis
- Most common cause of adult meningitis in most of sub-Saharan Africa
- Requires hospitalization and treatment with intravenous (IV) amphotericin B



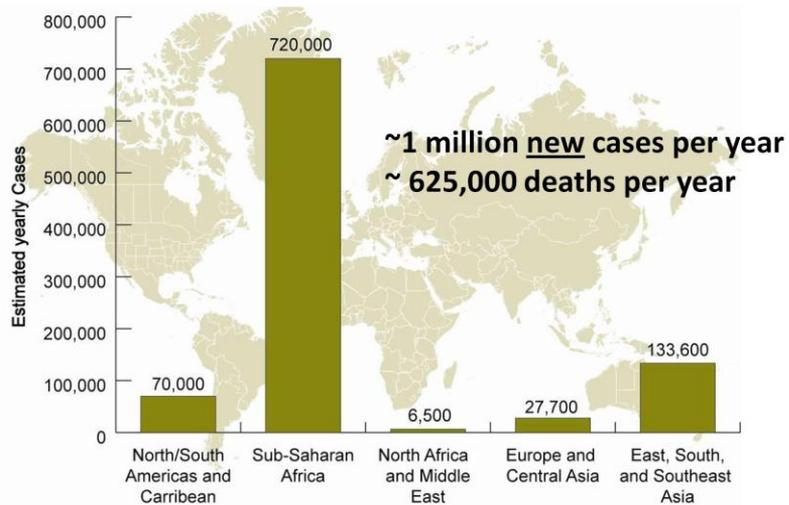
Cryptococcal infection usually presents as meningitis, which is a swelling of the meninges, the tissues that protect the brain and spinal cord as shown here in the diagram on the right. Cryptococcal meningitis, abbreviated as CM, is the most common cause of adult meningitis in most of sub-Saharan Africa. The condition requires hospitalization and treatment with the intravenous (IV) antifungal medication amphotericin B.

## Half of all CM patients die

- In low-resource settings, one-third to one-half of all CM patients die
- Why is the death rate so high?
  - Patients present with disease too advanced for treatment to be effective
  - CM can occur even after patients with advanced HIV begin anti-retroviral treatment
  - Medication needed to treat CM (amphotericin B) is expensive or unavailable

In low-resource settings, one-third to one-half of all patients with CM will die from it. There are several reasons that the death rate is so high in these areas of the world: first, patients often present with disease that is too advanced for treatment to be effective. Second, CM can occur even patients with advanced HIV begin anti-retroviral treatment. Third, amphotericin B, the medication that is needed to treat CM is very expensive or not available in these areas of the world; as a result, many patients with CM are treated sub-optimally.

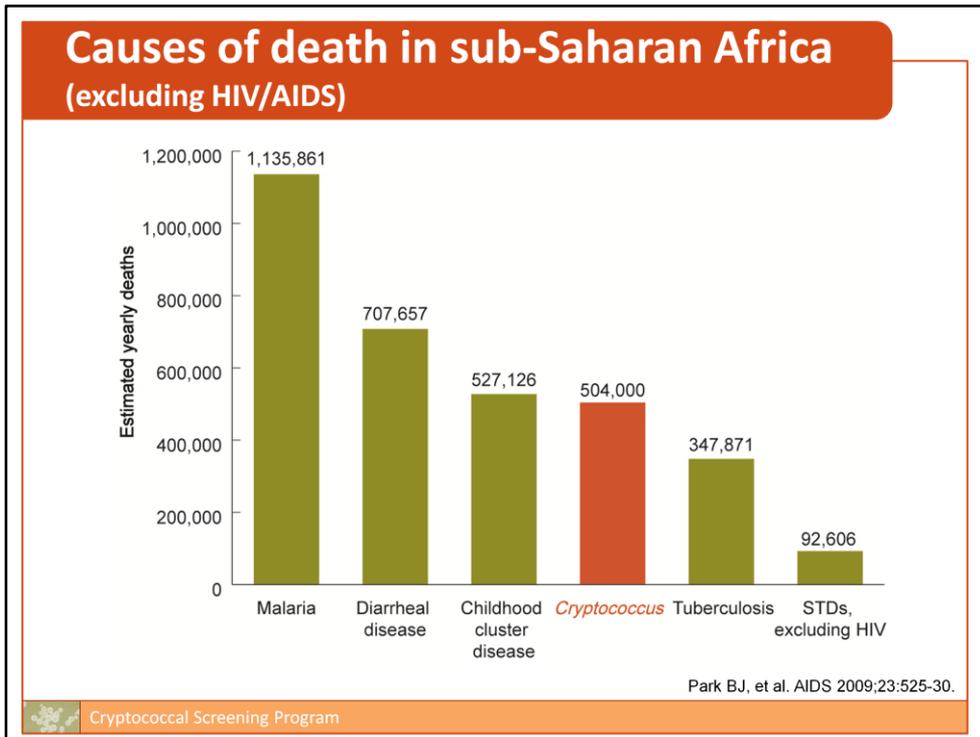
## Global burden of HIV-related CM



Park BJ, et al. AIDS 2009;23:525-30.

