KINGDOM OF CAMBODIA

Nation Religion King

Ministry of Health

Guidelines for Screening of Cryptococcal Infections in HIV-Infected Patients

July 2018

National Center for HIV/AIDS, Dermatology and STD

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Director of NCHADS

Dr. Ly Penh Sun

I. Background and Rationale

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 (CM). In low resource settings and especially in sub-Saharan Africa and Asia, cryptococcosis appears more frequently and is one of the more prominent AIDS-defining illnesses. Presumably the transmission is via inhalation. This pulmonary infection may remain subclinical in immune-competent patients, but is almost always followed by disseminated disease in HIV patients. Apart from the lungs, the manifestation after hematogenic spread is in the central nervous system. For this reason, a lumbar puncture (LP) and cerebrospinal fluid (CSF) examination is obligatory in cases suspected of cryptococcal meningitis (Ref.1).

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 as HIV/AIDS patients. It can cause diseases in the brain, lungs, skin, and bones however meningoencephalitis is the most common form of cryptococcal disease in HIV/AIDS patients.

Cryptococcus almost always occurs with severe immunodeficiency. In a collection of 114 cases, 87% had less than 100 CD4 T cells/µl (CD4<100/µl). Cryptococcosis is fatal if untreated. Treatment is lengthy and complicated. Relapses were frequent in the pre-ART era and occurred in at least 15% of cases. In addition, cryptococcosis occurs relatively frequently in the presence of an immune reconstitution inflammatory syndrome (Ref.1). Additionally, well-conducted recent studies using amphotericin B (AmB) in South Africa and Thailand reported early mortality of 20-33% (Ref.7).

Cryptococcus is an important public health issue since cryptococcal infection is a leading cause of death among people living with HIV/AIDS; it is the most common cause of adult meningitis in most of Africa; death rates for patients diagnosed with CM are 30-70% in Africa and Asia, though the rate in Cambodia is currently unknown. There are several reasons that the death rate is so high in these areas: first, patients often present with disease that is too advanced for treatment to be effective. Second, CM occurs even when 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 (Ref.2).

Data in 2016 from four provinces in Cambodia showed that of 394 patients who had cerebrospinal fluid tested 15.7% (62) were *Cryptococcus* positive. Diagnostic tests included India ink, isolation by routine agar culture and limited Cryptococcal Antigen Lateral Flow Assay (CrAg LFA). Unfortunately, there was no data on *Cryptococcus* specific death rates (Ref.8).

Chapter 17 of the National HIV clinical management guidelines for adults and adolescents details clinical manifestations, diagnosis, treatment, and case management of CM (Ref.6). This guideline will complement the National HIV clinical management guidelines for adults and

adolescents, outlining standard procedures for screening of patient specimens for cryptococcal infection. This enables early diagnosis and treatment and contributes to reduced mortality from CM among people with HIV/AIDS in Cambodia.

II. Goal and Objectives

The purpose of the guidelines is to enable early diagnosis and treatment of patients to reduce morbidity and mortality of cryptococcal disease.

The specific objectives are:

1. To provide clear paths for cryptococcal disease screening,
2. To enable early diagnosis of crytococcal disease,
3. To enable timely treatment,
4. To improve preventable mortality from cryptococcal disease.

III. When to consider the diagnosis of Cryptococcosis and Steps for implementation of Cryptococcus screening

There are three circumstances where cryptococcosis is highly suspected among patients; patients presenting with meningitis (regardless of HIV status); patients with clinical presentations related to raised intracranial pressure or encephalitic symptoms or cutaneous lesions or pulmonary manifestations (suggestive of cryptococcosis); and in HIV-infected patients whose CD4 cell count is less than 100 cells/mm^3 and/or initiate ART since less than 6 months.

3.1 Suspect cryptococcosis in all patients presenting with meningitis (regardless of HIV status):

- Patients may not be aware of their HIV status and may otherwise appear to be in a good state of health.
- HIV negative patients may also develop CM
- Fever, headache, malaise are the most common CM symptoms which develop over 1-2 weeks. Stiff neck, photophobia and vomiting may also be present.

In patients with above clinical presentations (3.1), please follow the figure 3.

3.2 Suspect cryptococcosis in patients with clinical presentation:

- Symptoms and signs related to raised intracranial pressure: headache, confusion, altered level of consciousness, 6th cranial nerve palsies with diplopia and visual impairment, papilledema (contra-indication for LP)
- Fever of unknown origin
- Encephalitic symptoms including memory loss and new onset psychiatric symptoms
- Cutaneous lesions (Fig. 1)
- Pulmonary involvement including cavitation, infiltration and consolidation

In patients with above clinical presentations (3.2), perform first serum cryptococcus antigen and LP if the serum is positive and there is no contra-indication for LP. IRIS must be suspected if

clinical signs appear in the first 6 months of ART and serum cryptococcus antigen must be performed, in that case, whatever the CD4 cell-count. Please refer to figure 4.

3.3 Cryptococcus screening in patients without clinical presentation

Although HIV-infected patients may not present any clinical sign and symptoms, if the CD4 cells are less than 100/mm^3 blood, the risk of cryptococcal disease is high; the serum CrAg must be performed. All new patients enrolled at the ART clinic, and patients who were lost to follow-up and return must have CD4 cell count (refer to figure 5):

3.3.1 If CD4 < 100 cells/mm^3

- Serum Cryptococcal antigen (CrAg) lateral flow assay (LFA) should be performed.
- If serum CrAg LFA is positive, a LP and CSF India ink and culture (if available) and CSF CrAg should be performed. If any of the tests performed on CSF are positive, the patient must be treated for cryptococcal meningitis.
- If serum CrAg LFA is positive, but LP is not feasible or CSF India ink or CSF CrAg is negative, pre-emptive treatment of cryptococcal disease shall be initiated.

3.3.2 If CD4 > 100 cells/mm^3

If CD4 cells at baseline is greater than 100 cells/mm^3, ART should be initiated without delay following the National HIV clinical management guidelines for Adults and Adolescents.

