Cryptococcal Screening Program Training Manual for Healthcare Providers

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

CS232487-A 08/2012

Cryptococcal Screening Program Training Manual

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Suggested Course Syllabus

Welcome (5 minutes)

Review training modules (40 minutes)

Questions and answers (15 minutes)

Case studies (30 minutes)

Review of patient educational materials (15 minutes)

Summary & post-training quiz (15 minutes)

Total time: 2 hours

Image courtesy of World Health Organization

Overview of *Cryptococcus*

The infection caused by Cryptococcus " is one of the most dangerous HIV-related issues…HIV therapy programs should not neglect to address this still lethal disease."

Vicent Esposito and Antonio Chirianni, HIV Therapy 2010

What is *Cryptococcus*?

Cryptococcus is a fungus, found in the soil, which produces spores that can be inhaled. If a person's immune system is weakened (for example, by HIV), *Cryptococcus* can cause a life-threatening infection in the brain called cryptococcal meningitis.

Why is *Cryptococcus* an important public health issue?

- Cryptococcal infection is a leading cause of death among people living with HIV/AIDS.
- *Cryptococcus* is the most common cause of adult meningitis in most of Africa.
- Death rates for patients diagnosed with cryptococcal meningitis are 30-70% in Africa and Asia.
- Optimal medication to treat cryptococcal meningitis is often unavailable or very expensive.
- Medical management of cryptococcal meningitis is intensive, requiring frequent lumbar punctures and lifelong medication.

Module 1: What is *Cryptococcus*?

Training objectives

- Understand what *Cryptococcus* is and where it is found in the environment
- Understand how *Cryptococcus* infects HIV/AIDS patients
- Understand the high death rates associated with cryptococcal meningitis
- Describe the global public health burden of cryptococcal meningitis

Supplies needed

- Module 1 slides (optional)

What is *Cryptococcus*?

- *Cryptococcus* is a fungus found in soil throughout the world.
- Spores are inhaled from the environment by humans.
- There is no person-to-person transmission of *Cryptococcus*.

Cryptococcal infection

- After inhalation, the fungus can cause an acute lung infection, or, more frequently, cause no symptoms at all.
- The fungus may stay dormant in the body for months to years.
- Reactivation of infection can occur in immunosuppressed people, such HIV/AIDS patients.
- Adult HIV/AIDS patients with a CD4 count < 100 are at highest risk for reactivation.
- When *Cryptococcus* reactivates in the body, it can cause disease in the brain, lungs, skin, and bones.
- Meningitis (inflammation of the tissue surrounding the brain) is the most common form of cryptococcal disease in HIV/AIDS patients.
- Encephalitis (infection of the brain itself) can also occur together with meningitis.

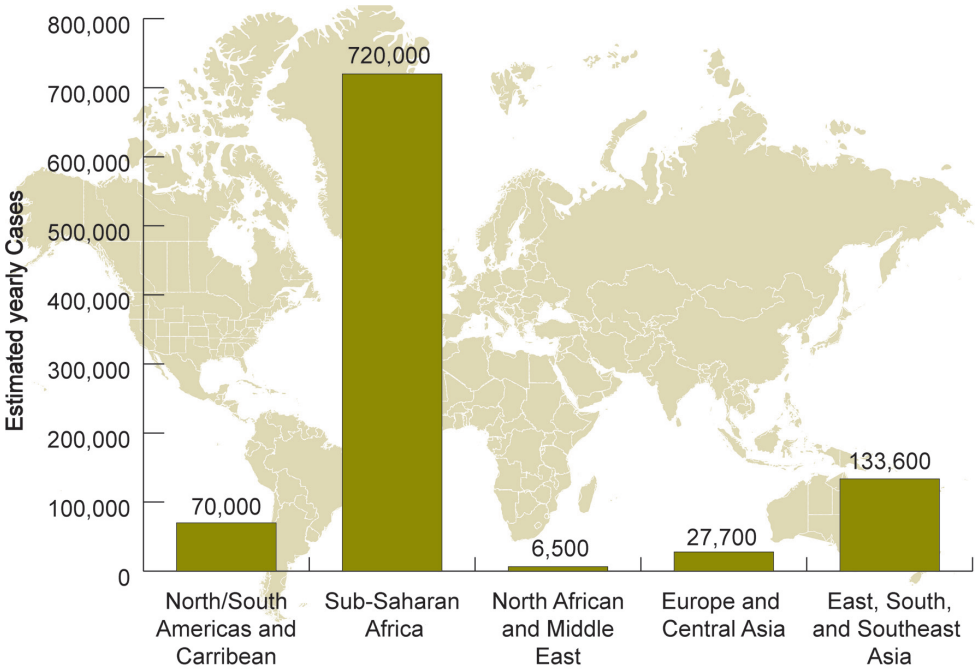
Module 1: What is *Cryptococcus*?

Death from cryptococcal meningitis

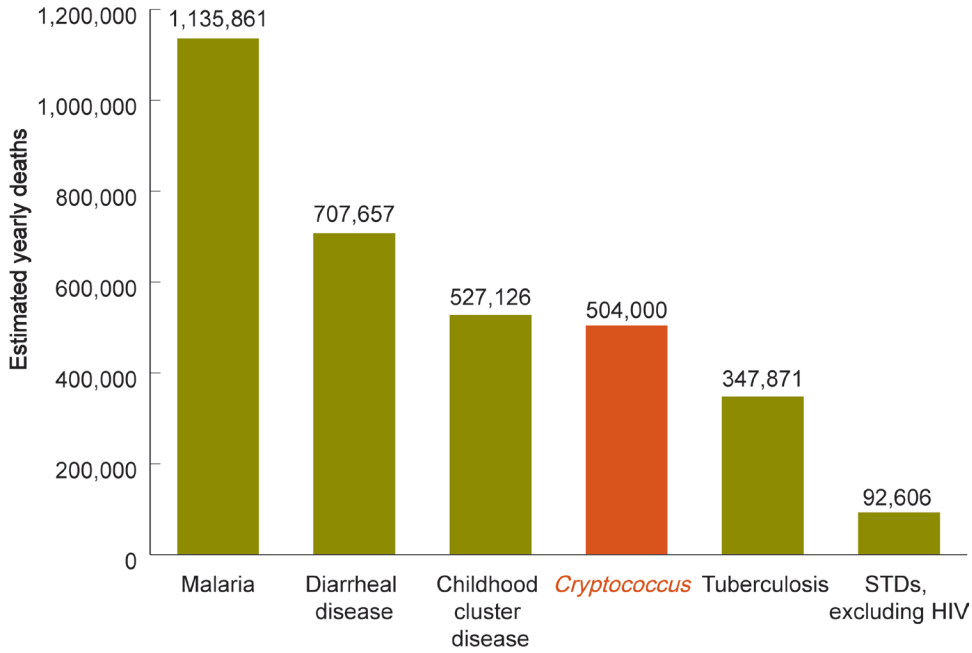
- Cryptococcal meningitis is a common cause of death among HIV/AIDS patients.
- Even when patients are treated with anti-retroviral medications and anti-fungal therapy, 30%-70% die from their cryptococcal infection.
- In areas of the world where cryptococcal infection is common, it is estimated to cause as many deaths as tuberculosis.

Image courtesy of World Health Organization

Globally, approximately 1 million new cases and 625,000 deaths occur per year from HIV-related cryptococcal meningitis.



Leading causes of death in sub-Saharan Africa, excluding HIV



Images adapted from B.J. Park et al. AIDS 2009; 23: 525-30.

Module 1: What is *Cryptococcus*?

Discussion questions

- Have you encountered many cases of cryptococcal meningitis while caring for patients?
- Do you feel that you have enough knowledge to care for patients with cryptococcal disease?
- Do you feel comfortable caring for patients with cryptococcal disease?