Cryptococcal Screening Program

This slide shows the global burden of HIV-related CM. Worldwide, there are approximately 1 million new cases and 625,000 deaths from CM each year. As you can see, sub-Saharan Africa has the highest number of estimated cases per year, followed by East, South, and Southeast Asia.



This figure shows the leading causes of death in sub-Saharan Africa, not including HIV/AIDS. Each year, *Cryptococcus* is believed to cause more deaths than tuberculosis in this area of the world.

## Preventable CM deaths

- Of all CM patients admitted to a hospital
  - One-third will die in the hospital
    - More than half of those who survive their hospital stay will die post-discharge
  - Three-quarters will have had a prior diagnosis of HIV
  - One-third % will have already started ART

*Preventable CM*

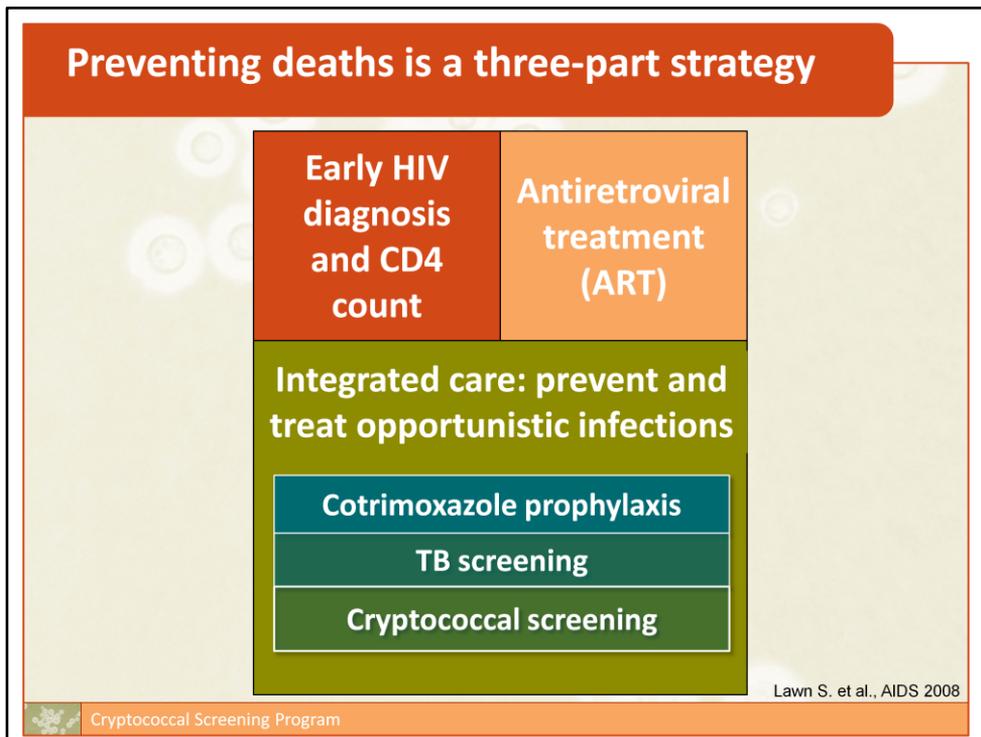
This slide shows the proportion of deaths from CM that may be prevented. Of all patients admitted to a hospital with active CM, one-third of them will die in the hospital, and more than half of the patients who survive their hospital stay will die after being discharged. Of this same group of all patients admitted to a hospital with active CM, three-quarters of them will have had a prior diagnosis of HIV, and one-third of them will have already started ART. This is the group of people in which deaths due to cryptococcal meningitis are preventable.

## Reducing deaths by preventing cryptococcal meningitis

- Copenhagen Consensus 2011 – The Ranking by the Expert Panel
  - “Prevent cryptococcal meningitis” on list of top HIV/AIDS priorities
- WHO “Rapid Advice” for the Diagnosis, Prevention, and Management of Cryptococcal Disease
  - First guidelines to conditionally recommend cryptococcal screening



There has recently been increased attention to reducing HIV/AIDS-related deaths by preventing cryptococcal meningitis. In 2011, the Copenhagen Consensus, a group of the world’s leading economic experts, included “prevent cryptococcal meningitis” on their list of top global HIV/AIDS investment priorities. In December 2011, the World Health Organization released their “Rapid Advice” guidelines for the Diagnosis, Prevention, and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents, and Children. These guidelines are the first ever to conditionally recommend cryptococcal screening as a strategy to prevent deaths due to CM.



Preventing deaths due to cryptococcal infections can be thought of as part of a larger, three-part strategy to reduce HIV/AIDS-related deaths. The first component is HIV diagnosis and CD4 testing, and the second part is access to antiretroviral treatment. Cryptococcal screening fits into the third component, as part of a larger integrated care strategy to prevent and treat other opportunistic infections. This is similar to cotrimoxazole prophylaxis and TB screening.