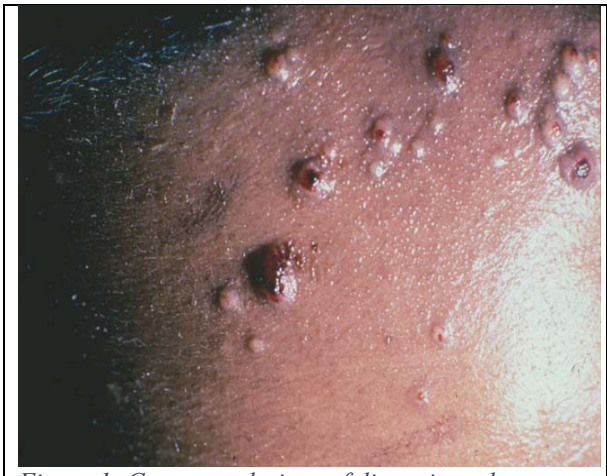


Figure 1: Cutaneous lesions of disseminated cryptococcosis.

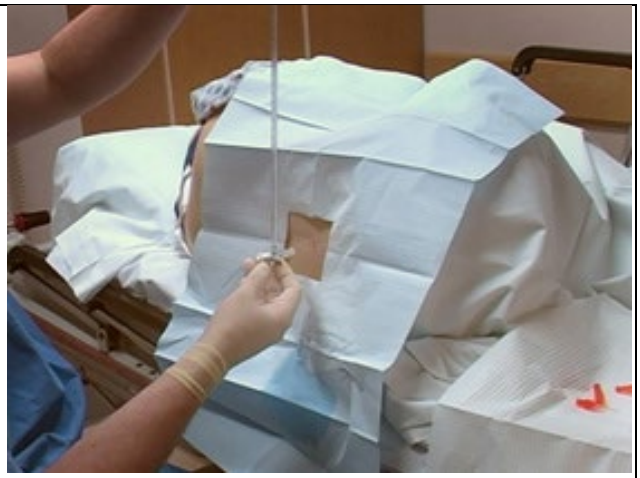


Figure 2: Measurement of CSF opening pressure using manometer

3.4 LP is essential to establish an etiological diagnosis of suspected CM. The following steps should be followed:

3.2.1 Health facility has ready access to and no contraindication for LP:

- If CrAg assay is accessible and rapid result is assured, LP and rapid CSF CrAg assay are recommended.
- If CrAg assay is not accessible and/or rapid result is not assured, LP and CSF India ink test and culture (if available) are recommended.
- If second episode of CM (either relapse or recurrence), recommend fungal culture.

3.2.2 Health facility has no immediate access to LP or contraindication for LP:

- If CrAg assay is accessible and rapid result is assured, rapid serum or plasma CrAg assay is recommended.
- If CrAg assay is not accessible and/or rapid result is not assured, immediate referral for further investigation and treatment is recommended.
- Note: patients with contra-indications to LP (i.e: focal neurological signs, seizures <2 weeks, mass lesion on CT scan) and positive CrAg result may also have another underlying disease (i.e: toxoplasmosis) and should be evaluated and treated accordingly.

Figure 3: Diagnostic approach in HIV-infected adults, adolescents and children with suspected first episode of cryptococcal meningitis:

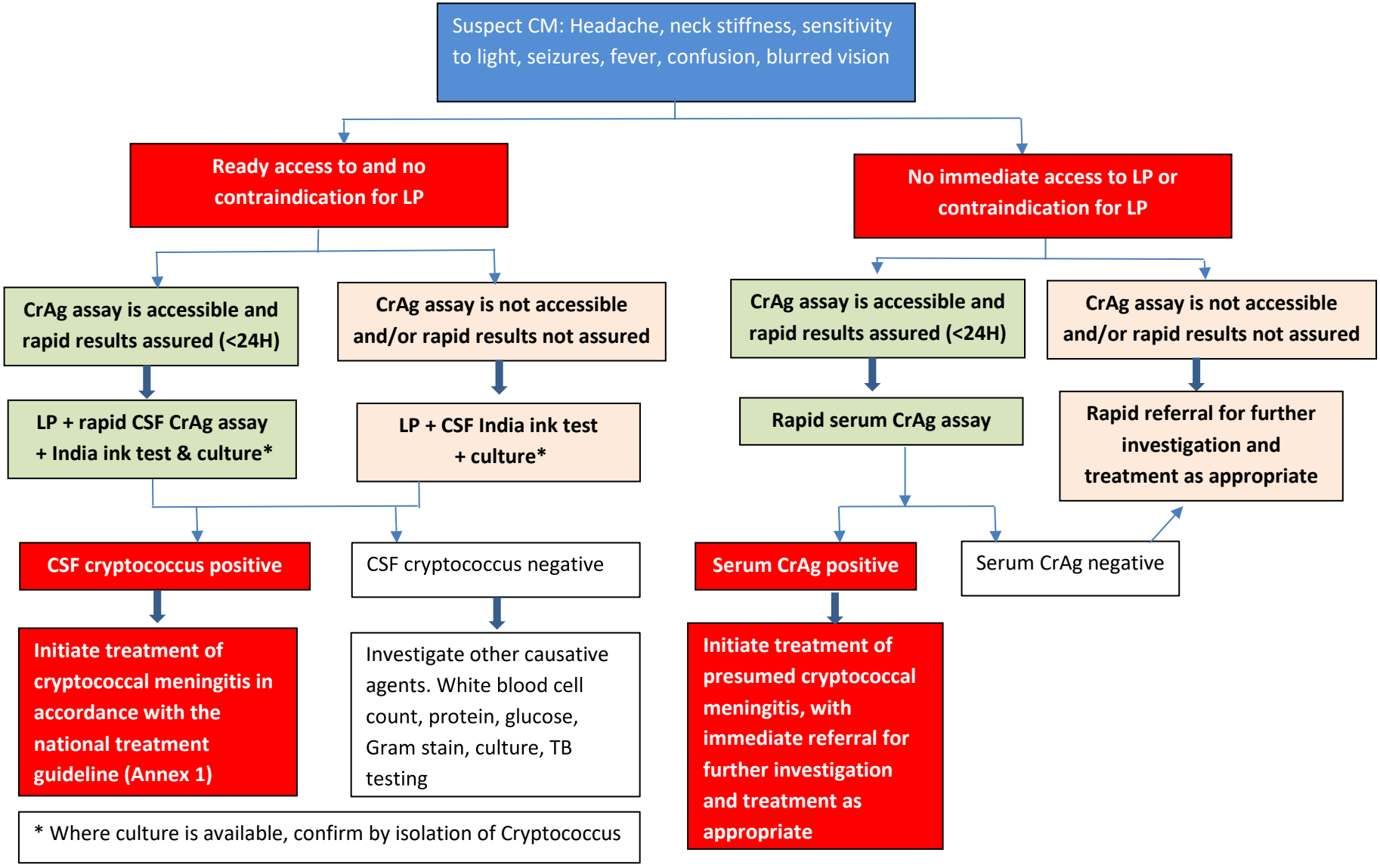


Figure 4: Diagnostic approach in HIV-infected adults, adolescents and children with suspected non-meningitis cryptococcal disease

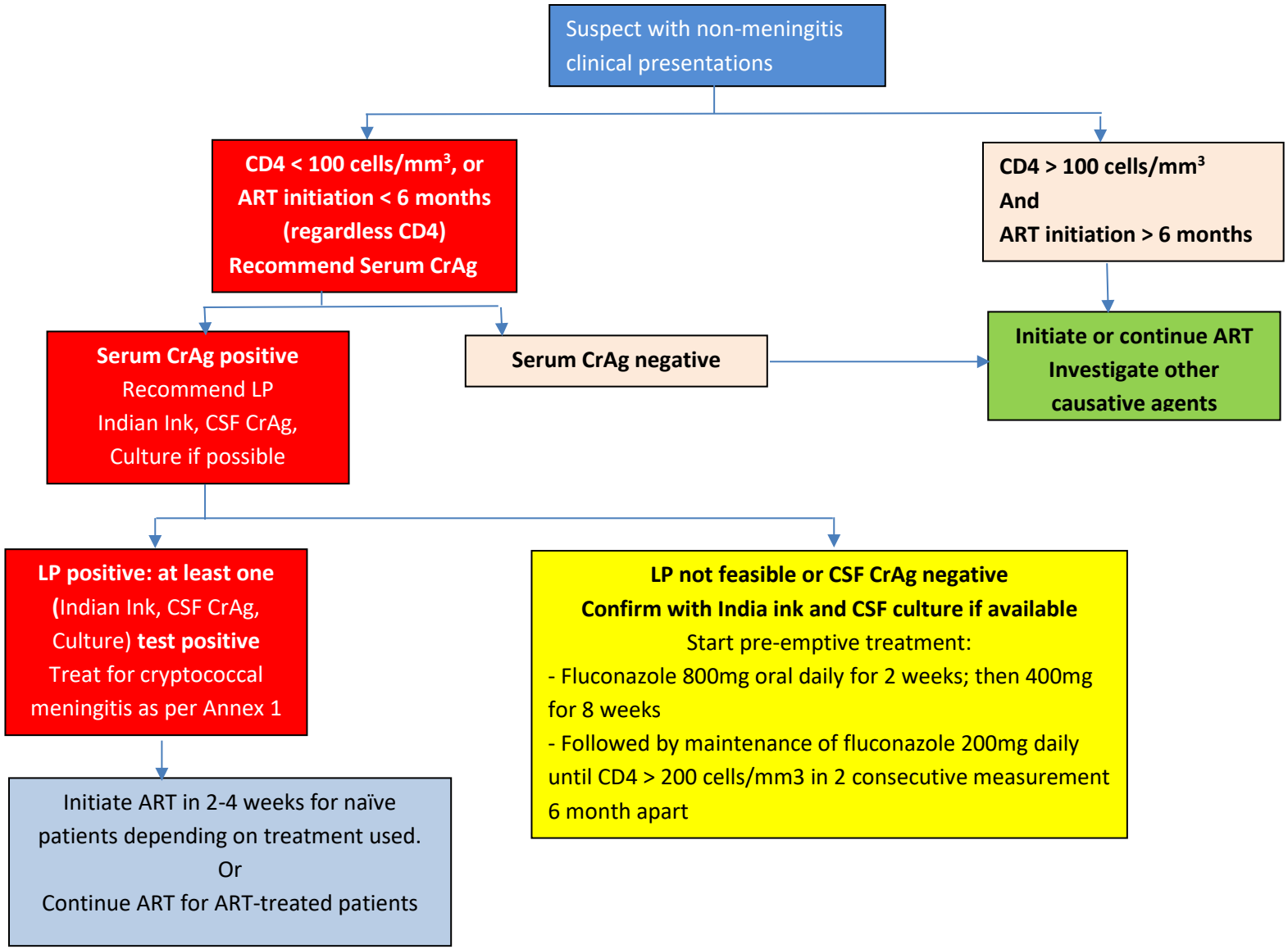
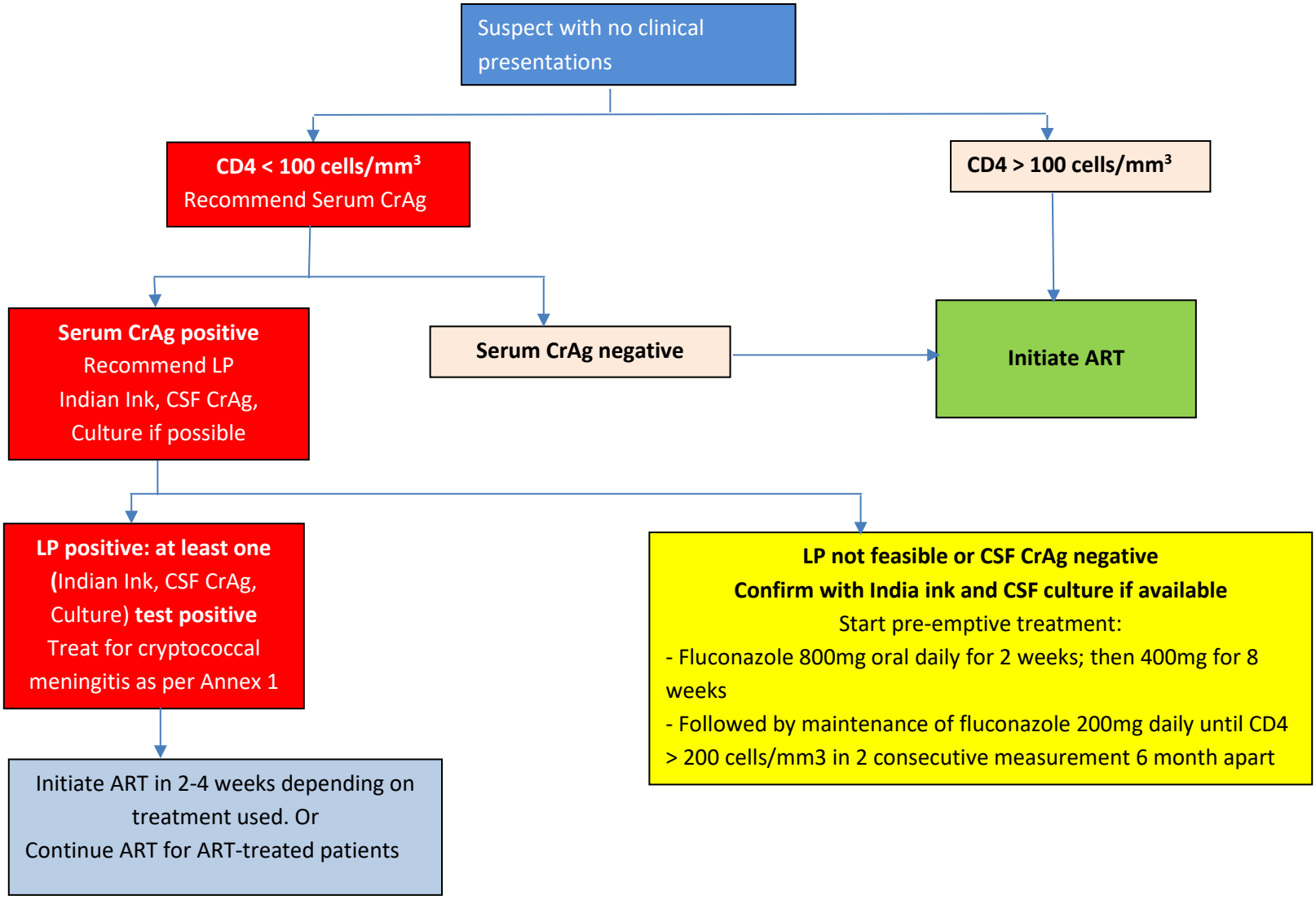