Module 2: Recognizing Signs and Symptoms of Cryptococcal Disease

Training objectives

- Identify the common signs and symptoms of cryptococcal meningitis
- Recognize other clinical presentations of cryptococcal disease
- Identify other diseases that may look like cryptococcal meningitis in HIV/AIDS patients

Supplies needed

- Module 2 slides (optional)

Cryptococcal disease

- After inhalation, the fungus can cause an acute lung infection, or, more frequently, cause no symptoms at all.
- When *Cryptococcus* reactivates in the body, it can cause disease in the brain, lungs, skin, and bones.
- In the brain, *Cryptococcus* causes meningitis (inflammation of the tissue surrounding the brain).
- Meningitis is the most common form of cryptococcal disease in HIV/AIDS patients.
- Cryptococcal disease should be suspected in any patient presenting with meningitis. It should be suspected in an HIV-infected patient who presents with symptoms consistent with meningitis, such as headache or confusion.

Module 2: Recognizing Signs and Symptoms of Cryptococcal Disease

Signs and symptoms of cryptococcal meningitis may include:

Symptoms

- Change in mental status (ranging from confusion to lethargy to coma)
- Headache
- Nausea with or without vomiting
- Changes in vision or hearing (e.g. double vision, blindness, deafness)

Signs

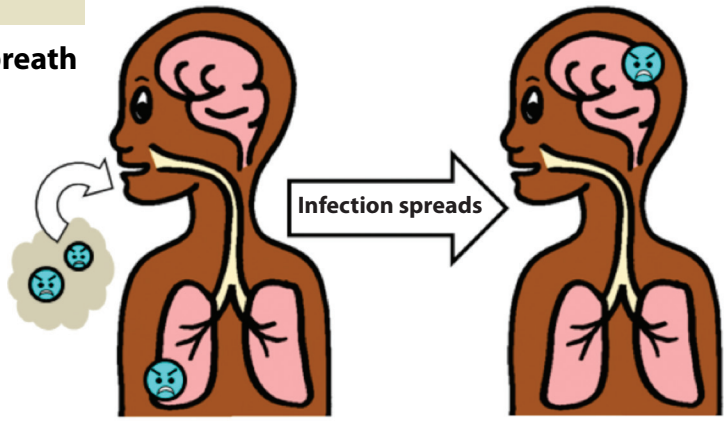
- Papilloedema
- Seizures
- Cranial nerve palsies (e.g., eye movement problems)

Many of these signs/symptoms are due to inflammation of the meninges (the membranes that protect the brain and spinal cord) or increased intracranial pressure (elevated pressures in the brain).

Clinical course of cryptococcal disease

No symptoms or symptoms of lung infection

- **Shortness of breath**
- **Cough**
- **Fever**



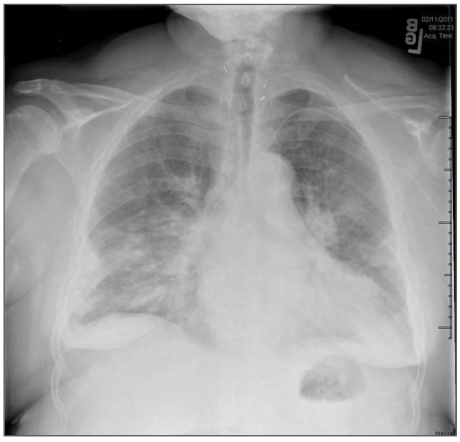
Meningitis

- **Headache**
- **Fever**
- **Confusion or coma**
- **Neck stiffness**
- **Sensitivity to light**
- **Nausea, vomiting**

Module 2: Recognizing Signs and Symptoms of Cryptococcal Disease

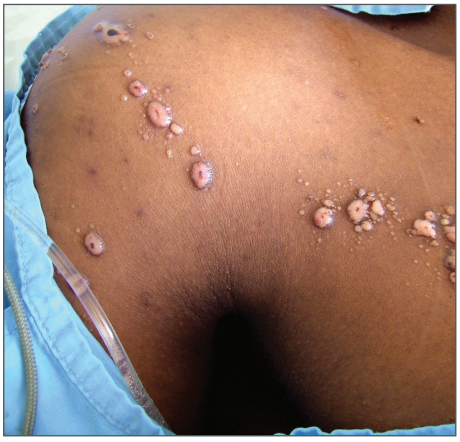
Other clinical presentations of cryptococcal disease

- **Lung:** Ranges from mild pneumonia to acute respiratory distress syndrome (ARDS); Shortness of breath, cough, and fever are the most common symptoms
- **Skin:** Papules, pustules, nodules, ulcers are common skin lesions
- **Bone:** Most commonly the vertebrae and ribs



Chest x-ray of cryptococcal infiltrate

Source: John Baddley



Cryptococcal skin lesion

McCarthy et al 2007, South African Journal of HIV Medicine

Other diseases that may look like cryptococcal meningitis in persons with HIV/AIDS

- TB meningitis is the most common
- Meningoencephalitis caused by other organisms (mycobacterial, viral, bacterial, spirochetes, other)
- Space-occupying lesions (lymphoma, *Toxoplasma gondii*, abscess, etc.)
- HIV encephalopathy
- Other conditions (toxic, metabolic, autoimmune, intracranial bleed, etc.)

Discussion questions

- What signs and symptoms do your patients with cryptococcal disease usually have?
- What diseases mimic or look like cryptococcal disease at your clinic?

Module 3: Diagnosing Cryptococcal Disease

Training objectives

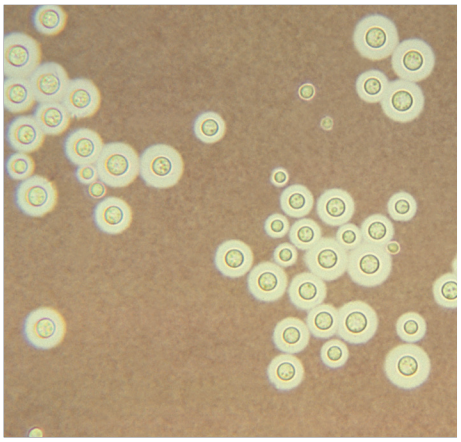
- Describe the current methods used to diagnose *Cryptococcus* infection
- Explain the new dipstick test and the characteristics of this test
- Understand which test to use when diagnosing cryptococcal meningitis
- Understand the role of lumbar puncture in diagnosing cryptococcal meningitis

Supplies needed

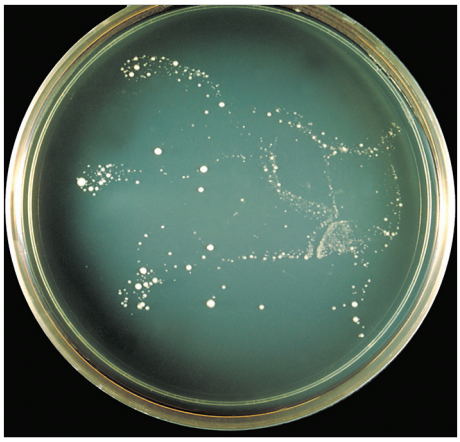
- Module 3 slides (optional)
- Cryptococcal lateral flow assay test kit (for demonstration)

Current diagnostic methods

There are several ways to detect *Cryptococcus spp.* infections. Traditional methods include observation of the organism with a microscope, and growth of the organism in culture. Observation using microscopy requires a special but simple stain called India Ink. Both microscopy and culture are accurate methods to detect cryptococcal organisms, but they are not very sensitive (in a small number of cases they may not detect the organism even if it is present in the body, leading to a missed diagnosis). In addition, culture results may take days to weeks to obtain the final results.