## Cryptococcal screening

- What is screening?
  - A strategy to detect disease in people who do not yet have signs or symptoms of the disease

 Cryptococcal Screening Program

Now we will talk about cryptococcal screening. What is screening? A general definition of screening is: a strategy to detect disease in people who do not yet have signs or symptoms of the disease.

## What makes a good screening program?

- Disease should be an important public health issue
- Need an appropriate screening test
- Early treatment (of asymptomatic disease) should be more effective than treatment of symptomatic disease
- Screening should be cost-effective

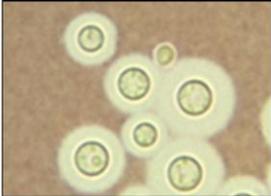
So, what makes a good screening program? A few of the most important points are shown here. We have just discussed the reasons why cryptococcal disease is an important health issue.

## What makes a good screening program?

- Disease should be an important public health issue
- Need an appropriate screening test
- Early treatment (of asymptomatic disease) should be more effective than treatment of symptomatic disease
- Screening should be cost-effective

The second component of a good screening program is that there should be a test that can detect the disease before patients develop signs and symptoms.

## Traditional methods versus antigen detection

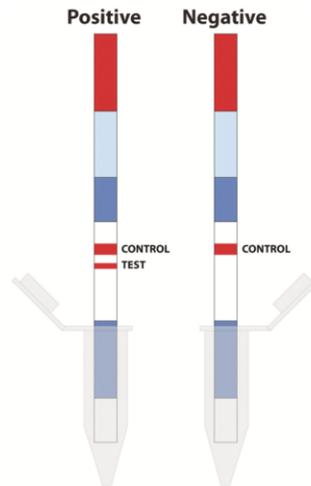
TRADITIONAL METHODS in resource-limited settings		ANTIGEN DETECTION
MICROSCOPY	CULTURE	
<ul style="list-style-type: none"><li>• India Ink staining</li><li>• Less sensitive</li></ul>	<ul style="list-style-type: none"><li>• Less sensitive</li><li>• Requires days to weeks for final results</li></ul>	<ul style="list-style-type: none"><li>• Sensitive &amp; specific</li><li>• Potential use in urine, whole blood</li><li>• Use before symptom onset</li></ul>
		

Cryptococcal Screening Program

This new antigen detection test has several advantages over traditional methods that are available in resource-limited areas for detecting *Cryptococcus*, which include microscopy and culture. Both of these methods have limited sensitivity, which means that the test is not always positive in people with the infection. Also, culture can take weeks to obtain a final result. In contrast, antigen detection is highly sensitive and specific, and the results are available quickly. The dipstick is currently being validated for use in urine and whole blood. This would allow for diagnosis to occur at the point-of-care and would increase access to cryptococcal diagnostics in resource-limited settings. Most importantly, the test can be positive in patients who do not yet have symptoms of meningitis, which makes it the ideal test to be used for screening.

## A new test for detecting cryptococcal disease

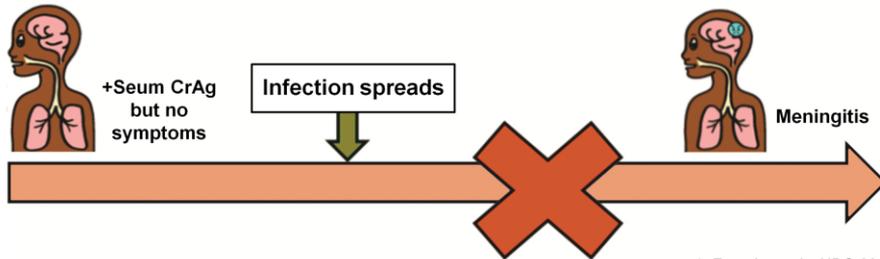
- The new dipstick test is:
  - Simple and quick  
*Results in 10 minutes*
  - Accurate  
*Highly sensitive, accurate (>95%)*
  - Affordable  
*\$2-4 per test*
- Detects cryptococcal antigen (CrAg) in serum and cerebrospinal fluid (CSF)



Recently, a new dipstick test has been developed for detecting cryptococcal disease. The test is simple to use, and the results are available in 10 minutes. It is accurate over 95% of the time, and it costs approximately \$2 to \$4 per test. The test works by detecting cryptococcal antigen (abbreviated “CrAg”), an indicator of infection, in serum (a component of blood) and in cerebrospinal fluid (CSF).