Figure 5: Diagnostic approach in naïve HIV-infected adults, adolescents and children without any suspected cryptococcal disease



Lumbar Puncture

Note: All patients where CSF is collected should have the following tests;

- CrAg –if supplies of the CrAg LFA are limited, consider only performing CrAg LFA when India ink test is negative
- Direct white blood cell count
- Protein (CSF supernatant)
- Glucose (CSF supernatant)
- India ink and Gram stain (CSF centrifuged deposit).

For laboratories with microbiology capacity;

- Culture on routine media (CSF centrifuged deposit)-sheep blood agar, chocolate agar, sabarouds agar (optional)

For laboratories with TB testing and TB culture capacity;

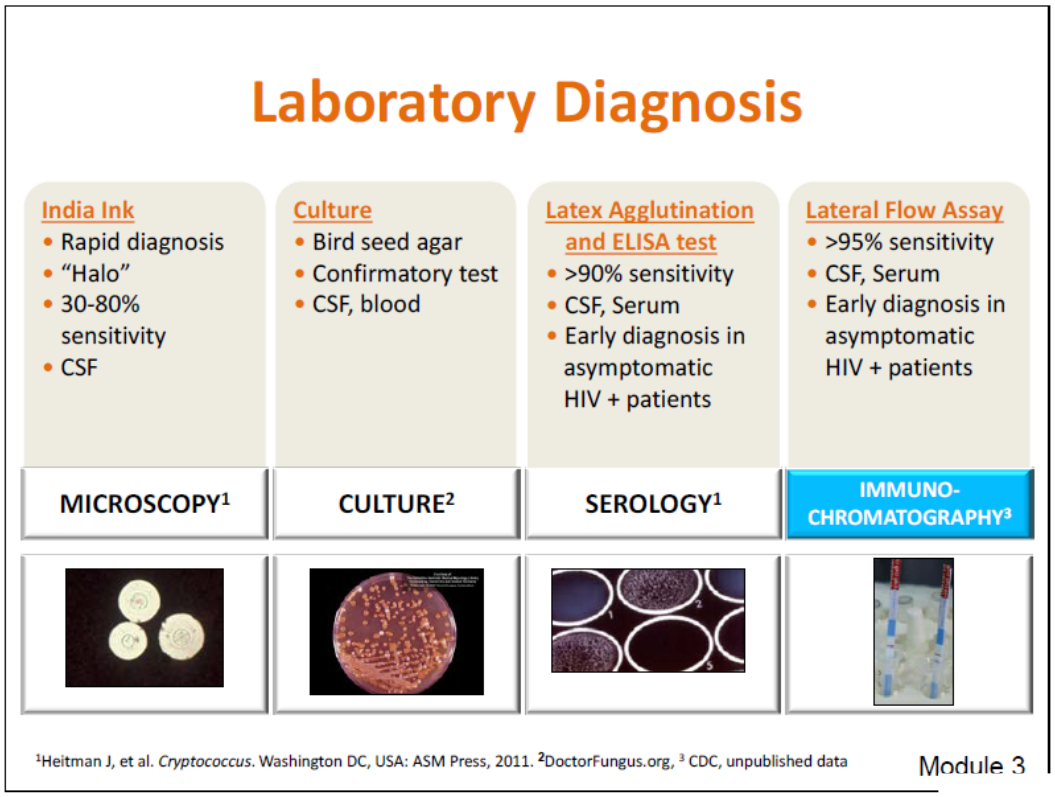
- Consider TB microscopy, GeneXpert, TB culture