India Ink microscopy



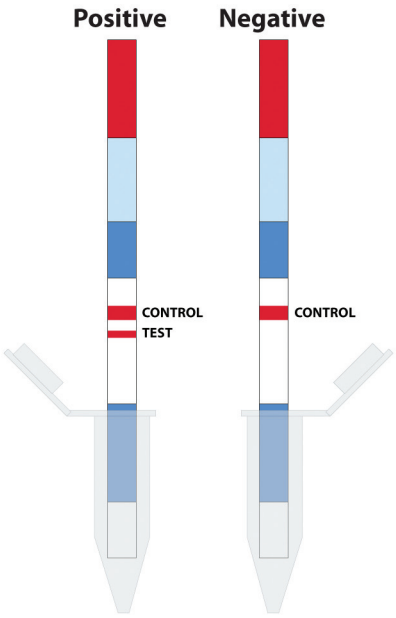
Culture

Module 3: Diagnosing Cryptococcal Disease

Cryptococcal antigen, a chemical marker for infection, is produced by the fungus *Cryptococcus*. Traditional tests that detect cryptococcal antigen (latex agglutination and enzyme immunoassay) are both sensitive and accurate, but are not always available. A new antigen detection test, called the Lateral Flow Assay (LFA), is a rapid dipstick test. The test cannot be used to monitor clinical response to treatment, because serum (a component of blood) may remain positive for cryptococcal antigen for days to months after successful treatment. Antigen can also be detected in cerebrospinal fluid (CSF) and serum weeks to months before meningitis symptoms develop.

Method	Usual Specimen type
India Ink microscopy	CSF (Cerebrospinal fluid)
Culture	CSF, blood, or appropriate tissue
Antigen detection • Latex agglutination (LA) • Enzyme immunoassay (EIA) • Lateral flow assay (LFA)	 CSF or serum CSF or serum CSF or serum

Dipstick test



The new lateral flow assay (LFA) is…

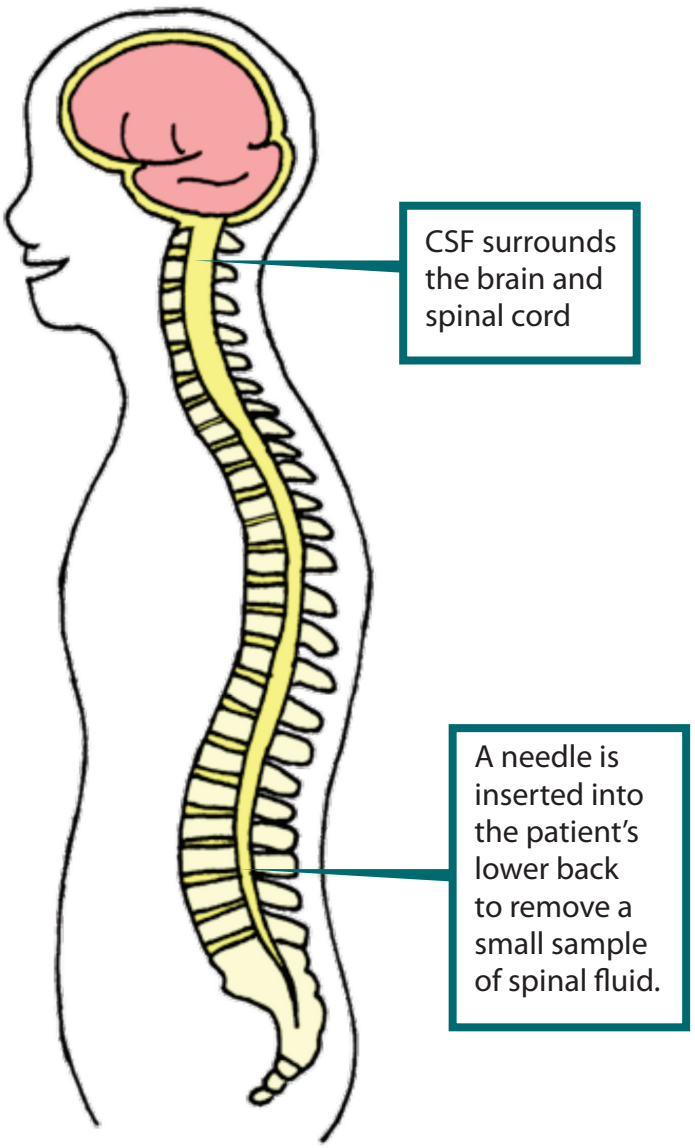
- Effective: The test is sensitive, accurate (>95%), and highly predictive of who is at risk for developing cryptococcal meningitis.
- Simple and quick: The results of the LFA are available in 10 minutes.
- Affordable (approximately $2-4 per test)

Module 3: Diagnosing Cryptococcal Disease

How to diagnose cryptococcal meningitis

Patients with signs or symptoms of meningitis and patients with evidence of cryptococcal disease anywhere in the body need to be evaluated for cryptococcal meningitis. To diagnose cryptococcal meningitis, it is necessary to examine the cerebrospinal fluid (CSF) around the brain. CSF is collected by performing a procedure called a lumbar puncture, in which a needle is put into the patient's back and a small amount of CSF is removed from the spinal column. This procedure should only be performed by trained physicians.

Three tests should be performed on CSF to detect *Cryptococcus*: (1) India Ink stain, (2) a cryptococcal antigen detection test, and (3) fungal culture. At least one of these tests should be positive in order to confirm the diagnosis of cryptococcal meningitis. Other CSF tests (see next section) will help you determine whether the patient's symptoms are due to *Cryptococcus* or other organisms.



Performing a lumbar puncture (for trained physicians only)

Lumbar puncture is important for both diagnosis and treatment of CM. A lumbar puncture is required to obtain CSF to establish a diagnosis of cryptococcal meningitis. It is also used to measure intracranial pressure and to remove CSF in patients with elevated intracranial pressure.

Before performing a lumbar puncture, you should ensure that there are no focal neurologic deficits. If there are, perform a head CT first to rule out a space-occupying lesion. In resource-limited settings where CT scans are not available, you may consider proceeding without imaging, but this decision should be discussed with a senior clinician, weighing potential risks and benefits.

When performing a lumbar puncture, always record the opening pressure (normal: <20 cm). When evaluating a patient for cryptococcal meningitis, request the following: microscopy (cell count, Gram stain, India Ink stain), chemistry (protein, glucose), bacterial culture, and tests for *Cryptococcus* (cryptococcal antigen, fungal culture). To rule out other common causes of meningitis in HIV/AIDS patients, consider ordering adenine deaminase and mycobacterial smear and culture (tuberculosis), TPHA or FTA (syphilitic meningitis), and *Toxoplasma* antibodies (toxoplasmosis).

How to diagnose non-meningeal cryptococcal disease

If non-meningeal cryptococcal disease is suspected, an antigen detection test, India Ink stain, or culture of the relevant clinical specimen may be useful (for example, a skin biopsy or sputum sample). Any patient with a positive test needs to be evaluated with a lumbar puncture for cryptococcal meningitis.

Discussion questions

- What kind of test do you currently use/order when you suspect cryptococcal disease?
- Is lumbar puncture currently available where you care for patients?
- How often do your patients refuse a lumbar puncture?
- What challenges do you encounter if you have to refer patients to another facility for lumbar puncture?

Module 4: Treating Cryptococcal Meningitis

Training objectives

- Describe the current treatment for adult cryptococcal meningitis
- Understand the importance of managing intracranial pressure
- Describe common side effects from fluconazole therapy
- Describe other uses of fluconazole
- Describe important fluconazole drug interactions
- Define immune reconstitution inflammatory syndrome (IRIS)

Supplies needed

- Module 4 slides (optional)

Treatment of adult cryptococcal meningitis

Treatment of cryptococcal meningitis consists of three phases: **induction, consolidation**, and **maintenance**. **Induction** is given to rapidly clear the organism from the body. **Consolidation** is given to ensure that the organism is completely eradicated. **Maintenance** is given to prevent recurrence of disease after treatment; this phase is also known as secondary prophylaxis.

