

Cryptococcal Screening Program

**Training Modules
for Healthcare Providers**

Clinical case scenario

- 27-year-old male with AIDS
- CD4 count: 34 cells/mm³
- Presents to clinic to start anti-retrovirals
- Complains of mild headache but is otherwise well, started on anti-retrovirals
- Two months later develops low grade fever, nausea, confusion

What do you suspect as a diagnosis?

Could this have been prevented?

Learning Objectives

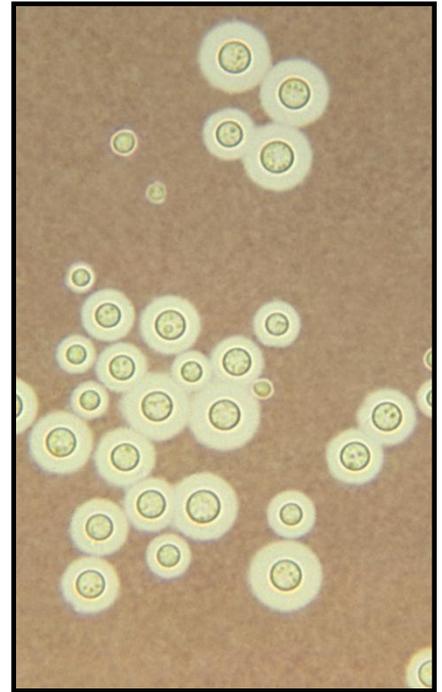
- Upon completion of this activity, participants should be able to:
 - Understand the public health burden and high mortality from cryptococcal meningitis
 - Describe current practices for diagnosing and treating cryptococcal meningitis
 - Explain the rationale for early cryptococcal antigen screening
 - Manage a patient with a positive cryptococcal antigen test

Overview

- Module 1:** What is *Cryptococcus*?
- Module 2:** Recognizing signs, symptoms of *Cryptococcus*
- Module 3:** Diagnosing cryptococcal disease
- Module 4:** Treating cryptococcal meningitis
- Module 5:** Preventing cryptococcal meningitis
- Module 6:** Decision-making guide for cryptococcal screening
- Module 7:** Your role as a health care provider

What is *Cryptococcus*?

- Fungus found in soil associated with certain types of trees
- Fungal spores are inhaled from environment
- The fungus cannot spread from person to person