## Cryptococcal antigen (CrAg)

- Antigen test can detect CrAg in serum a median of 22 days (range: 5-234) before symptoms of meningitis develop<sup>1</sup>
- CrAg is highly predictive of who will develop CM
- Possible to identify early cryptococcal disease, prevent progression to meningitis through early treatment



1. French et al., AIDS 2002

Cryptococcal Screening Program

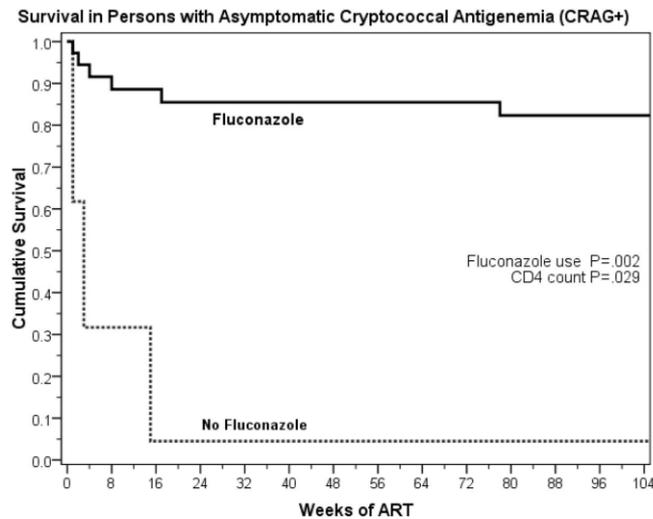
The antigen test can detect cryptococcal antigen in serum a median of 22 days before symptoms of meningitis develop. The presence of CrAg in the serum is highly predictive of who will develop meningitis. This means that there is a window of time where cryptococcal disease can be identified early and treated in order to prevent the early, asymptomatic infection from progressing to meningitis.

## What makes a good screening program?

- Disease should be an important public health issue
- Need an appropriate screening test
- Early treatment (of asymptomatic disease) should be more effective than treatment of symptomatic disease
- Screening should be cost-effective

The third component of a good screening program is that early treatment of asymptomatic disease should be more effective than treatment of later, symptomatic disease.

## Survival of people with asymptomatic cryptococcal antigenemia starting ART



Meya et al., CID 2010

Cryptococcal Screening Program

This is a survival curve showing outcomes for a group of people with asymptomatic cryptococcal antigenemia starting ART. The solid line shows that a large percentage of people survived among those who were treated with fluconazole. The dashed line shows that a very low percentage of people survived among those who did not receive fluconazole.

## What makes a good screening program?

- ✓ Disease should be an important public health issue
- ✓ Need an appropriate screening test
- ✓ Early treatment (of asymptomatic disease) should be more effective than treatment of symptomatic disease
- ✓ Screening should be cost-effective

The last component of a good screening program is that the screening should be cost-effective.

## Cost-effectiveness of screening

- Depends on the prevalence of antigenemia, and is likely to be cost-effective in populations where the prevalence of antigenemia is greater than 3%<sup>1</sup>
- South Africa: 98 patients screened to identify 1 CrAg-positive patient, at a cost of \$206<sup>2</sup>
- Uganda: using latex agglutination, \$190 to prevent one CM case, \$266 to prevent one death<sup>1</sup>
- Uganda: using lateral flow assay, \$28 to prevent one CM case, \$40 to prevent one death, \$1.57/per disability-adjusted life year saved.

1. Meya et al., CID 2010; 2. Jarvis et al., CID 2010; 3. Rajasingham et al., J AIDS 2012

Cryptococcal Screening Program

One study showed that 3% prevalence of cryptococcal antigenemia is the breakpoint at which the point at which the cost of treating CM with amphotericin B is greater than the cost of screening. This means that cryptococcal screening is likely to be cost-effective in populations where the prevalence of antigenemia is greater than 3%. A study from South Africa showed that 98 patients needed to be screened to identify 1 CrAg-positive patient, at a cost of \$206. In Uganda, screening using the latex agglutination test cost \$190 to prevent one CM case, and \$266 to prevent one death. Estimates from Uganda that using the lateral flow assay for screening would cost \$28 to prevent one CM case and \$40 to prevent one CM death, which translates to \$1.57 per disability-adjusted life year saved.

## Fluconazole donations

- Since 2000, Pfizer's Diflucan Partnership Program present in 63 countries in Africa, Asia, Latin America, and the Caribbean
- Provides fluconazole free of cost to governments and non-governmental organizations
- Countries with HIV prevalence >1% may be eligible
- Indications: cryptococcal meningitis and esophageal candidiasis

 Cryptococcal Screening Program

Since 2000, Pfizer's Diflucan Partnership Program has worked in 63 countries to provide fluconazole free of cost to governments and non-governmental organizations in order to treat patients with cryptococcal meningitis or esophageal candidiasis. Countries where the HIV prevalence is greater than 1% may be eligible to participate in this program, which further increases the cost-effectiveness of cryptococcal screening. You can find more information about Pfizer's program online at: <http://www.directrelief.org/DiflucanPartnership/EN/DiflucanProgramOverview.aspx>.

## Implementing a cryptococcal screening program

- Who should be screened?
  - All HIV/AIDS patients
  - HIV/AIDS patients starting ART
  - HIV/AIDS patients with a particular CD4 count
    - CD4 < 200
    - CD4 < 150
    - CD4 < 100

Cryptococcal Screening Program

Now that we've talked about why cryptococcal screening is an important public health intervention, I'd like to talk in more detail about some practical considerations when implementing a cryptococcal screening program.