Induction phase	Consolidation phase	Maintenance Phase
2 weeks	**8 weeks** *Begin ART after 2 weeks of consolidation therapy*	**1 year** on ART and CD4 ≥ 200 if viral load monitoring not available, or CD4 ≥ 100 and a suppressed viral load.

Amphotericin B is an intravenous medication that is given only in hospitals as it requires close monitoring for side effects. **Fluconazole** is an oral medication that is available in some areas of the world free of cost through the Diflucan Partnership Program (Pfizer). The World Health Organization (WHO) guidelines on the "Diagnosis, Prevention, and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents, and Children" (2011) recommend the treatment regimen described on the following page for **adults** (see table on following page). For patients receiving amphotericin B, WHO's minimum toxicity prevention, monitoring, and management regimen is also presented on the following page. If viral load monitoring

is **not** available, maintenance treatment for cryptococcal meningitis should be given until the patient is stable and adherent to ART and anti-fungal maintenance for at least one year and has a CD4 count greater than or equal to 200. If viral load monitoring is available, maintenance treatment should be given until the patient is stable and adherent to ART and anti-fungal maintenance for at least one year, has a suppressed viral load, and has a CD4 count greater than or equal to 100.

Regimen desirability	Drugs available	Pre-hydration + electrolyte replacement + toxicity monitoring / management	Induction phase options (2 weeks)	Consolidation phase options (8 weeks)	Maintenance / secondary prophylaxis options
First choice	AmB ± flucytosine	Available	**a.** AmB 0.7 -1 mg/kg/day + flucytosine 100 mg/kg/day **b.** AmB 0.7 -1 mg/kg/day + fluconazole 800 mg/day	Fluconazole 400-800 mg/day	Fluconazole 200 mg/day
Second choice	AmB	Not available for full 2-week induction period	AmB 0.7 -1 mg/kg/day short course (5-7 days) + fluconazole 800 mg/day (2 weeks)	Fluconazole 800 mg/day	
Third choice	AmB not available	Not available	**a.** Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day **b.** Fluconazole 1200 mg/day alone	Fluconazole 800 mg/day	

World Health Organization (2011). "Rapid advice: Diagnosis, Prevention, and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents, and Children.

Module 4: Treating Cryptococcal Meningitis

Minimum package for amphotericin B toxicity prevention, monitoring and management

Pre-emptive hydration and electrolyte supplementation

- **Adults:** One liter of normal saline solution with one ampule (20 mmol) of KCL over 2-4 hours before each controlled infusion of amphotericin B (with one liter of 5% dextrose) and one to two 8mEq KCL tablets orally twice daily. An additional one 8mEq KCL tablet twice daily may be added during the second week. If available, magnesium supplementation should also be provided (two 250mg tablets of magnesium trisilicate twice daily).
- **Adolescents and Children:** Up to one liter of normal saline solution with one ampule (20 mmol) of KCL at 10-15 ml/kg over 2-4 hours before each controlled infusion of amphotericin B. If saline is unavailable, then other intravenous rehydration solutions that contain potassium can be used eg. Darrow's or Ringer's Lactate solutions.
- Potassium replacement should not be given patients with pre-existing renal impairment or hyperkalemia.
- A test dose for amphotericin B is not recommended.

Monitoring

- Serum potassium and creatinine (baseline and twice weekly), especially in the second week of amphotericin B administration.
- Hemoglobin (baseline and weekly).
- Careful attention to fluid monitoring of intake and output, and daily weight.

Management

- If significant hypokalemia (K <3.3mmol/l), increase potassium supplementation to two KCL ampules (40 mmol), or one or two 8mEq KCL tablets three times daily. Monitor potassium daily.
- If hypokalemia remains uncorrected, double magnesium oral supplementation.
- If creatinine increases by >2 fold from baseline value, either temporary omission of an amphotericin B dose, or increase pre-hydration to one liter 8 hourly. Once improved, restart at 0.7 mg/kg/day and consider alternate day amphotericin B. If creatinine remains elevated, discontinue amphotericin and continue with fluconazole at 1200 mg/day. Monitor creatinine daily.

World Health Organization (2011)

Managing intracranial pressure (for trained physicians only)

Intracranial pressure (ICP) is elevated in most patients with cryptococcal meningitis and, if left untreated, can lead to death. Managing ICP is an important part of caring for patients with cryptococcal meningitis. ICP should be measured at the time of lumbar puncture using a manometer (see picture below). Physicians should refer to the following Infectious Diseases Society of America (IDSA) 2010 guidelines for managing elevated ICP: "If the CSF pressure is ≥25 cm of CSF and there are symptoms of increased intracranial pressure during induction therapy, relieve by CSF drainage (by lumbar puncture, reduce the opening pressure by 50% if it is extremely high or to a normal pressure of ≤20 cm of CSF). If there is persistent pressure elevation >25 cm of CSF and symptoms [of meningitis], repeat lumbar puncture daily until the CSF pressure and symptoms have been stabilized for >2 days and consider temporary percutaneous lumbar drains or ventriculostomy for persons who require repeated daily lumbar punctures."

Measurement of CSF opening pressure using manometer.

Source: McCarthy et al 2007, South African Journal of HIV Medicine

General information about fluconazole (Diflucan)

Fluconazole (brand name Diflucan) is an oral anti-fungal medication available in 50, 100, 150, or 200 mg tablets. It is usually taken in pill format but can also be taken as an oral suspension. Fluconazole can be taken with or without food and can be taken at any time of day.

Indications for fluconazole use

Fluconazole can be used as treatment or prophylaxis for a variety of systemic and superficial fungal infections. In addition to treating cryptococcosis, fluconazole is also commonly used to treat candidiasis of the vagina, esophagus, and mouth/throat (also called "oropharyngeal candidiasis" or "thrush").

Module 4: Treating Cryptococcal Meningitis

Side effects of fluconazole therapy

Fluconazole is an oral medication with several possible side effects including:

- Diarrhea, nausea, abdominal pain
- Headache, dizziness
- Rash
- Liver toxicity
- Teratogenicity (can cause damage to fetus, especially during the 1st trimester)

Fluconazole drug interactions

Fluconazole can interact with other medications, including some drugs used to treat HIV/AIDS and tuberculosis. These include nevirapine (an anti-retroviral drug) and rifampicin (a tuberculosis drug). Patients on nevirapine should be monitored closely for signs of liver toxicity because combination use with fluconazole increases nevirapine levels. Concomitant use of rifampicin and fluconazole decreases levels of fluconazole in the blood.

The Diflucan Partnership Program (DPP)

Since 2000, Pfizer has provided fluconazole for the treatment of two major opportunistic fungal infections associated with HIV/AIDS: esophageal candidiasis and cryptococcal meningitis. Through the Diflucan Partnership Program, fluconazole is available free of cost to government and nongovernmental organizations in certain resource-limited countries where the prevalence of HIV/AIDS is greater than 1%.

More information about the DPP is available on the web at:
http://www.directrelief.org/DiflucanPartnership/EN/DiflucanProgramOverview.aspx

Side effects of amphotericin B therapy

Amphotericin B is an intravenous medication with many potentially serious side effects. It should only be given in settings where side effects and response to therapy can be closely monitored. Serious side effects of amphotericin B therapy include acute infusion reactions, renal toxicity, and electrolyte abnormalities.