Cryptococcus spp.
stained with India Ink

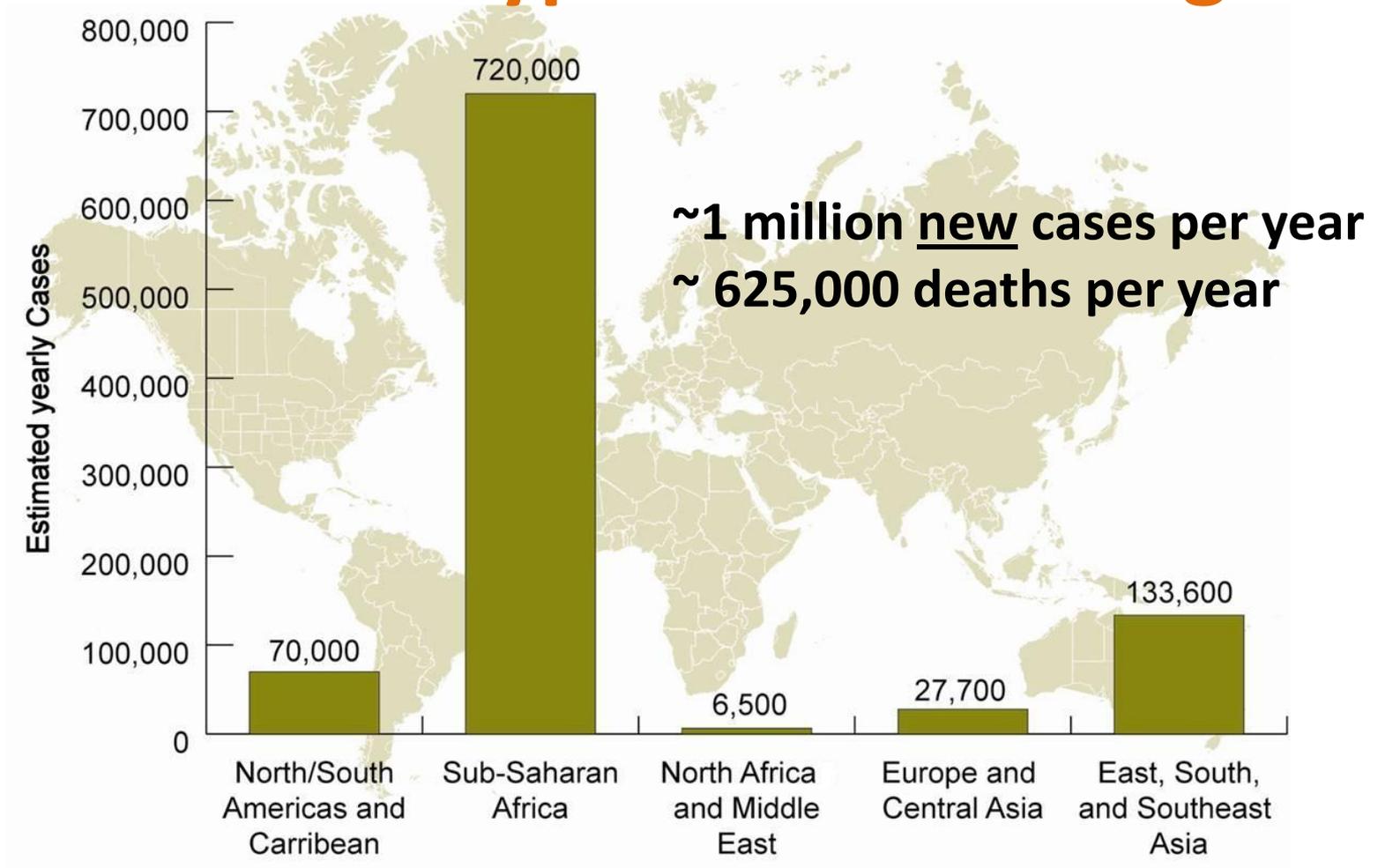
Cryptococcal infection

- Fungus can cause acute lung infection or no symptoms at all
- Incubation period unknown, may be dormant for many years
- Reactivation in immunosuppressed persons (HIV/AIDS, especially CD4 <100)
- Meningitis is the most common presentation