One of the first decisions to make when implementing a screening program is: who should be screened? HIV/AIDS patients are at highest risk in the pre-ART period when their CD4 counts are low. Patients with CD4 less than 100 are at highest risk: more than 80% of CrAg-positive cases occur in this group. However, a smaller sub-set of infections occur in patients with CD4 between 100 and 200, and rarely can occur in patients with higher CD4 counts. Should all HIV/AIDS patients be screened or only those who are beginning ART? If CD4 count is used to identify the highest risk group for screening, what CD4 cutoff should be used?

## Where should patients be screened?

- Laboratory
  - Test done automatically by the laboratory (reflex)
  - Test ordered by health care provider
- Point-of-care
  - Using point-of-care CD4 to identify high risk patients
  - Using WHO stage to identify high risk patients

Another central question is where cryptococcal screening should take place: in the laboratory or at the point-of-care? If a laboratory method is chosen, the test can be done automatically by the lab, which is also called a reflex test. Alternatively, the test can be ordered by the health care provider. The other approach is point-of-care testing, which could be done in parallel with point-of-care CD4 testing, or using WHO stage to identify high-risk patients.

## Reflex laboratory-driven screening strategy



CD4 <100



- **Advantages:** minimizes extra blood draws, not provider-initiated, test results received with CD4 count
- **Disadvantage:** delays in receiving CD4 result would result in delay of CrAg test result

In a reflex laboratory-driven strategy, leftover plasma from CD4 count testing can be used to test for cryptococcal antigen. In a strategy targeted to those at highest risk, only samples found to have a CD4 count less than 100 would be tested automatically. The advantages of this method are that it minimizes extra blood draws on the patient, health care providers don't have to remember to order the test, and the CrAg test results can be received at the same time as the CD4 count. A disadvantage of this strategy is that any delay in CD4 reporting would also result in delays to receiving the CrAg test result.

## What about a point-of-care (POC) screening strategy?

- POC crypto screening will only be possible when the new CrAg test has been validated for use in whole blood and / or urine
- Could occur in combination with POC CD4 testing or with WHO stage of HIV infection in settings where POC CD4 testing is not available
- **Advantage:** minimize patient loss to follow-up and treatment delays
- **Disadvantage:** lack of quality control

 Cryptococcal Screening Program

Given the recent interest in point-of-care (POC) CD4 testing, it is hopeful that screening for *Cryptococcus* at the point-of-care will be possible in the future. This will only be possible once the new CrAg test has been validated for use in whole blood or urine. POC CrAg screening could occur in combination with POC CD4 testing, or in combination with the WHO stages of HIV infection in settings where POC CD4 testing is not available. The major advantage of POC screening is that health care providers would be able to receive results immediately, thus minimizing patient loss to follow-up and treatment delays. However, the main disadvantage to this type of screening strategy is the lack of quality control associated with POC testing.

## What is the role of lumbar puncture (LP) in screening?

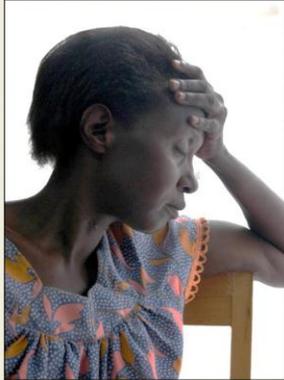
- Three options for serum CrAg+ patients
  - Offer LP to all serum CrAg+ patients
  - Treat empirically with fluconazole, no LP
  - Offer LP based on serum CrAg titer cutoff or a symptom screen
- Positive serum CrAg test alone cannot distinguish between early disease and meningitis



Photo source: McCarthy et al., South African J of HIV Medicine 2007

A positive serum CrAg test by itself cannot distinguish whether the patient has early disease, or whether the patient has already developed meningitis. Healthcare providers will need to perform a lumbar puncture (LP) to determine whether the organism has already entered the brain and the patient has meningitis. There are three options for serum CrAg-positive patients. The first option is to offer a lumbar puncture to all serum CrAg-positive patients. The second option is to treat all CrAg-positive patients empirically with fluconazole, without performing any lumbar punctures. Lastly, LPs can be offered based on a serum CrAg titer cutoff, or based on the presence of certain symptoms.

## Which symptoms should be used to decide who gets a lumbar puncture?



- Balance sensitivity and specificity:
- Highly sensitive symptoms: (i.e. fever, headache)
  - May lead to unnecessary LPs
  - Costly
  - Not feasible everywhere
- Highly specific symptoms (neck stiffness)
  - May miss patients with active CM
- Few data on use of symptoms to screen for CM

Photo courtesy of World Health Organization

Cryptococcal Screening Program

If the presence of certain symptoms is used to decide who gets a lumbar puncture, which symptoms should be used? Some symptoms of cryptococcal meningitis are more sensitive (for example, fever and headache), which means that a large proportion of patients with CM have these symptoms, but these symptoms can also indicate other diseases. Decisions based on highly sensitive symptoms may lead to unnecessary LPs, which is costly, and is not always feasible in resource-limited settings. Other symptoms are more specific (for example, neck stiffness), which means that these symptoms are highly indicative of meningitis, but are not seen in every patient with meningitis. Decisions based on highly specific symptoms may exclude patients with active CM. There are few data on the use of symptoms alone as a screening tool for CM.