IV. Current diagnostic methods available in Cambodia

There are three categories of methods that can be used to diagnose cryptococcal disease:

1. India (or China) ink microscopy, which can be used on CSF
2. Culture, which can be used on CSF, blood, sputum, tissues and body fluids
3. Cryptococcal antigen detection tests for serum and CSF

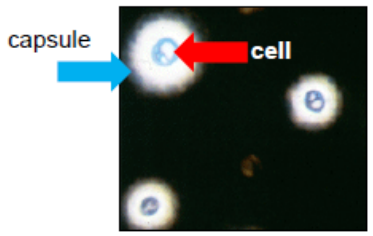
There are several methods to detect cryptococcal antigen in CSF or serum: latex agglutination (LA), enzyme immunoassay (EIA), and lateral flow assay (LFA).



4.1 India ink

Cryptococcal yeast cells (indicated by the red arrow in the picture on the right) are surrounded by a characteristic polysaccharide capsule (indicated by the blue arrow). India ink is a stain that reveals this extracellular capsule when visualized under the microscope. India ink is usually performed on CSF to diagnose cryptococcal meningitis. The benefit of this test is that it can be performed quickly; however, the drawback is that it has low sensitivity, which can lead to missed diagnoses.

- Biologic principle: *Cryptococcus* yeast cells are spherical and irregular in size, surrounded by a characteristic polysaccharide capsule–Visualized microscopically, India Ink stains the background, revealing the extra cellular capsule
- Specimen type: Usually cerebrospinal fluid (CSF)
- Diagnosis:
    - Pros: rapid, inexpensive
    - Cons: low sensitivity, technical subjectivity



C. neoformans: India Ink preparation

4.2 Culture

Cryptococcus neoformans grows on routine media including Sheep Blood agar and Chocolate agar. CSF, blood, sputum, body fluids and tissues are inoculated onto routine media. Colonies resembling yeast should be tested for urease hydrolysis. *Crytococococcus neoformans* are urease positive. Other yeast (Other species of *Cryptococcus*, *Rhodotorula*, *Trichosporon*) are urease positive, but are isolated rarely from CSF.

- Biologic principle: *Cryptococcus* grows well on routine media and demonstrates positive hydrolysis of urea
- Specimen type: Cerebrospinal fluid (CSF), sputum, blood, body fluids and tissues
- Diagnosis:
    - Pros: inexpensive, confirmatory isolation of the causative agent using routine microbiological techniques
    - Cons: delayed result of 2 days or greater, laboratory infrastructure required, low sensitivity

4.3 Antigen detection

4.3.1 Latex agglutination (LA)

The latex agglutination test uses latex particles which are coated with anti-cryptococcal antibody. A visible reaction occurs when these particles come in contact with serum or CSF that contains the cryptococcal polysaccharide antigen. LA can be used to test serum or CSF, and takes 20 to 45 minutes to perform. The major benefit of LA is that it is has a high sensitivity (> 90%). However, it can be expensive and requires extensive laboratory infrastructure, including refrigeration.

- Biologic principle: Anti-cryptococcal antibody-coated latex particles agglutinate with specimens containing cryptococcal antigen (CrAg)
- Specimen type:
    - Serum or CSF
    - Process time: 20 min – 45 min
- Diagnosis:
    - Pros: sensitive > 90%
    - Cons: expensive, requires extensive laboratory infrastructure, requires sample pre-treatment

4.3.1.1 LA sample pre-treatment

For CSF, after centrifuging the sample, place supernatant into a sterile container. Place the supernatant sample in a boiling water bath for 5 minutes, and then allow it to cool for 3 to 4 minutes before testing.

For serum, add the sample to the prepared pronase, which is a reagent that reduces non-specific interference. Then incubate the serum/pronase solution at 56 degrees Celsius for 15 to 30 minutes depending on the manufacturer's instructions. To terminate the reaction, either add a drop of Pronase inhibitor or boil the solution for 5 minutes depending on the manufacturer's instructions.

LA Sample Pre-treatment:

- CSF
    1. Heat to 100°C for 5 min
- Serum
    1. Add serum to Pronase (reduces non-specific interference)
    2. Incubate serum/Pronase solution at 56°C for 15-30 minutes depending on kit manufacturer
    3. Terminate enzymatic digestion: add 1 drop of Pronase inhibitor or boil the solution for 5 minute

4.3.1.2 LA step by step procedure

To perform the LA test, add 25 microliters of the pre-treated specimen and the positive and negative controls to the appropriate rings of the ring slide, using a new pipette tip for each reagent and specimen. Add 25 microliters of cryptococcal latex to each ring, and use a separate applicator stick to thoroughly mix the contents of each ring. Rotate the slide by hand or place it on a rotator set to approximately 100 rpm for 5 minutes. Read and record the reactions immediately.

LA Step by Step Procedure:

1. Add 25 µl of the following onto separate rings of ring slide
   - *Cryptococcus* Antigen Positive Control
   - *Cryptococcus* Antigen Negative Control
   - Each pronase treated serum or heat treated CSF specimen
2. Add 25 µl of Cryptococcal Latex to each ring. Using separate applicator sticks, thoroughly mix the contents of each ring
3. Rotate by hand or on a rotator set to 100 rpm (+/-25) for 5 min at room temperature
4. Read and record the reactions immediately.