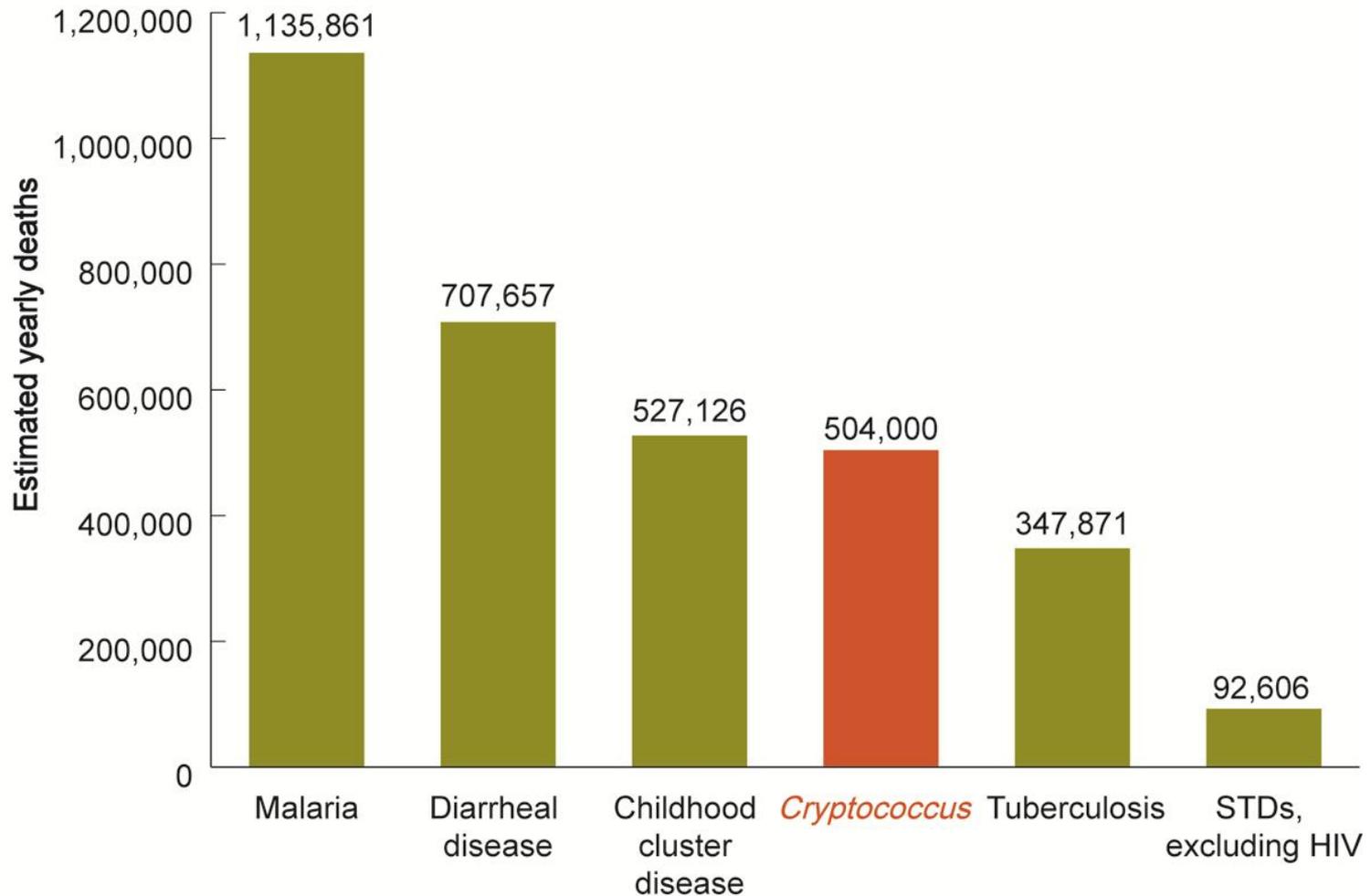
Death from cryptococcal meningitis

- Cryptococcal meningitis is a common cause of death among HIV/AIDS patients
- High mortality (30%-70% in sub-Saharan Africa) despite antiretroviral treatment (ART) and antifungal therapy
- In some areas of the world, it is estimated to cause more deaths than tuberculosis

Global burden of HIV-related cryptococcal meningitis



Causes of death in sub-Saharan Africa (excluding HIV/AIDS)



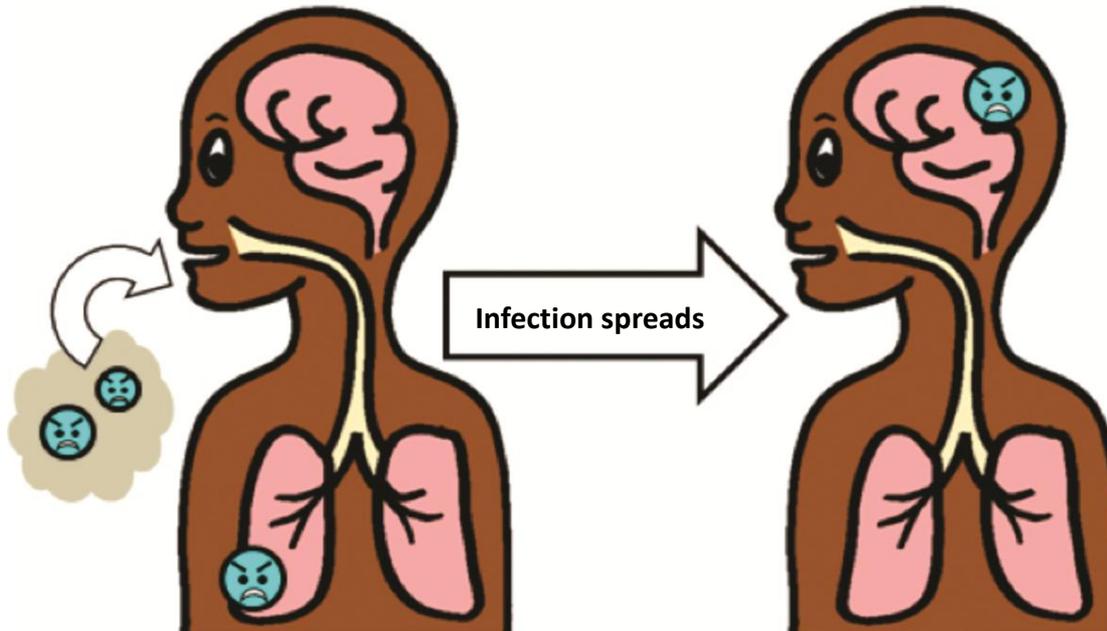
Signs and symptoms of cryptococcal meningitis