## What is the treatment for cryptococcal disease?

- Treatment of cryptococcal meningitis
  - WHO guidelines: amphotericin B + flucytosine or high-dose fluconazole (first choice)
  - Where amphotericin B not available: high-dose fluconazole
- Treatment of asymptomatic, early cryptococcal disease
  - Little evidence on ideal treatment dose and duration
  - WHO recommendations:
    - 800 mg daily fluconazole for 2 weeks
    - 400 mg daily fluconazole for 8 weeks
    - 200 mg daily fluconazole until CD4 >200 for 6 months

Per WHO guidelines, available at [http://whqlibdoc.who.int/publications/2011/9789241502979\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241502979_eng.pdf)

 Cryptococcal Screening Program

In 2011, WHO released rapid advice guidelines that include information on how to treat cryptococcal meningitis. Combined amphotericin B and flucytosine is recommended for treating cryptococcal meningitis. However, these medications are often unavailable in many parts of the world. In these situations, high-dose fluconazole is used. There is little evidence on the ideal treatment dose and duration for asymptomatic, early cryptococcal disease. WHO recommends 800 mg of fluconazole per day for two weeks, followed by 400 mg per day for eight weeks, followed by 200 mg for at least 6 months on ART with CD4 > 200.

## What is the ideal timing of ART initiation after treatment for cryptococcal disease?

- Available data from patients with cryptococcal meningitis (CM):
  - Less than 3 days after diagnosis of CM is NOT recommended<sup>1</sup>
  - Most guidelines suggest at least 2 weeks post-diagnosis of CM
- Randomized controlled trials are ongoing to determine the optimal timing for ART after diagnosis of CM
- No published data on timing of ART initiation for asymptomatic, CrAg-positive patients with early cryptococcal disease

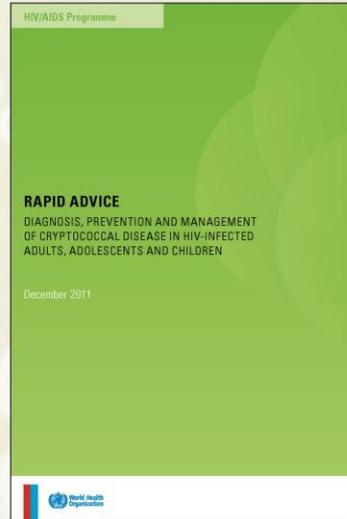
1. Zolopa et al., ACTG A5164 PLOS One 2009

 Cryptococcal Screening Program

The timing of ART initiation after a diagnosis of CM or of cryptococcal antigenemia is very important. As with treatment information, published data pertains only to patients with cryptococcal meningitis. Published data show that starting ART less than three days after the diagnosis of CM is NOT recommended. Most guidelines suggest that 2 weeks is the minimum time to begin ART after a diagnosis of CM; however, trials are still ongoing in order to determine the optimal timing. There are no published data on the ideal timing of ART initiation for asymptomatic patients with early cryptococcal disease.