Ring slide for Latex Agglutination test

4.3.1.3 LA Interpretation of Results

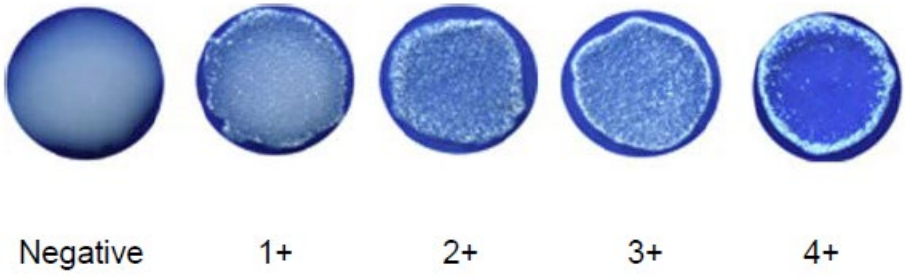
The results of a latex agglutination test are interpreted, on a scale ranging from negative to 4+.

- Negative (-), on the far left, is a homogeneous suspension of particles with no visible clumping.
- One plus (1+) is fine granulation against a milky background.
- Two plus (2+) is small but definite clumps against a slightly cloudy background.
- Three plus (3+) is large and small clumps against clear background.
- Four plus (4+) is large clumps against a very clear background.

Depending on the test manufacturer, specimens that are positive at 1+ or greater should be titrated.

Positive results are reported as the highest dilution showing a 2+ or greater reaction.

LA Interpretation of Results



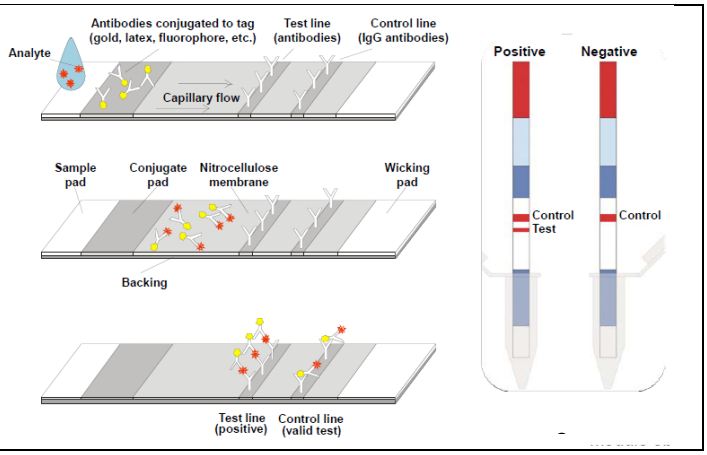
4.3.2 Lateral Flow Assay (LFA)

The lateral flow assay is a dipstick sandwich immuno-chromatographic assay which detects cryptococcal antigen. If cryptococcal antigen is present in the patient sample, the antigen binds to antibodies embedded in the

test strip, and the antigen-antibody complex moves along the test strip until it is immobilized by anti-cryptococcal antibodies at the test line. The LFA has been validated for use in serum and CSF.

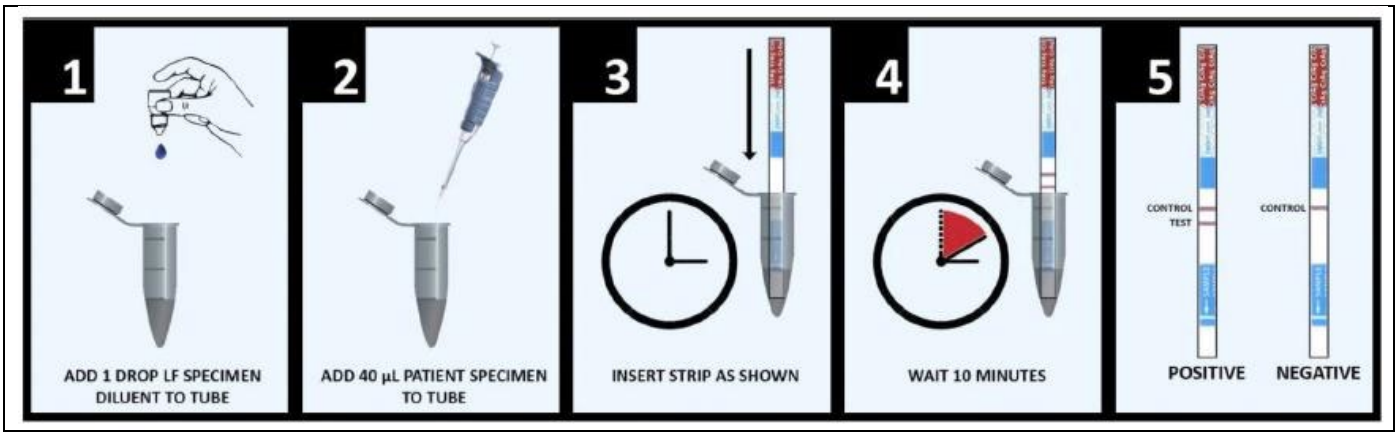
Lateral Flow Assay (LFA)

- Biologic principle:
  - Sandwich immuno-chromatographic assay
  - If cryptococcal antigen (CrAg) present, binds to gold-conjugated antibodies embedded in the test strip
  - Antigen-antibody complex moves up test strip until immobilized by anti-cryptococcal antibodies at test line
- Specimen type: Serum, CSF