- Headache
- Fever
- Change in mental status (ranging from confusion to lethargy to coma)
- Blurry vision (and other cranial nerve deficits)
- Neck stiffness
- Sensitivity to light
- Nausea and vomiting
- Seizures
- Papilledema

Clinical course of cryptococcal disease

No symptoms or symptoms of lung infection

- Shortness of breath
- Cough
- Fever



Meningitis

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

Other clinical presentations of cryptococcal disease

- Lung
 - Ranges from mild pneumonia to acute respiratory distress syndrome (ARDS)
 - Fever, cough, and dyspnea are common symptoms
- Skin
 - Papules, pustules, nodules, ulcers
- Bone
 - Most commonly vertebrae and ribs



Other diagnoses to consider in HIV/AIDS patients

- Meningoencephalitis caused by other organisms
 - Mycobacterium tuberculosis
 - Bacterial meningitis
 - Viral encephalitis
 - Syphilitic meningitis
 - Other organisms

Other diagnoses to consider in HIV/AIDS patients

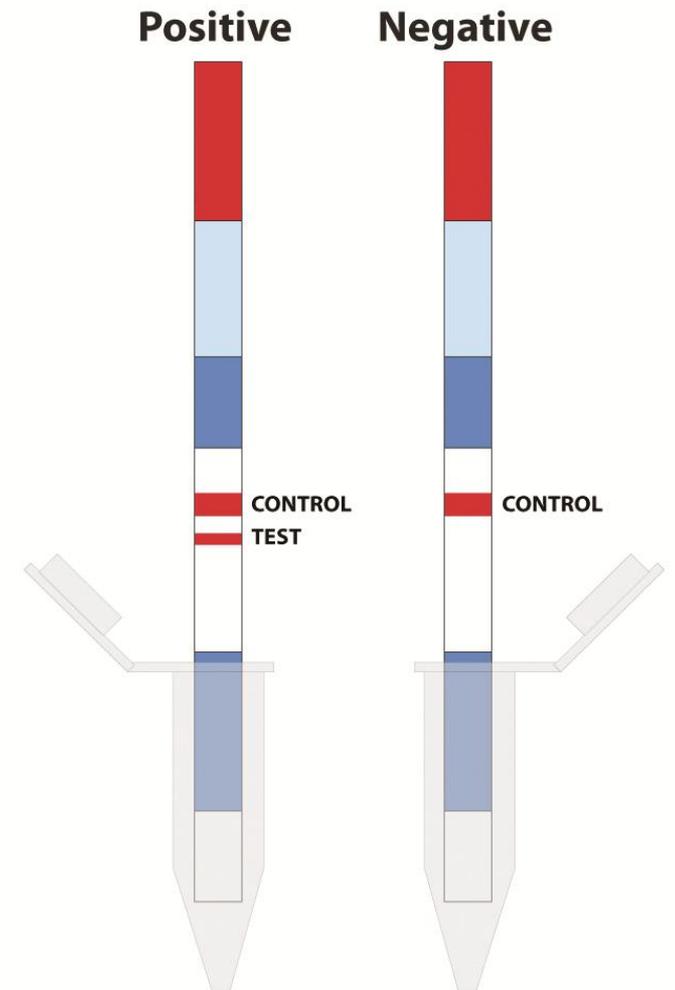
- Space-occupying lesions
 - Lymphoma (and other neoplasms)
 - Toxoplasma gondii (and other parasitic organisms)
 - Abscess
- HIV encephalopathy
- Other: (toxic, metabolic, auto-immune, intracranial bleed, etc.)

Current diagnostic methods

- India Ink microscopy (CSF)
- Culture (CSF or blood)
- Antigen detection
 - Latex agglutination (CSF or serum)
 - Enzyme immunoassay (EIA) (CSF or serum)
 - Lateral flow assay (LFA) (CSF or serum)