Immune reconstitution inflammatory syndrome (IRIS)

Some patients with HIV/AIDS can actually get sicker after they start anti-retroviral treatment (ART). Clinical worsening or new presentation of cryptococcal disease after starting ART is called cryptococcal immune reconstitution inflammatory syndrome (IRIS). There are two types of IRIS: unmasking and paradoxical. Unmasking IRIS refers to a new diagnosis of cryptococcal disease after ART is started. Paradoxical IRIS refers to worsening of known existing cryptococcal disease or recurrence of previously treated cryptococcal disease. IRIS generally occurs in the first weeks to months after ART is started, but can occasionally occur later. Because IRIS can be life-threatening, it is currently recommended that ART-naïve patients diagnosed with cryptococcal meningitis should receive some anti-fungal therapy before ART is started. According to WHO, ART initiation should be delayed until there is evidence of clinical response to anti-fungal therapy **and** induction and consolidation treatment has been given:

- For meningeal disease:
  - » If the patient received amphotericin B, begin ART after 2-4 weeks
  - » If the patient received high-dose fluconazole, begin ART after 4-6 weeks
- For non-meningeal disease:
  - » If the patient received amphotericin B, begin ART after 2 weeks
  - » If the patient received high-dose fluconazole, begin ART after 4 weeks

Discussion questions

- Is amphotericin B generally available for patients with cryptococcal meningitis?
- Are you able to prescribe fluconazole?
- What are the barriers to prescribing fluconazole in your setting?
- Are patients able to get fluconazole free of cost by using the Diflucan Partnership Program?
- What side effects have patients taking fluconazole had?

Module 5: Preventing Cryptococcal Meningitis

Training objectives

- Describe the importance of preventing cryptococcal meningitis
- Understand the advantages and disadvantages of primary prophylaxis
- Describe the rationale behind cryptococcal screening

Supplies needed

- Module 5 slides (optional)

Why is preventing cryptococcal meningitis important?

As you learned in Module 1, cryptococcal disease is common among HIV/AIDS patients and is responsible for a large number of deaths in this population, especially among those with CD4 <100. In resource-limited settings, a lack of diagnostic tools can lead to a delay in identifying cryptococcal meningitis, and anti-fungal therapy is often costly or not available at all. Even when anti-fungal therapy is given, patients who already have cryptococcal meningitis often do poorly because they are diagnosed late in the course of disease. Patients are most at risk for getting sick from *Cryptococcus* before they start ART (when their CD4 counts are low) and immediately after starting ART (due to cryptococcal IRIS). Cryptococcal meningitis may account for 20% of early deaths among patients starting ART.

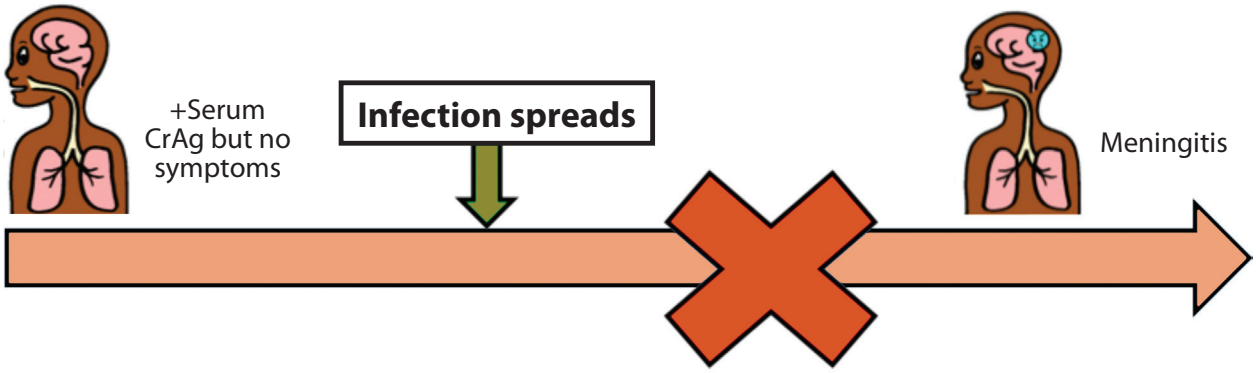
Primary prophylaxis

One strategy to prevent cryptococcal meningitis deaths is to treat all HIV/AIDS patients with a CD4 <100 with low-dose fluconazole, such as 200 mg daily. This strategy has been shown to decrease the number of cryptococcal infections, but has not consistently been shown to decrease rates of death from cryptococcal disease. There are several concerns about widespread use of fluconazole including cost, drug resistance, drug adverse events, and safety in vulnerable populations (pregnant women and patients with liver disease).

Cryptococcal screening

Cryptococcal screening is another strategy to prevent deaths from cryptococcal meningitis. Cryptococcal antigen (a chemical marker that is found in people with active disease) can be detected in the blood weeks to months before the patient develops symptoms of disease. Patients who are found to have cryptococcal antigen in their body are much more likely to develop meningitis than those who do not have antigen. The presence of cryptococcal antigen is highly predictive for the development of cryptococcosis.

Instead of treating everyone with a CD4 count < 100 (primary prophylaxis), patients with low CD4 counts can be screened for cryptococcal antigen in their blood, and treated with fluconazole only if they test positive. The benefit of this strategy is that it minimizes unnecessary treatment of patients who are at lower risk of getting sick from *Cryptococcus*. This decreases costs and concerns about drug resistance, side effects, and safety.



Discussion questions

- What infections common among HIV/AIDS patients do you currently give primary prophylaxis medications for?
- What other infections common among HIV/AIDS patients do you currently screen for?

Module 6: Decision-Making Guide for Cryptococcal Screening

Training objectives

- Use the decision-making guide to manage an adult patient with a positive screening cryptococcal antigen test
- Understand how cryptococcal screening fits into routine HIV care

Supplies needed

- Module 6 slides (optional)

Cryptococcal screening principles

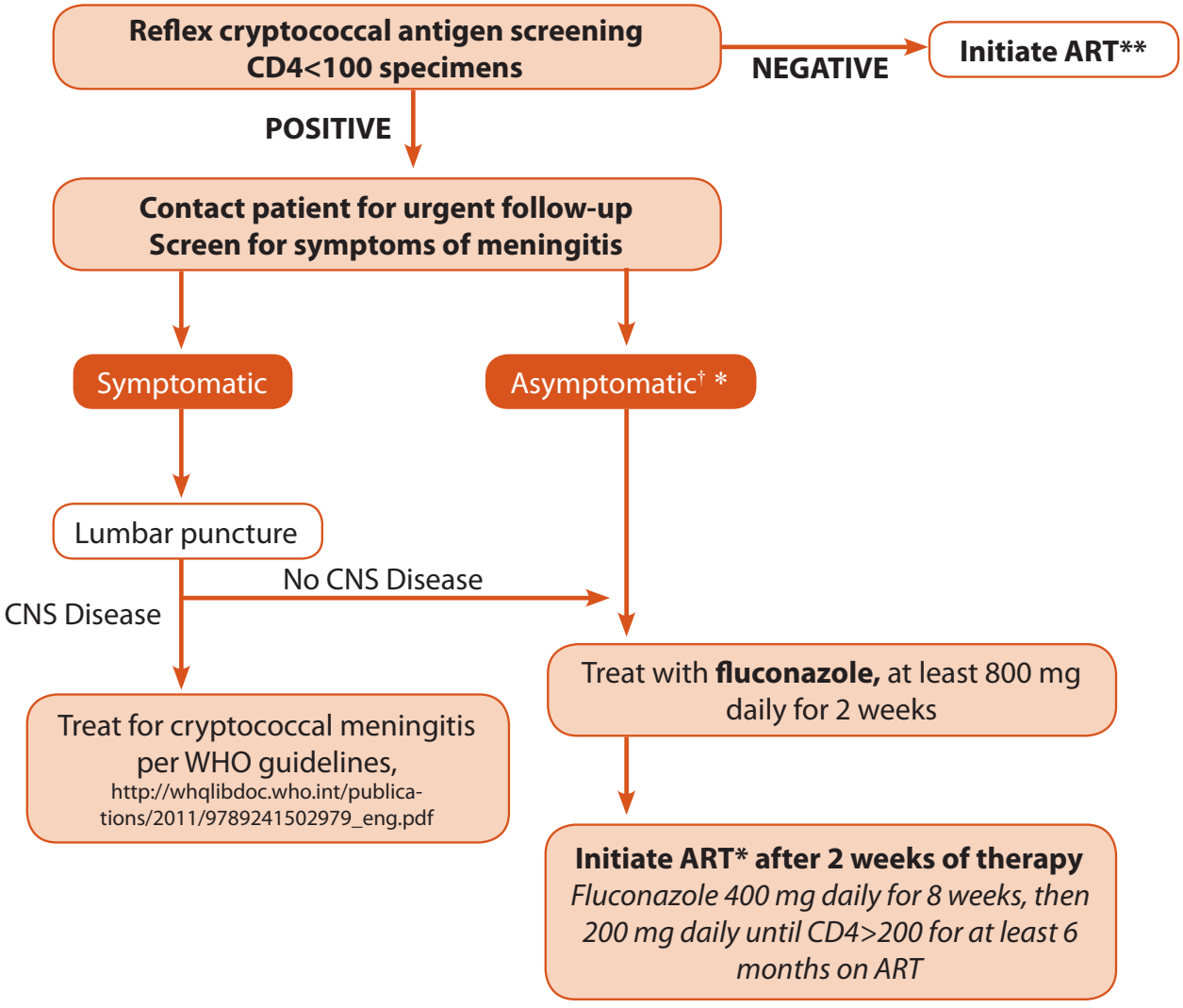
1. Identify patients at risk (CD4 less than 100)
2. Test for cryptococcal antigen before onset of meningitis symptoms
3. Treat with oral fluconazole
4. Prevent cryptococcal meningitis deaths