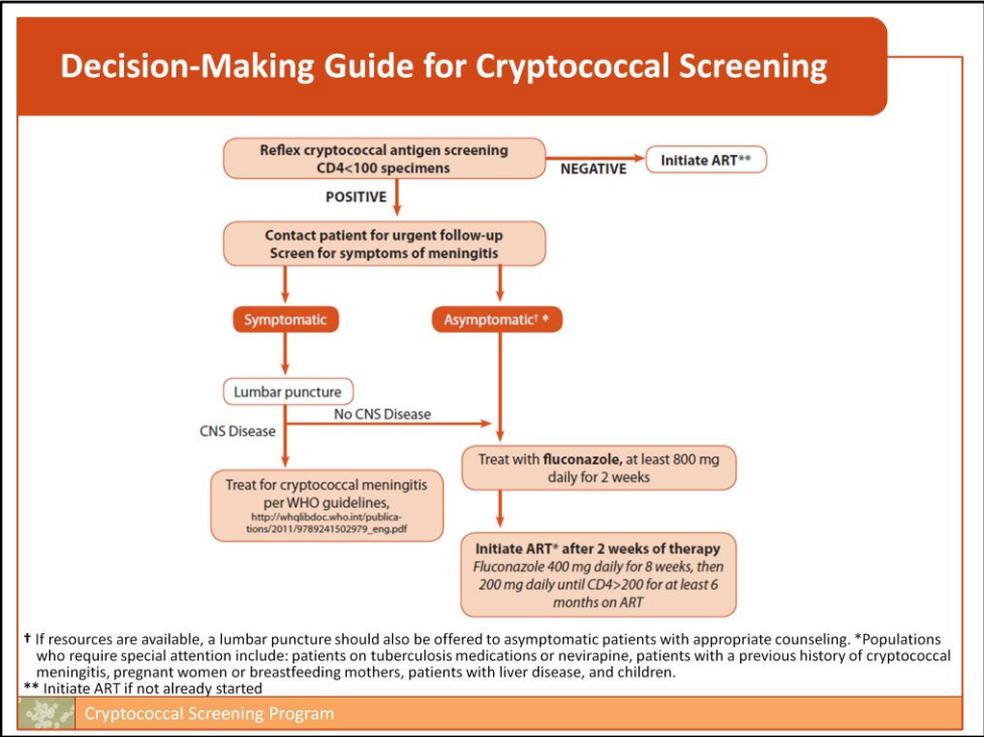
## WHO Rapid Advice guidelines

- Conditionally recommend screening
- Provide information on treatment of CM and asymptomatic antigenemia



Cryptococcal Screening Program

As mentioned at the beginning of the presentation, the WHO “Rapid Advice” guidelines for the Diagnosis, Prevention, and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents, and Children recommend screening for infection, and provide comprehensive treatment information for CM and for asymptomatic antigenemia.

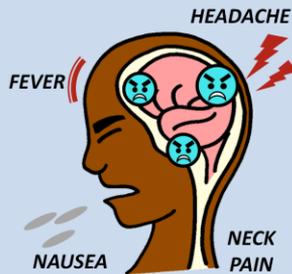


This is an example based on WHO guidelines of how healthcare providers should treat cryptococcal disease. After reflex laboratory CrAg screening of all specimens with CD4 < 100, CrAg-negative patients can begin ART immediately. CrAg-positive patients should be screened for symptoms of meningitis. Asymptomatic patients can begin treatment with fluconazole for 2 weeks, then begin ART. Symptomatic patients should receive a lumbar puncture, and patients with evidence of central nervous system disease should be treated for CM according to the WHO guidelines.

# HIV and Brain Infection: Testing Saves Lives!

## What is the infection?

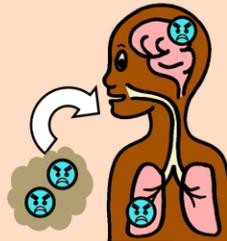
Some people with HIV can get a brain infection called *Cryptococcus* or "Crypto." If it is not treated, you could get very sick. Crypto is caused by a small germ.



## How is it spread?

This germ lives in the soil but is too small to see. It can enter our bodies through the air we breathe. Most people are strong enough not to get sick. In an HIV+ person it may start growing and can spread to the brain.

**The germ CANNOT spread from person to person!**



## What can I do?

Even if you do not feel sick now, you might already have this infection. Your doctor will test you as part of your regular visit. If you have the Crypto germ, you will need to take medicine so that you do not get sick later.



Finally, cryptococcal screening programs should not only raise awareness among healthcare providers about the burden, diagnosis, and treatment of cryptococcal disease. Patients should also be educated on what CM is and why it is important for CrAg-positive patients to take fluconazole. This is an example of a wall poster on cryptococcal screening that can be used for patient education.

## Conclusions

- Cryptococcal infection is an important public health problem among people with HIV/AIDS
- A new test for cryptococcal antigen can detect the infection early, before it develops into life-threatening meningitis
- Using this test to screen those at highest risk of developing CM is cost-effective and can save lives
- Screening and early treatment for CM can be part of an integrated HIV/AIDS treatment and care strategy
- Implementing cryptococcal screening programs in Africa and Asia may help save thousands of lives every year

In conclusion, cryptococcal infection is an important public health problem, and causes a large burden of disease among people living with HIV/AIDS. A new test for cryptococcal antigen can detect the infection early, before it develops into life-threatening meningitis. Using this new test to screen for cryptococcal antigen among people at highest risk is a cost-effective strategy to prevent deaths, and patients who receive early antifungal treatment have better outcomes than patients who do not. Like cotrimoxazole prophylaxis and preventive therapy for tuberculosis, screening and early treatment for cryptococcal infection can be part of an integrated HIV/AIDS treatment and care strategy. Finally, implementing cryptococcal screening programs in Africa and Asia may help to save thousands of lives every year.

## Thank You

- For more information, please contact Centers for Disease Control and Prevention

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E-mail: [cdcinfo@cdc.gov](mailto:cdcinfo@cdc.gov)

Web: <http://www.cdc.gov>

- The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



## Frequently asked questions

- What is the prevalence of cryptococcal antigenemia?
- How does screening compare to prophylaxis?
- Why do the benefits of targeted screening outweigh those of prophylaxis?
- What are the data for and against prophylaxis?
- Have there been data published on CrAg screening?
- What are some other types of antigen detection tests for cryptococcal disease?
- How does the new LFA compare to other tests?

These are a few of the most frequently asked questions about cryptococcal screening. The answers to each of these questions can be found on the following slides.