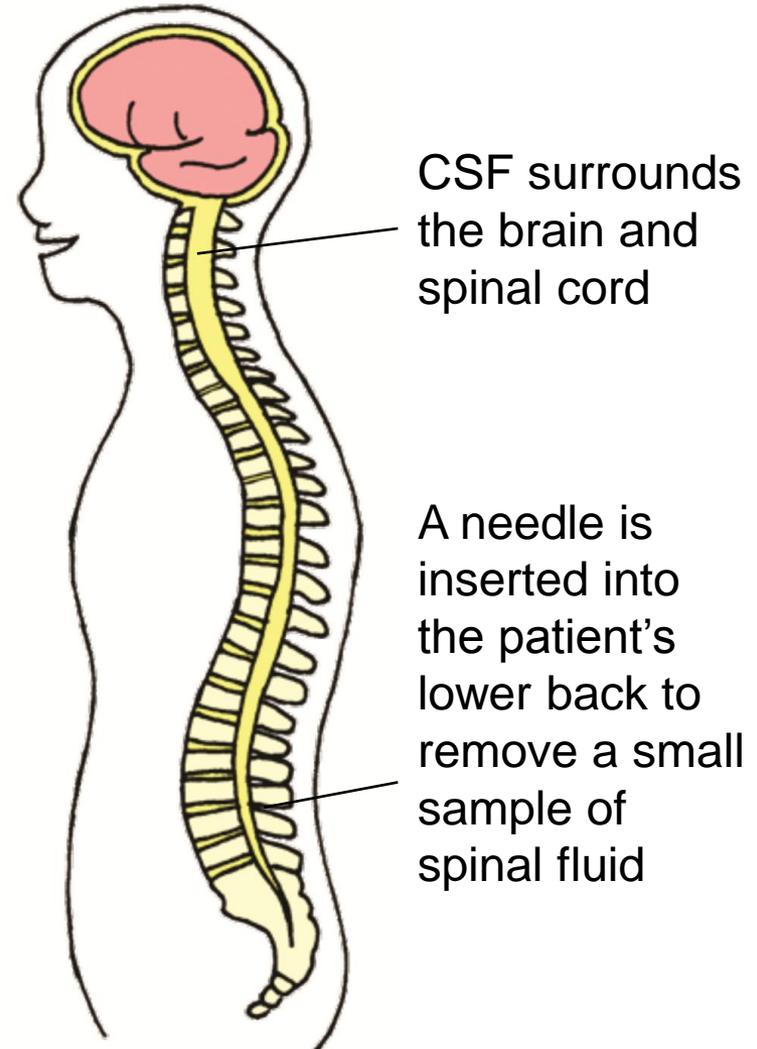
The new lateral flow assay (LFA) is...

- Simple and quick: Results available in 10 minutes
- Effective: Highly sensitive and accurate (>95%)
- Affordable (\$2-4 per test)
- Approved for use in serum (a component of blood) and cerebrospinal fluid (CSF)



How to diagnose cryptococcal meningitis

- Necessary to examine CSF
- CSF collected with lumbar puncture
- India Ink, cryptococcal antigen detection test, and fungal cultures should be performed on CSF; at least one of these tests should be positive to confirm CM



Performing a lumbar puncture

- Lumbar puncture (LP) is essential to both diagnosis and management
 - Obtain CSF to establish diagnosis
 - Alleviate symptoms by relieving intracranial pressure
 - Performed only by trained physicians

Performing a lumbar puncture

- If focal neurological deficits present, perform head CT scan first to rule out space-occupying lesions
 - In settings where CT scan not available, consider proceeding with LP, but discuss, weighing potential risks and benefits, with a senior clinician

Performing a lumbar puncture

- Measure opening CSF pressure (normal <20 cm CSF)
- Routinely order:
 - Microscopy (cell count, gram stain, India ink stain)
 - Chemistry (protein, glucose)
 - Bacterial culture
 - Cryptococcal antigen test and fungal culture

Performing a lumbar puncture

- Consider ordering:
 - Adenine deaminase (ADA)
 - Smear and culture for *Mycobacterium tuberculosis*
 - TPHA for syphilitic meningitis
 - *Toxoplasma gondii* IgM and IgG antibodies

How to diagnose non-meningeal cryptococcal disease

- An antigen test, India Ink, or culture on 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 for cryptococcal meningitis by LP

Treatment of adult cryptococcal meningitis

Regimen desirability	Drugs available	Induction phase options (2 weeks)	Consolidation phase options (8 weeks)	Maintenance / secondary prophylaxis
First choice	AmB ± flucytosine	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	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	a. Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day b. Fluconazole 1200 mg/day alone	Fluconazole 800 mg/day	

Managing intracranial pressure (ICP)

- Measure opening pressure with every LP performed
- If CSF pressure ≥ 25 cm and there are symptoms of raised ICP, reduce the opening pressure by 50% (if extremely high) or to normal pressure (≤ 20 cm)
- Repeat LP daily until CSF pressure and symptoms have been stabilized for > 2 days