Decision-making guide

When you order a CD4 count test, the laboratory will automatically perform a cryptococcal antigen test on all patients whose CD4 count is <100. A patient with a positive cryptococcal antigen test should be contacted urgently to return to the clinic for follow-up, so it is important to keep a detailed record of patients' contact information. The patient should be assessed for symptoms of meningitis and for special situations (see decision-making guide on the following page). If the patient has any symptom of meningitis (headache lasting longer than 24 hours, fever, confusion or coma, blurry vision, or neck stiffness), he or she will need a lumbar puncture. Patients with a lumbar puncture that shows *Cryptococcus* in the spinal fluid will need to be hospitalized for two weeks of amphotericin B therapy (refer back to the WHO guidelines on page 16 of this training manual).

Module 6: Decision-Making Guide for Cryptococcal Screening

If the patient does not have any symptoms of meningitis at the time of the clinic visit or if the lumbar puncture is negative for *Cryptococcus* in the CSF, the patient should be started on fluconazole as outlined in the decision-making guide for cryptococcal screening for your country or the recommendations in the WHO guidelines (Module 4). Patients who develop meningitis symptoms despite fluconazole treatment need to undergo a lumbar puncture.



† If resources are available, a lumbar puncture should also be offered to asymptomatic patients with appropriate counseling.
*Populations who require special attention include: patients on tuberculosis medications or nevirapine, patients with a previous history of cryptococcal meningitis, pregnant women or breastfeeding mothers, patients with liver disease, and children.
**Initiate ART if not already started

Module 6: Decision-Making Guide for Cryptococcal Screening

Other clinical conditions

Patients on tuberculosis medications

Tuberculosis medications (including INH) and fluconazole can be started at the same time. Because both fluconazole and TB medications can damage the liver, these patients should preferably be started on an efavirenz-based ART regimen. Patients should be monitored closely for signs of liver damage including right upper quadrant abdominal pain, nausea/ vomiting, or jaundice (yellowing of the skin and eyes). If there are signs of toxicity, then liver function tests should be ordered.

Patients on nevirapine

For patients starting ART, use efavirenz-based regimen rather than nevirapine, since nevirapine might increase the risk of liver damage. If patient is already on nevirapine, then the patient should be monitored closely for signs of liver damage including right upper quadrant abdominal pain, nausea/vomiting, or jaundice (yellowing of the skin and eyes). If there are signs of toxicity, then liver function tests should be ordered.

Patients with previous history of cryptococcal meningitis

Patients with a previous history of CM do not need to be routinely screened. However, if the patient has new symptoms of meningitis, he/ she will need to be evaluated for relapse disease and/or IRIS. If the patient does not have new symptoms, the health care provider should ensure that the patient has received or is receiving adequate maintenance therapy (fluconazole 200 mg until CD4 count >200 cells/µl on ART and for a minimum of 12 months total) after being treated with induction and consolidation therapy.

Pregnancy or breastfeeding mothers

Because fluconazole can be harmful to a fetus, all women of childbearing age should have a pregnancy test. The risks, benefits and alternatives to fluconazole treatment should be discussed with the patient. Consultation with a physician experienced in the care of HIV/AIDS patients is recommended. Mothers who are breastfeeding also require consultation with an experienced physician as fluconazole can be transmitted through breast milk to the infant. Women of childbearing age who are not yet pregnant and are starting fluconazole treatment should be advised to avoid becoming pregnant during treatment.

Liver disease

Patients with history of liver disease (cirrhosis, hepatitis, etc.), jaundice (yellowing of the skin and eyes), or abnormal liver enzyme tests may deserve careful monitoring because fluconazole may cause liver damage. Consultation with a physician experienced in the care of HIV/AIDS patients is recommended.

Children

Screening is not recommended for children as CM is less common in this group. All children who are serum CrAg-positive should be referred for lumbar puncture (LP). Children with a positive LP should be managed according to your country-specific guidelines or the WHO guidelines, available on page 25 of the document available at: http://whqlibdoc.who.int/publications/2011/9789241502979_eng.pdf.

What should I do if a lumbar puncture cannot be performed?

1. If a lumbar puncture is contraindicated but the patient is symptomatic and has a positive serum CrAg test, the patient should be treated with amphotericin B.
2. If a lumbar puncture cannot be performed because resources are not available, the patient should be transferred to the nearest facility where such services are available.
3. If a lumbar puncture cannot be performed because the patient refuses the procedure, every effort at proper patient education and discussion of risk and benefits should be made. If the patient still refuses, he or she will need to be treated like a patient for whom a lumbar puncture is contraindicated (see #1)