## What is the prevalence of cryptococcal antigenemia?

Author	Year	Country	Setting / population	Prevalence
Desmet	1989	Zaire	Newly diagnosed HIV+	12.2%
Negrone	1995	Argentina	HIV+, CD4 <300	6.7%
Swinne	2002	Rwanda	Randomly selected HIV+ sera	4.2%
Tassie	2003	Uganda	Inpatient, outpatient HIV+ stage 3 or 4	10.7%
Liechty	2007	Uganda	HIV+ initiating ART at clinic, CD4 <100	5.8%
Micol	2007	Cambodia	HIV+ at hospital ART program, CD4 <200	10.8%
Jarvis	2009	South Africa	HIV+ initiating ART at clinic, CD4 <100	13.0%
Meya	2010	Uganda	HIV+ initiating ART at clinic, CD4 <100	8.8%
Pongsai	2010	Thailand	HIV+ initiating ART at clinic, CD4 <100	12.9%
Mamoojee	2011	Ghana	HIV+ initiating ART at clinic, CD4 <100	2.0%
Wajanga	2011	Tanzania	HIV+ inpatients	5.1%
Oyella	2012	Uganda	HIV+ inpatients, CD4 <100	19%
Osazuwa	2012	Nigeria	HIV+ initiating ART at clinic, CD4 <100	12.7%
Linares	2012	Peru	HIV+, ART-naïve stored plasma	3.6%



## How does screening compare to prophylaxis?

- Prophylaxis
  - Treat all HIV/AIDS patients with CD4 <100 with fluconazole
  - Mixed evidence on whether this improves survival
- Screening
  - HIV/AIDS patients with CD4 <100 receive screening test to detect early, asymptomatic disease; treatment of disease with fluconazole

There are two main strategies that could be used to prevent cryptococcal meningitis deaths: prophylaxis and screening. In a prophylaxis-based approach, all HIV/AIDS patients with a CD4 count under 100 would receive oral fluconazole; however, there is mixed evidence about whether this improves survival. In a screening strategy, this same group of HIV-infected patients with CD4 under 100 would receive a screening test to detect early, asymptomatic disease. Then, only the patients who test positive for early disease would receive treatment with fluconazole.

## Why do the benefits of targeted screening outweigh those of prophylaxis?

- Treat approximately 10% (vs. 100%) of HIV/AIDS patients with CD4 <100
- Minimize unnecessary drug exposure
  - Adverse events (and concern about FLC use during pregnancy)
  - Drug interactions (TB meds and FLC)
- Minimize azole resistance
- Potentially more cost-effective

The benefits of targeted screening outweigh those of prophylaxis for several reasons. First, only about 10% of HIV/AIDS patients with CD4 counts under 100 would be treated with fluconazole in a targeted screening program, versus 100% of this group in a primary prophylaxis approach. This minimizes unnecessary drug exposure and the associated potential for adverse events, including the concern about fluconazole use during pregnancy. This also reduces the possibility for potentially harmful drug interactions between fluconazole and TB medications, which are commonly used by this group of patients. Targeted screening also minimizes the potential for azole resistance and is potentially more cost-effective than primary prophylaxis.

## What are the data for and against prophylaxis?

- Studies from USA, Europe have not shown survival benefit from primary prophylaxis
- Randomized controlled trial (RCT) from Thailand suggested improved survival<sup>1</sup>
- RCT from Uganda: Fluconazole prevented cryptococcal disease among CrAg-negative patients<sup>2</sup>

1. Chetchotisakd et al., HIV Medicine 2004; 2. Parkes-Ratanshi et al., Lancet ID 2011



## Have there been data published on CrAg screening?

- South Africa<sup>1</sup>
  - CrAg positivity independent predictor of mortality
  - Of the 7% positive for CrAg, 91% had CD4<100
  - 98 patients screened to identify 1 CrAg+ patient, at a cost of \$206
- Cambodia<sup>2</sup>
  - Without CrAg test, 29% of infections would have been missed
- Uganda<sup>3</sup>
  - Fluconazole use associated with survival (vs. ART alone)
  - \$190 to prevent one CM case; \$266 to prevent one death

1. Jarvis et al., CID 2010; 2. Micol et al., 2007; 3. Meya et al., CID 2010



## What are some other types of antigen detection tests for cryptococcal disease?

- Latex agglutination<sup>1</sup>
  - Use on: serum and CSF
  - 83-100% sensitivity; 97-100% specificity
- EIA (Enzyme immunoassay)<sup>2</sup>
  - Use on: serum and CSF
  - 99% sensitivity, 97% specificity

1. Currie et al., J Clin Microbiol 1993; 2. Gade et al., J Clin Microbiol 1991



## How does the new LFA compare to other tests?

- Jarvis et al. 2011<sup>1</sup>
  - LFA showed strong correlations between serum, plasma, and urine specimens
  - Agreement between LFA results and ELISA method for each of the three specimen types
- Lindsley et al. 2011<sup>2</sup>
  - High level of agreement between LFA results and EIA testing of serum

1. Jarvis et al., CID 2011; 2. Lindsley et al., CID 2011