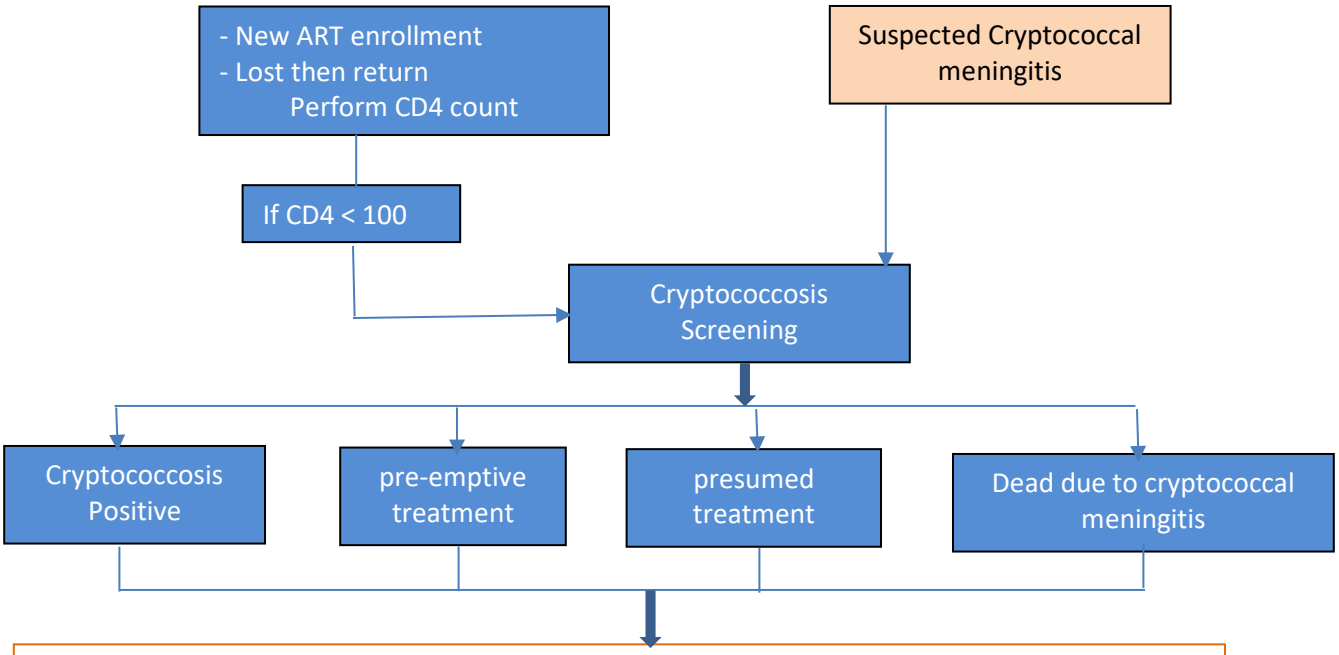


The lateral flow assay is simple to use, and the results are available in 10 minutes. It is accurate over 95% of the time, and it costs approximately $2 to $4 per test. The test is performed in 5 steps:

1. Add one drop of specimen diluent to a tube,
2. Add 40 microliters of patient specimen (serum or CSF) to the tube,
3. Insert the test strip into the tube,
4. Wait 10 minutes, and
5. Interpret the results.



V. Monitoring Framework



Indicators

1. Number (%) of newly enrolled patients screened for cryptococcosis
2. Number (%) patients screened cryptococcosis positive
3. Number (%) patients received pre-emptive treatment
4. Number (%) patients received presumed treatment
5. Number (%) dead due to cryptococcal meningitis

1. Number (%) of newly enrolled patients at ART clinics screened for cryptococcosis	
Description	HIV-infected patients whose CD4<100cells/mm^3 highly at risk to the cryptococcal infection. As well as patients on ART who were lost to follow-up and return, and patients with clinical meningitis signs and symptoms should be screened for cryptococcosis. Screening and primary prophylaxis are not recommended for children, given the low incidence of cryptococcal meningitis in this age group
Purpose	This indicator measures level of care for early diagnosis of cryptococcal disease and provide on time case management at the ART clinics.
Method of Measurement	Count number of newly enrolled patients who are should be screened for cryptococcal infection at the ART clinic in the reporting period; compute for the percentage using numerator and denominator below.
Frequency	Quarterly
Numerator	Number of patients screened for cryptococcal infection
Denominator	Number of newly enrolled patients eligible for cryptococcal infection screening.
Source	ART electronic database, ART patient files.
Interpretation	Cryptococcus is a common infection among HIV-infected whose CD4 is less than 100/µl. In Cambodia the infection rate was about 16%. Failure to screen for cryptococcal infection regularly and systemically indicates low quality of care. The facility should review reasons for not screening for cryptococcus, determine what interventions would help to optimize screening, and take actions to correct the problem.

2. Number (%) of patients screened cryptococcosis positive	
Description	HIV-infected patients whose CD4<100cells/mm^3 highly at risk to the cryptococcal infection. As well as patients on ART who were lost to follow-up and return, and patients with clinical meningitis signs and symptoms should be screened for cryptococcosis.
Purpose	This indicator measures magnitude of cryptococcal infection burden, so that facility and program can plan for appropriate interventions to response effectively to the burden.
Method of Measurement	Count number of patients screened for cryptococcal infection at the ART clinic in the reporting period; compute for the percentage using numerator and denominator below.
Frequency	Quarterly
Numerator	Number of patients screened for cryptococcal infection resulted positive.
Denominator	Number of all patients screened for cryptococcal infection.
Source	ART electronic database, ART patient files.
Interpretation	Cryptococcus is a common infection among HIV-infected whose CD4 is less than 100/µl. In Cambodia the infection rate was about 16%. Failure to screen for cryptococcal infection regularly and systemically leads to not being able to identify the positive rate. Facility and program will not be able to plan appropriate response. High positivity rate may due to but not limit to: - Late enrollment at ART clinic that lead to late ART, - Poor adherence to the ART. The facility should take appropriate actions to respond to the specific causes of the cryptococcal disease.

3. Number (%) patients received pre-emptive treatment	
Description	Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 cell count <100/mm^3.
Purpose	The indicator measures the coverage of pre-emptive fluconazole treatment among suspected patients with non-meningitis clinical presentation who have Serum CrAg positive patients.
Method of Measurement	Count number of patients screened for Cryptococcus at the ART clinic; patients whose test positive; and those who received pre-emptive fluconazole treatment in the reporting period.
Frequency	Quarterly
Numerator	Number of patients whose serum CrAg positive received pre-emptive fluconazole treatment in the reporting period.
Denominator	Number of patients screened serum CrAg positive.
Source	ART electronic database, ART patient files.
Interpretation	High rate of failure to provide pre-emptive Fluconazole treatment is an issue of quality of care since the development of invasive cryptococcal disease, especially among patients whose CD4<100/mm^3 is high, and can lead to fatality. Facility should review the reasons why facility performs low rate of pre-emptive Fluconazole treatment.