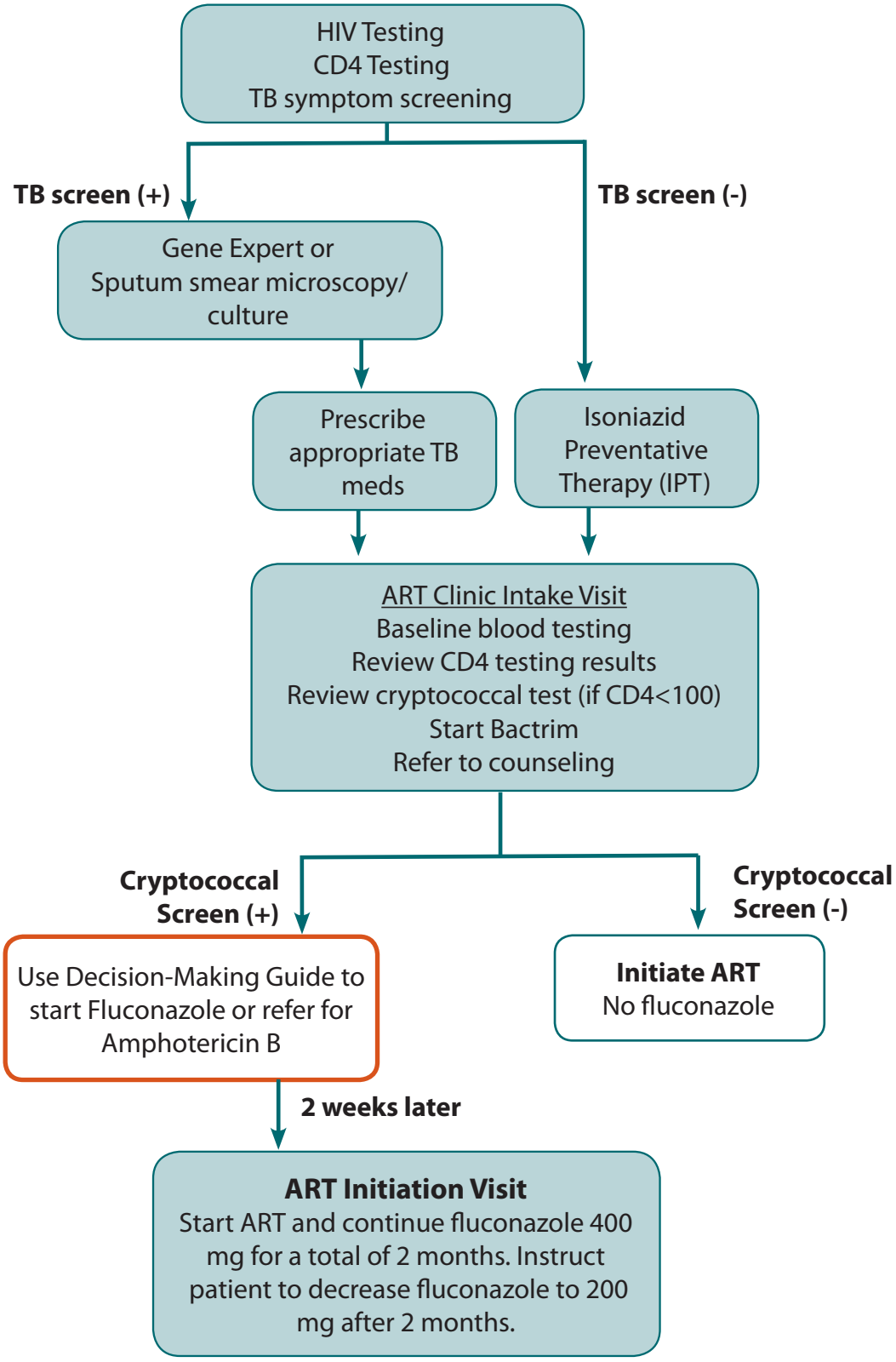
What should I do if amphotericin B therapy is not available?

If amphotericin B is not available or cannot be given safely, the patient should be transferred to a facility where amphotericin B is available. If the patient cannot be transferred, use of high-dose fluconazole (induction phase, fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day) may be considered in consultation with a physician experienced in HIV/AIDS care, however, this is not the recommended treatment regimen. Amphotericin B should always be the drug of first choice as it clears *Cryptococcus* from the body much faster than fluconazole.

How does screening fit into routine HIV care?

Like co-trimoxazole prophylaxis and isoniazid preventive therapy (IPT), cryptococcal screening and treatment of antigenemia with oral fluconazole can be part of an integrated care and treatment strategy for HIV/AIDS patients. In areas where cryptococcal disease prevalence is high, an integrated approach can help reduce early mortality among HIV/AIDS patients starting ART.

Module 6: Decision-Making Guide for Cryptococcal Screening



Module 7: Your Role as a Health Care Provider

Training objectives

- Understand what you can do as a health care provider as part of the screening program for cryptococcal antigen
- Be able to counsel your patients on fluconazole adherence

Supplies needed

- Module 7 slides (optional)

What you can do as a health care provider

- Educate yourself on cryptococcal screening and preventive management of HIV/AIDS patients starting ART.
- Save lives by screening your patients and treating them with oral fluconazole before symptoms of cryptococcal meningitis develop.
- Counsel your patients on fluconazole adherence.
- Provide regular feedback to coordinators regarding the program's operation so that they can make improvements.
- Build awareness of cryptococcal meningitis by teaching other health care providers about this screening strategy.

How to counsel your patients

First, patients should understand that cryptococcal antigenemia can be deadly if it is not treated. For this reason, you should emphasize the importance of taking fluconazole, even if the patient does not have any symptoms. It is also important to make sure that patients understand how many fluconazole pills to take.

Finally, encourage patients to contact the clinic immediately if they begin to experience side effects related to fluconazole therapy, which include diarrhea, nausea, abdominal pain, headache, dizziness, rash, or symptoms of liver toxicity.

Discussion questions

- What difficulties do you anticipate having when screening patients for *Cryptococcus*?
- What difficulties do you anticipate with patients' adherence to fluconazole?

Case Studies

Image courtesy of World Health Organization

Case Study 1: Symptomatic Presentation of Cryptococcal Meningitis

Highlights the typical presentation and basic management of cryptococcal meningitis

Patient history and initial presentation

A 49 year-old, newly-diagnosed HIV-positive man is referred to your clinic with a CD4 count of 9. He has been having watery diarrhea for 1 month, and has lost 10 kg over the past 2 months. He lives by himself and drinks 1 bottle of wine and 2 glasses of brandy per day.

He reports no headache, fever, confusion, neck stiffness, or sensitivity to light. However, he is very wasted, mildly dehydrated, and has oral candidiasis.

Patient management

Baseline bloods are ordered: full blood count, creatinine, ALT, and RPR
Stool sample is collected and sent to the lab.
Serum cryptococcal antigen (CrAg) test reviewed: **positive**
The patient is told to complete readiness classes and return to the clinic in 2 weeks to begin ART

Medications prescribed

Nystatin mouth wash
Bactrim 2 tabs/day
Vitamin B complex 2 tabs/day
Thiamine 200 mg/day (in view of alcohol history and possible malabsorption)
Vitamin C 100 mg/day

Case Study 1: Symptomatic Presentation of Cryptococcal Meningitis

Patient progress

The patient does not return to your clinic to start ART. Three months later, he presents to the hospital with a headache, neck stiffness, and confusion. A lumbar puncture shows that his intracranial pressure is very high (45 cm), and that his spinal fluid contains *Cryptococcus* (India Ink and CrAg positive). Daily therapeutic LPs are performed to reduce his intracranial pressure, and his creatinine, potassium, and magnesium are monitored. He is started on amphotericin B with pre-hydration.

Patient progress

Despite appropriate management, the patient dies on day 5 of admission.

Discussion points

1. On his return visit, the patient had markers of severe cryptococcal meningitis: altered mental status and raised opening CSF pressure.
2. Although patients with low-level cryptococcal antigenemia may clear the infection with ART alone, many patients have a delay in starting ART (either due to other medical conditions such as TB or issues with access to care). This patient should have been prescribed fluconazole at his intake visit (followed by ART one to two weeks later) in order to prevent his silent cryptococcal infection from progressing to meningitis.
3. A delay in presentation can lead to severe meningitis with high mortality (up to 50%).

Case Study 2: Asymptomatic Presentation of Cryptococcal Meningitis

Highlights the potential treatment complications associated with cryptococcal meningitis

Patient history and initial presentation

A 40-year old man is referred to your clinic after a 2-week hospital stay with pneumocystis pneumonia, where he was treated with cotrimoxazole and steroids, and made a good recovery. He is newly diagnosed with HIV with a CD4 count of 11. Upon presentation to the clinic, he has a headache, but no fever, confusion, or neck stiffness. However, he has severe oral candidiasis, one Kaposi's sarcoma (KS) lesion on his back, and nerve pain in his feet.

