

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

MARCH 2018



**More than 1 in 10
HIV-related deaths
are as a result
of cryptococcal
meningitis.**

**Three quarters
of deaths from
cryptococcal
meningitis are in
sub-Saharan Africa.**

The burden of morbidity and mortality associated with HIV infection has decreased over the past decade as access to antiretroviral therapy (ART) has increased. Despite this progress, up to half the people living with HIV (PLHIV) present to care with advanced disease and many people continue to die from HIV-related opportunistic infections.

Cryptococcal meningitis¹ is a serious opportunistic infection which is a major cause of morbidity and mortality in PLHIV with advanced disease, accounting for an estimated 15% of all AIDS-related deaths globally. An estimated 223,100 cases of cryptococcal meningitis result in 181,000 deaths each year among people living with HIV. Cryptococcal disease is rare in children with HIV, even in areas with a high disease burden among adults.

Mortality from cryptococcal meningitis is highest in low-income countries. Delays in diagnosis, as a result of limited access to rapid diagnostic assays and lumbar puncture and the limited availability and high cost of first-line antifungal drugs are major contributors to this high mortality. Another important factor is the limited ability in low-income countries to monitor and manage treatment-limiting toxicities as well as the complications of raised intracranial pressure, and immune reconstitution inflammatory syndrome.

In March 2018 WHO released updated guidelines: Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children.



WHO / James Oatway: Namibia
Living with HIV / AIDS at the Katatura State Hospital in Windhoek, Namibia.

These guidelines provide new or updated recommendations and good practice guidance on the following areas:

- the optimal approach to diagnosing cryptococcal meningitis;
- strategies for preventing invasive cryptococcal disease through cryptococcal antigen screening and pre-emptive fluconazole therapy;
- treating cryptococcal meningitis with combination antifungal therapy regimens
- preventing, monitoring and managing amphotericin B drug toxicity;
- recommendations against adjunctive therapy with systemic corticosteroids;
- recommendations on the timing of antiretroviral therapy (ART) initiation.

¹ Cryptococcal meningitis is by far the commonest manifestation of cryptococcal disease representing 70–90% of HIV-related cryptococcal disease. Other less common disease presentations include pulmonary disease and skin, lymph node and bone involvement.

Recommendations

Diagnosis of cryptococcal meningitis

1. For adults, adolescents and children living with HIV suspected of having a first episode of cryptococcal meningitis, prompt lumbar puncture with measurement of cerebrospinal fluid (CSF) opening pressure and rapid cryptococcal antigen assay is recommended as the preferred diagnostic approach. (*Strong recommendation, moderate-certainty evidence for adults and adolescents; low-certainty evidence for children*)

See guidelines for further guidance on diagnosis in specific contexts

Prevention and screening

Overarching principle: Screening for cryptococcal antigen is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying infection when managing people presenting with advanced HIV disease.

Recommendations: Screening^a 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 cells/mm³ (*strong recommendation; moderate-certainty evidence*) and may be considered at a higher CD4 cell count threshold of <200 cells/mm³ (*conditional recommendation; moderate-certainty evidence*).

When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm³ (*strong recommendation; moderate-certainty evidence*) and may be considered at a higher CD4 cell count threshold of < 200 cells/mm³ (*conditional recommendation; moderate-certainty evidence*).

Screening and primary prophylaxis are not recommended for children, given the low incidence of cryptococcal meningitis in this age group.

^aAll people living with HIV with a positive cryptococcal antigen result on screening should be carefully evaluated for signs and symptoms of meningitis and undergo a lumbar puncture if feasible with CSF examination and CSF cryptococcal antigen assay (or India ink if cryptococcal antigen testing is unavailable) to exclude active cryptococcal disease.

Treatment of cryptococcal meningitis

Induction

The following is recommended as the preferred induction regimen.

- For adults, adolescents and children, a short-course (one-week) induction regimen with amphotericin B deoxycholate and flucytosine is the preferred option for treating cryptococcal meningitis among people living with HIV (*strong recommendation, moderate-certainty evidence for adults, low-certainty evidence for children and adolescents*).

The following induction regimens are recommended as alternative options:

- **Two weeks of fluconazole (1200 mg daily, 12 mg/kg/day for children and adolescents) + flucytosine** (*strong recommendation, moderate-certainty evidence*).
- **Two weeks of amphotericin B deoxycholate + fluconazole (1200 mg daily, 12 mg/kg/day for children and adolescents)** (*strong recommendation, moderate-certainty evidence*).