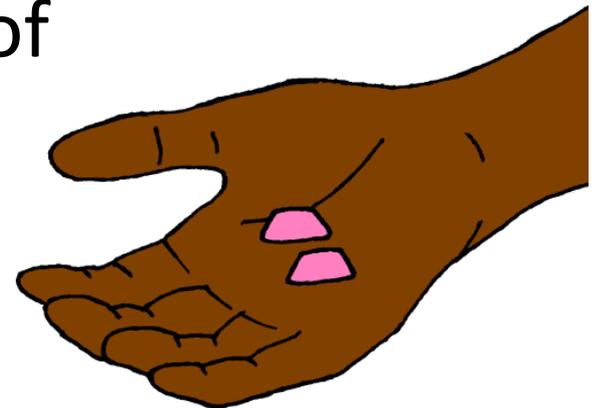


Side effects of therapy

- Fluconazole
 - Diarrhea, nausea, abdominal pain
 - Headache, dizziness
 - Rash
 - Liver toxicity
 - Teratogenicity (damage to fetus)
- Amphotericin B
 - Infusion-related acute reaction (fever, chills, hypotension) and phlebitis
 - Renal toxicity and electrolyte abnormalities

General information about fluconazole (Diflucan)

- Oral antifungal medication available in 50, 100, 150, or 200 mg tablets
- Can also be taken as an oral suspension
- Can interact with nevirapine and tuberculosis medications; patients on these drugs should be monitored for signs of liver toxicity



The Diflucan Partnership Program

- Since 2000, Pfizer has provided fluconazole free of charge to government and non-governmental organizations in resource-limited countries where the prevalence of HIV/AIDS is >1%.
- Approved for
 - Esophageal candidiasis
 - Cryptococcal meningitis



The Diflucan Partnership Program

- More information on the web at:
<http://www.directrelief.org/DiflucanPartnership/EN/DiflucanProgramOverview.aspx>



Immune reconstitution inflammatory syndrome (IRIS)

- Clinical worsening or new presentation of cryptococcal disease
 - Associated with immune system recovery after starting ART
- Types
 - Unmasking IRIS - new cryptococcal disease
 - Paradoxical IRIS - recurrence or worsening of known cryptococcal disease
- To prevent IRIS, ART should be delayed until after treatment for cryptococcal disease is started

Clinical case scenario revisited

- 27-year-old male with AIDS
 - CD4 34 cells/mm³
- Presents to clinic to start anti-retrovirals
 - Complains of mild headache, but is otherwise well, so is started on anti-retrovirals
 - Two months later develops low grade fever, nausea, confusion
- Diagnosed with cryptococcal meningitis
- Admitted to hospital for Amphotericin B therapy, but subsequently dies

Could this have been prevented?

Why is preventing cryptococcal meningitis important?

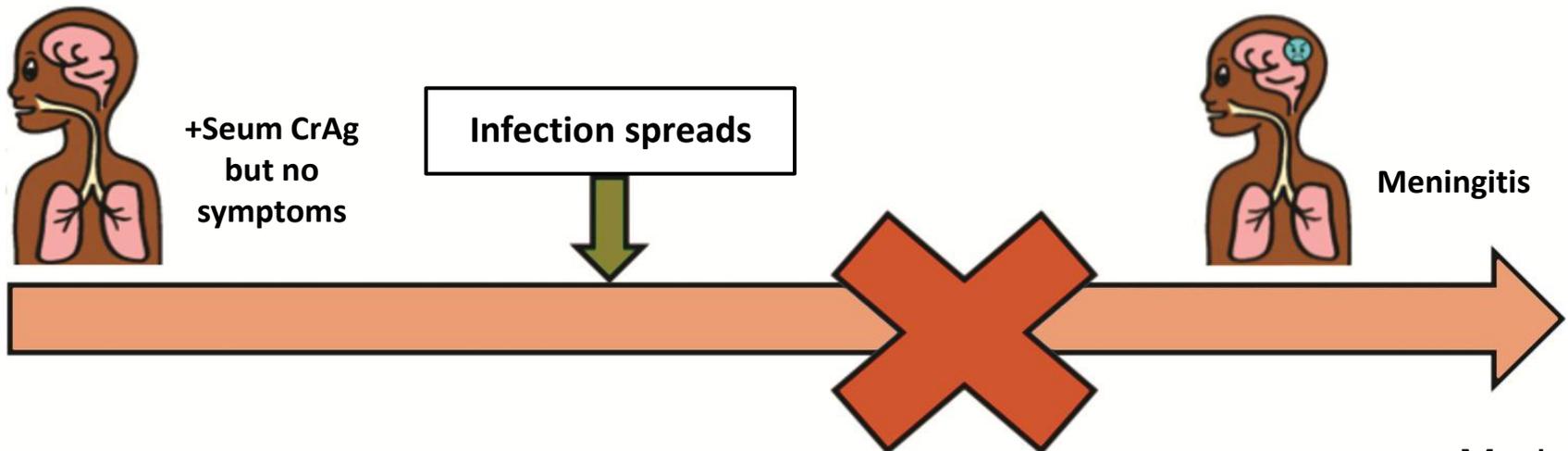
- Patients at highest risk: CD4 <100
- Majority of cryptococcal cases occur among patients before they start ART
- ART-associated cases (related to IRIS) are also common
 - Cryptococcal meningitis accounts for 20% of early deaths among HIV-infected patients starting ART