Patient management

Baseline bloods are ordered: full blood count, creatinine, ALT, and RPR
Serum cryptococcal antigen (CrAg) test reviewed: **positive**
Lumbar puncture performed: CSF CrAg test positive, India Ink positive
Patient admitted to hospital for management of cryptococcal meningitis

Medication prescribed

Amphotericin B 1 mg/kg/day with pre-hydration

Patient progress

On day 4 of hospital admission, the patient's creatinine is too high, which means his kidneys are failing. He is given fluids and the dose of amphotericin B is lowered. On day 10, the amphotericin B causes him to develop thrombophlebitis (swelling in the veins due to blood clots) and has become anemic. He completes 14 days of amphotericin B and is discharged on fluconazole.

At his post-hospital discharge clinic visit, the patient is doing well and does not complain of headaches.

He is continued on fluconazole 800 mg/day and is started on ART (AZT, 3TC, EVZ in view of his poor kidney function and peripheral neuropathy (nerve pain).

Case Study 2: Asymptomatic Presentation of Cryptococcal Meningitis

Discussion points

1. Late-stage HIV patients often have multiple other conditions, so it is important to look for cryptococcal meningitis.

2. Amphotericin B can have serious side effects, including abnormal heart rhythms, kidney failure, low potassium, abdominal discomfort, infusion reactions, phlebitis, anemia, and low white blood cell count.

3. Fluconazole can interact with some ART medications, and this is an important consideration when starting ART. For patients starting ART, use efavirenz-based regimen rather than nevirapine, since nevirapine might increase the risk of liver damage. If the patient is already on nevirapine then he or she should be monitored closely for signs of liver damage including right upper quadrant abdominal pain, nausea/vomiting, or jaundice (yellowing of the skin and eyes). If there are signs of toxicity, liver function tests should be ordered.

Case Study 3: Previous Cryptococcosis

Highlights the importance of determining whether the patient has a history of cryptococcal meningitis

Patient history and presentation

A 37 year-old woman comes to your clinic for the first time with a CD4 count of 19. She recently moved to Cape Town from Queenstown, leaving behind her medications and transfer letter. She reports no headache, fever, confusion, or neck stiffness, and there are no positive findings upon examination.

Patient management

Baseline bloods are ordered: full blood count, creatinine, ALT, and RPR
Serum cryptococcal antigen (CrAg) test reviewed: **positive**
The patient is told to complete readiness classes and return to the clinic in 2 weeks to begin ARTs.

Medication prescribed

Fluconazole 800 mg/day for 2 weeks
Bactrim 2 tablets/day
Vitamin B complex 2 tablets/day

Patient progress

At her follow-up visit, the patient is doing well. Her sister brought the patient's original medications and clinic transfer letter. You learn that the patient had previously been admitted to hospital with cryptococcal meningitis 2 months ago, and was prescribed fluconazole 200 mg/day, Bactrim, and Vitamin B complex.

Case Study 3: Previous Cryptococcosis

Discussion Points

1. Cryptococcal antigen can be present for up to 2 years after an episode of cryptococcosis. A patient with previous cryptococcal disease and a positive screening test needs to be evaluated for symptoms of cryptococcal meningitis.

2. A patient with previous cryptococcosis should remain on fluconazole prophylaxis until they have a CD4 count greater than 200 for at least 6 months on ART. If viral load testing is available, and the patient's viral load is suppressed, he or she can discontinue fluconazole if his or her CD4 count is greater than 100 for at least 6 months on ART.

3. Patients who have had previous cryptococcal disease are at risk of relapse of disease, especially if they have stopped taking their fluconazole prophylaxis. These patients are also at increased risk of cryptococcal Immune Reconstitution Inflammatory Syndrome (IRIS) when starting ART.

4. Any patient with a history of cryptococcosis who presents with a headache should be treated as if he or she has recurrent disease / IRIS until proven otherwise.

Case Study 4: Special Circumstances—on TB Medication

Highlights drug interactions and co-infections in patients with low CD4 count

Patient history and initial presentation

A 35 year-old man is referred to an ART clinic from a TB clinic after having been diagnosed smear-positive for pulmonary TB 4 weeks ago. He has started on regimen 1 (RHEZ). He is newly diagnosed with HIV, with a CD4 count of 50.

Upon presentation to the clinic, the patient feels well, and his respiratory symptoms are improving. He has no headache, fever, or neck stiffness. However, upon examination, the patient is wasted, has crackling in his lungs, and has a red, scaly rash.

Patient management

Baseline bloods are ordered: full blood count, creatinine, ALT, and RPR
Serum cryptococcal antigen (CrAg) test reviewed: **positive**
The patient is told to complete readiness classes and return to the clinic in 2 weeks to begin ART.

Medication prescribed

Fluconazole 800 mg/day for 2 weeks
Bactrim 2 tablets/day
Vitamin B complex 2 tablets/day

Patient progress

The patient telephones the clinic 2 days later, complaining of nausea and vomiting after taking the fluconazole and TB medications together. The patient is asked to return to clinic for an ALT test, which was normal. He is advised to divide the dose of fluconazole to 400 mg two times per day and to take the fluconazole separately from the TB medications. After this, the patient tolerates the medications well, and completes 6 months of TB treatment.

Case Study 4: Special Circumstances—on TB Medication

Discussion points

1. Many patients with CD4 counts less than 100 will also have TB. Because both fluconazole and TB medications can damage the liver, these patients should preferably be started on an efavirenz-based ART regimen.

2. Fluconazole and tuberculosis can both cause liver damage so it is necessary to check for symptoms and signs of liver toxicity (abdominal pain, nausea/vomiting, or yellowing of the skin and eyes) and measure ALT if concerned.

3. Fluconazole can cause nausea/gastrointestinal problems, as can TB medications. It may help to split the fluconazole dose to two times per day, and if severe nausea occurs, give an anti-emetic 30 minutes before.

Case Study 5: Special Circumstances—Pregnancy

Highlights the importance of evaluating for other clinical conditions and asking for specialist advice when needed

Patient history and initial presentation

A 23 year-old woman, 20 weeks pregnant, is referred to your clinic. She is newly-diagnosed HIV-positive with a CD4 count of 42. She reports no headache, fever, neck stiffness, or sensitivity to light, and there are no positive findings upon examination of the patient.

Patient management

Baseline bloods are ordered: full blood count, creatinine, ALT, and RPR

Serum cryptococcal antigen (CrAg) test reviewed: **positive**

Discussion Points

1. Management of a pregnant woman with incident cryptococcosis is complex and requires discussion with experienced specialists; this should not be undertaken lightly. There are several important points to consider.

    a. **Gestation of fetus**: fluconazole can cause birth defects, especially in the first trimester. However, the risks of cryptococcal meningitis to the mother and fetus are so high that appropriate anti-fungal therapy needs to be considered.

    b. **Symptoms:** symptomatic patients need a lumbar puncture and if positive, they will need amphotericin B. Asymptomatic patients should be counseled on risks and benefits of fluconazole therapy.

    c. **Timing of ART:** Even if fluconazole is not started in an asymptomatic pregnant patient, ART should not be delayed. However, when starting ART, one should watch for cryptococcal IRIS.

    d. **Type of ART:** the choice of ART should be made carefully. Fluconazole can interact with some ART medications, and this is an important consideration when starting ART.

        - Nevirapine: This is the preferred regimen for pregnant patients. Fluconazole can cause nevirapine to build up in the body, which can increase the risk of side effects, specifically liver toxicity. Check for symptoms and signs of liver toxicity (abdominal pain, nausea/vomiting, or yellowing of the skin and eyes) and measure ALT if concerned.

Case Study 5: Special Circumstances—Pregnancy

- Efavirenz: There are no known interactions between efavirenz and fluconazole; however, the use of efavirenz in pregnancy, especially in the first trimester, is not currently recommended.

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