Consolidation

Fluconazole (**400–800 mg daily, 6–12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily**) is recommended for the consolidation phase (*for eight weeks following the induction phase*) (*strong recommendation, low-certainty evidence*).

Maintenance (or secondary prophylaxis)

Fluconazole (**200 mg daily, 6 mg/kg/day for adolescents and children**) is recommended for the maintenance phase (*strong recommendation, high-certainty evidence*).

Note: a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management can be provided to minimize treatment toxicity during induction phase with Amphotericin B containing regimens and flucytosine.

Using adjunctive systemic corticosteroids in treating cryptococcal meningitis

Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating HIV-associated cryptococcal meningitis among adults, adolescents and children (*strong recommendation, high-certainty evidence for adults and adolescents, moderate-certainty evidence for children*).

Timing of ART

Immediate ART initiation is not recommended among adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred 4–6 weeks from the initiation of antifungal treatment.

(*Strong recommendation, low-certainty evidence for adults and very-low-certainty evidence for children and adolescents*)

The guidelines also contain good practice principles for the following:

- Preventing, monitoring and managing amphotericin B toxicity, through a minimum package of care that includes pre-hydration and electrolyte supplementation
- Monitoring for raised intracranial pressure through initial lumbar puncture and early repeat lumbar puncture with measurement of CSF opening pressure to assess for raised intracranial pressure, regardless of the presence of symptoms or signs of raised intracranial pressure.
- Managing raised intracranial pressure through measures which include therapeutic lumbar puncture
- Monitoring treatment response
- Diagnostic approach to persistent or recurrent symptoms
- Managing treatment failure



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WHO / SEARO / Arifin Fitrianto: Indonesia
Healthcare worker providing ART to a client

Implementation challenges and considerations

Rapid diagnostic tests

Since early diagnosis is key to improving mortality from cryptococcal disease, countries need to give priority to reliable access to rapid diagnostic cryptococcal antigen assays, preferably lateral flow assays for use in CSF and serum or plasma. In addition, health-care professionals need to have a low threshold for suspecting cryptococcal meningitis.

Lumbar puncture

Lumbar puncture is performed with variable frequency in low and middle income countries, but the opening pressure is rarely measured because access to manometers is lacking or because the diagnosis is made after the lumbar puncture is complete. However, lack of access to manometers should not preclude undertaking therapeutic lumbar punctures with CSF drainage for suspected raised intracranial pressure, which may save lives.

Access to optimal antifungal treatment

Lack of access to appropriate medications to treat cryptococcal meningitis is a major factor contributing to high mortality from cryptococcal meningitis in Africa. High drug costs, especially of amphotericin B, and limited access to flucytosine despite being included in several national guidelines are important issues. Liposomal amphotericin B is preferred over amphotericin B deoxycholate given its better safety profile. However, access to liposomal amphotericin B remains extremely limited in low- and middle-income countries because of its high cost.

Flucytosine is not registered and largely unavailable in most low- and middle-income countries, especially in sub-Saharan Africa. The induction regimen given priority in these guidelines contains flucytosine as does the alternative induction regimen (flucytosine and fluconazole) in settings where amphotericin B is not available. These regimens can potentially reduce mortality by half compared with using fluconazole monotherapy.

Barriers to access of antifungal drugs can be overcome by:

- increasing advocacy for drug price reduction and promoting generic production, particularly for amphotericin B and oral flucytosine;
- carrying out quality assurance of newly available generic formulations;
- ensuring national registration of all cryptococcal meningitis drugs and including them in national essential medicine lists (amphotericin B, flucytosine and fluconazole are now included in WHO Model List of Essential Medicines). In-country advocacy is required to simplify drug registration procedures.
- ensuring adequate supply chains at the national level; and
- developing appropriate drug-forecasting and monitoring systems

WHO Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children are available from:
<http://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/>

WHO Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy are available from:
<http://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/>

Package of care for advanced HIV disease

Preventing invasive cryptococcal disease through cryptococcal antigen screening and pre-emptive fluconazole therapy is a key component of the WHO recommended package of care for managing advanced HIV disease.

The WHO package of care for advanced HIV disease is a standardised, simplified package of priority interventions that should be offered to all people presenting or representing to care with advanced HIV disease to reduce HIV associated morbidity and mortality. It includes:

- screening, treatment and prophylaxis for major opportunistic infections (including cryptococcal disease and TB)
- rapid initiation of antiretroviral therapy (ART) and
- intensified treatment adherence support.

CD4 cell count testing remains important in order to identify people with advanced HIV disease so that they can be offered the package of care.

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HIV TREATMENT