Primary prophylaxis

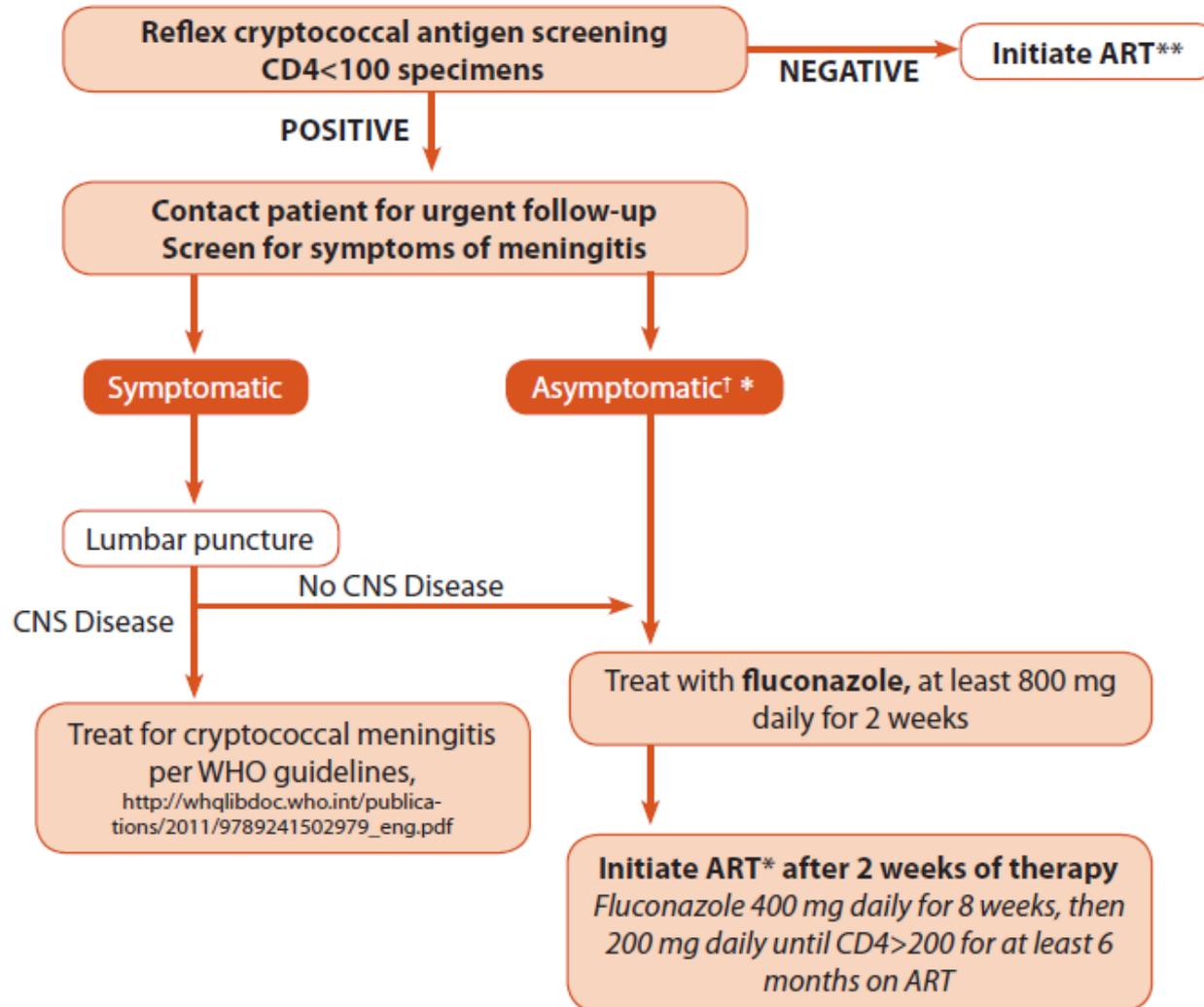
- Treatment of all HIV-infected patients with low CD4 with low-dose fluconazole (200 mg/day) to prevent cryptococcal infection
- Limitations
 - Limited improvement in mortality
 - Cost
 - Concern for widespread fluconazole resistance
 - Drug toxicity
 - Interaction with other TB and ART drugs
 - Use in women of child-bearing age