4. Number (%) patients received presumed treatment	
Description	Cryptococcal antigen screening and presumed cryptococcal meningitis treatment on time can prevent death from cryptococcal meningitis, which accounts for an estimated 15% of all AIDS-related deaths globally.
Purpose	The indicator measures the coverage of presumed cryptococcal meningitis treatment among suspected patients with meningitis clinical presentation who have Serum CrAg positive patients. And it also measures the ability and capacity of facility in managing suspected cryptococcal meningitis patients.
Method of Measurement	Count number of patients suspected cryptococcal meningitis patients screened Serum CrAg positive; and those who received presumed cryptococcal treatment in the reporting period.
Frequency	Quarterly
Numerator	Number of patient suspected cryptococcal meningitis received presumed cryptococcal meningitis treatment in the reporting period.
Denominator	All patients suspected cryptococcal meningitis in the reporting period.
Source	ART electronic database, ART patient files.
Interpretation	At facilities where lumbar puncture is not available, all suspected cryptococcal meningitis patients with Serum CrAg positive should receive presumed cryptococcal meningitis treatment. If the treatment rate is low, facility should review the reasons why patients left untreated. There may be some reasons but not limited to below: - Ability to diagnosed, - Capacity to diagnosed, - Drugs availability.

5. Number (%) dead due to cryptococcal meningitis	
Description	AIDS-related cryptococcal meningitis continues to cause a substantial burden of death in low and middle income countries. Mortality continues to be unacceptable high. In retrospective and prospective hospital-based studies performed in Brazil and Argentina, the case fatality rates have ranged from 26% to 63%
Purpose	This indicator measures the efficacy and effectiveness of the cryptococcosis treatment and interventions in the facility.
Method of Measurement	Count number of all patients diagnosed as cryptococcal meningitis; and number of patients died due to cryptococcal meningitis in the reporting period.
Frequency	Quarterly
Numerator	Number of patients died due to cryptococcal meningitis in the reporting period.
Denominator	Number of all patients diagnosed having cryptococcal meningitis in the reporting period.
Source	ART electronic database, ART patient files.
Interpretation	In-hospital acute mortality from cryptococcal meningitis continues to remain high, ranging between 30-50%, even with antifungal therapy (13). In Cambodia there is no data of death rate due to cryptococcal meningitis among HIV-infected patients. If there is high case fatality rate of cryptococcal meningitis in a facility, the facility should review carefully the reasons why such death rate occurred: - There was delay in cryptococcal meningitis diagnosis? - There was no ability to diagnose cryptococcal infection? - Care and treatment related issues? - Etc.

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VII. Annexes

Table 1: Treatment of cryptococcal meningitis (National HIV clinical management guidelines for Adults and Adolescents, NCHADS 2015

Phase/duration	Adult
1. Induction For 2 weeks	* Amphotericin B: 1 mg/kg + Fluconazole 800 mg daily
2. Consolidation For 8 weeks	Fluconazole 400 mg daily
3. Maintenance Until CD4 count remains >200 cells/mm^3 for two measurements at least 6 months apart.	Fluconazole 200 mg daily

* If Amphotericin is not available for adults, use Fluconazole 1,200 mg daily for 2 weeks and monitor liver functions

Table 2: Summary of treatment recommendations and dosage for HIV-infected adults with cryptococcal disease (meningeal and disseminated non-meningeal), WHO: Rapid Advice Diagnosis, Prevention and Management of Cryptococcal disease in HIV-infected Adults, Adolescents and Children

Target Population	Drug available	Pre-hydration + electrolyte replacement + toxicity monitoring/ management	Induction phase Options[1] (2 weeks)	Consolidation phase options (8 weeks)	Maintenance/ secondary prophylaxis options
Adults	Amphotericin B[2] ± flucytosine	Available	a. Amphotericin 0.7-1 mg/kg/day + flucytosine 100mg/kg/day b. Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day	Fluconazole 400-800mg/day	Fluconazole 200 mg daily
	Amphotericin B[2]	Not available for full 2 week induction period	Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 800 mg/day (2 weeks)	Fluconazole 800 mg/day	
	Amphotericin B not available	Not available	a. Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day b. Fluconazole 1200 mg/day alone	Fluconazole 800 mg/day	

[1] Route of administration: amphotericin B (IV); flucytosine (oral); fluconazole (oral and IV).
[2] Liposomal amphotericin B (3 mg/kg/day) may be considered as an alternative to conventional amphotericin B, if available

Table 3: Summary of treatment recommendations and dosage for HIV-infected adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal), WHO: Rapid Advice Diagnosis, Prevention and Management of Cryptococcal disease in HIV-infected Adults, Adolescents and Children

Target Population	Drug available	Pre-hydration + electrolyte replacement + toxicity monitoring/ management	Induction phase Options[1] (2 weeks)	Consolidation phase options (8 weeks)	Maintenance/ secondary prophylaxis options
Adolescents and Children[3]	Amphotericin B ± flucytosine	Available	**a**. Amphotericin 0.7-1 mg/kg/day + flucytosine 100mg/kg/day **b**. Amphotericin 0.7-1 mg/kg/day + Fluconazole 12mg/kg/day up to 800 mg/day	Fluconazole 6-12mg/kg/day up to 400-800 mg/day	Fluconazole 6 mg/kg/day up to 200 mg/day
	Amphotericin B	Not available for full 2 week induction period	Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 12mg/kg/day up to 800 mg/day (2 weeks)	Fluconazole 12mg/kg/day up to 800 mg/day	
	Amphotericin B not available	Not available	**a**. Fluconazole 12mg/kg/day up to 1200 mg/day ± flucytosine 100 mg/kg/day **b**. Fluconazole 12mg/kg/day up to 1200 mg/day alone	Fluconazole 12mg/kg/day up to 800 mg/day	

[3] Up to 19 years. Excludes first week of life.