Cryptococcal screening

1. Identify patients at risk (CD4 <100)
2. Test for cryptococcal antigenemia before symptom onset
3. Treat with oral fluconazole
4. Prevent cryptococcal meningitis deaths



Decision-Making Guide for Cryptococcal Screening



† 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

Check for other clinical conditions

- Patients on tuberculosis medications
 - TB medications and fluconazole can be started at the same time, but patients should be monitored for signs of liver toxicity, and an efavirenz-based regimen should be used
- Patients on nevirapine
 - The combination of nevirapine and fluconazole can increase risk of liver damage. Patients should be monitored for signs of liver toxicity

Check for other clinical conditions

- Patients with previous history of cryptococcal meningitis
 - Ensure that they received adequate maintenance therapy for prior episode
 - If new symptoms, need evaluation for relapse and/or IRIS

Check for other clinical conditions

- Pregnancy or breastfeeding mothers
 - Fluconazole may be harmful to the fetus
 - Women of childbearing age need a pregnancy test
 - If pregnant or breastfeeding, consult with an experienced physician
 - Women of childbearing age who start taking fluconazole should avoid getting pregnant while on this medication and should be counseled on appropriate birth control

Check for other clinical conditions

- Liver disease
 - Known liver disease (cirrhosis, hepatitis, etc.), jaundice (yellowing of the skin, eyes), or abnormal liver tests
 - Consult with an experienced physician.
- Children
 - Screening is not recommended for children; CM is uncommon in this group
 - Children should be treated with a weight-based fluconazole regimen.

How does screening fit into routine care?

- You will receive the results of the CrAg test at the same time you receive the CD4 count.
- If CrAg positive, arrange the initial ART intake visit as soon as possible
 - Use Cryptococcal Screening Decision-Making Guide to determine whether patient needs fluconazole or needs to be referred to hospital for lumbar puncture and / or Amphotericin B
 - Begin ART after 2 weeks of cryptococcal therapy
- If CrAg negative, patient should begin ART without delay

Clinical case scenario revisited

- 27-year-old male with AIDS
 - CD4 34 cells/mm³
- Presents to clinic to start anti-retrovirals
- Complains of mild headache, but is otherwise well
- Patient is screened with serum CrAg test
- Cryptococcal antigen test is positive, patient offered lumbar puncture (negative), and started on fluconazole

Clinical case scenario revisited

- Started on ART 2 weeks later
- Patient doing well six months after starting ART

What you can do as a health care provider

- Educate yourself on screening and preventive management of HIV/AIDS patients starting ART
- Begin saving lives by screening your patients
- Provide feedback to coordinators regarding program operation
- Teach other health care providers about this screening strategy
- Counsel your patients on fluconazole adherence

How to counsel your patients

- Patients should understand that cryptococcal meningitis can be deadly if not treated
- Emphasize the importance of taking fluconazole, even if patient has no symptoms
- Make sure patients know how many fluconazole pills to take
- Encourage patients to contact the clinic immediately if they experience side effects related to fluconazole

For more information,
consult the WHO “Rapid
Advice” guidelines for
the Diagnosis,
Prevention, and
Management of
Cryptococcal Disease in
HIV-Infected Adults,
Adolescents, and
Children

RAPID ADVICE

DIAGNOSIS, PREVENTION AND MANAGEMENT
OF CRYPTOCOCCAL DISEASE IN HIV-INFECTED
ADULTS, ADOLESCENTS AND CHILDREN

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