World Health Organization

GUIDELINES

GUIDELINES FOR

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

MARCH 2018

HIV TREATMENT

World Health Organization

GUIDELINES FOR

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

MARCH 2018

SUPPLEMENT TO THE 2016 CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION

Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children, March 2018.

ISBN 978-92-4-155027-7

Suggested citation. Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children, March 2018. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

CONTENTS

DEFINITION OF KEY TERMS

Adult	Age older than 19 years
Adolescent	Age 10–19 years
Advanced HIV disease	For adults, adolescents and children five years or older, advanced HIV disease is defined as a CD4 cell count <200 cells/mm^3 or a WHO clinical stage 3 or 4 event at presentation for care. All children with HIV younger than five years old should be considered as having advanced disease at presentation
Child	Age 0–9 years
Cryptococcal antigen positivity	Positive serum, plasma, or cerebrospinal fluid cryptococcal antigen. A positive cerebrospinal fluid antigen test indicates cryptococcal meningitis
Cryptococcal disease	Infection with *Cryptococcus* species that impairs normal body function, detected by abnormal clinical symptoms or signs
Cryptococcal infection	Growth of *Cryptococcus* species in the body documented by direct growth of the organism (culture) or indirect detection (positive antigen test in a person without prior cryptococcal disease or India ink stain). A positive culture or first positive antigen test usually implies active disease
Cryptococcoma	Localized, solid, tumour-like mass caused by growth of cryptococcal organism and associated inflammatory response; can be intracranial or extracranial
Cryptococcus species	The most common species causing human disease in the context of HIV-infection is *Cryptococcus neoformans*; infections from *Cryptococcus gattii* have been reported occasionally
Meningeal disease	Disease presenting with nervous system signs or symptoms, specifically involving the meningeal layer surrounding the brain
Non-meningeal disease	Disease that does not involve the brain but involves either only a single site in the body (localized) or involves two non-contiguous sites in the body (disseminated)
Persistent symptoms	Symptoms consistent with cryptococcal disease that fail to resolve after two weeks of initial antifungal induction treatment
Raised intracranial pressure	Cerebrospinal fluid opening pressure ≥20 cm H_2O
Recurrent symptoms	Symptoms consistent with cryptococcal disease that reappear after full resolution following treatment for the initial episode of cryptococcal meningitis
Suboptimal treatment	Treatment with inadequate drug regimen, dose or duration of induction, consolidation or maintenance therapy; may also result from drug interactions or drug resistance
Sustained clinical response	Resolution of clinical symptoms and signs of cryptococcal disease for at least two continuous weeks
Treatment failure or microbiological relapse	Lack of clinical or mycological response in a person in whom raised intracranial pressure or cryptococcal immune reconstitution inflammatory syndrome is not the only cause; includes people who received suboptimal treatment or who received optimal treatment but failed to clinically respond or who were poorly adherent

ACKNOWLEDGEMENTS

Guideline Development Group

The following individuals contributed to developing these guidelines in 2011 and 2015:

Ploenchan Chetchotisakd (Khon Kaen University, Thailand); **Nelesh Govender** (National Institute for Communicable Diseases, South Africa); **Tom Harrison** (St George's University of London, United Kingdom); **Tara Horvath** (GRADE methodologist, University of California at San Francisco, USA); **Jonathan Kaplan** (United States Centers for Disease Control and Prevention, USA); **Saye Khoo** (University of Liverpool, United Kingdom); **Nagalingeswaran Kumarasamy** (Chair: YR Gaitonde Centre for AIDS Research and Education, India); **Lut Lynen** (Institute of Tropical Medicine, Belgium); **Graeme Meintjes** (University of Cape Town, South Africa); **Tammy Meyers** (Chris Hani Baragwanath Hospital, South Africa); **Neeraj Mohan**, Clinton Foundation HIV/AIDS Initiative, India); **Conrad Muzoora** (Mbarara University of Science and Technology, Uganda); **Peter Pappas** (University of Alabama at Birmingham, USA); **John Perfect** (Duke University Medical Center, USA); **Benjamin Ryan Phelps** (United States Agency for International Development, USA); **Emilia Rivadeneira** (United States Centers for Disease Control and Prevention, USA); **Papa Salif Sow** (Dakar University Hospital, Senegal); **Yazdanpanah Yazdan** (Centre Hospitalier de Tourcoing, France).

The following individuals contributed to the development of updated recommendations in 2017:

Rosie Burton (Médecins Sans Frontières, South Africa); **Mohamed Chakroun** (Fattouma Bourguiba Teaching Hospital, Tunisia); **Ploenchan Chetchotisakd** (Khon Kaen University, Thailand); **Tom Chiller** (United States Centers for Disease Control and Prevention, USA); **Aleny Couto** (Ministry of Health, Mozambique); **Lisa Frigati** (Tygerberg Hospital and Stellenbosch University, South Africa); **Nelesh Govender** (National Institute for Communicable Diseases, South Africa); **Joseph Jarvis** (Botswana-Harvard Partnership, Botswana); **Nagalingeswaran Kumarasamy** (YR Gaitonde Centre for AIDS Research and Education, India); **Thuy Le** (Oxford University Clinical Research Unit, Viet Nam); **Angela Loyse** (St George's University of London, United Kingdom); **Graeme Meintjes** (Chair: University of Cape Town, South Africa), **Nandi Siegfried** (Independent Clinical Epidemiologist and GRADE methodologist, South Africa).

External Review Group

The following individuals externally reviewed this guideline and previous drafts:

Sabrina Bakeera-Kitaka (Makerere University College of Health Sciences, Uganda); **Rui Bastos** (Mozambique AIDS Programme, Mozambique); **Tihana Bicanic** (St George's University of London, United Kingdom); **David Boulware** (University of Minnesota, USA); **Mark Cotton** (Tygerberg Hospital, South Africa); **Jeremy Day** (Hospital for Tropical Diseases, Viet Nam); **Serge Paul Eholie** (Treichville University Hospital, Côte d'Ivoire); **Brian Eley** (University of Cape Town, South Africa); **Martyn French** (University of Western Australia, Australia); **Tendani Gaolathe** (National AIDS Programme, Botswana); **Kalle Hoppu** (Poison Information Centre, Finland); **Prakash Jeena** (University of KwaZulu Natal, South Africa); **Haruna Jibril** (Princess Marina Hospital, Botswana); **David Lalloo** (Liverpool School of Tropical Medicine, United Kingdom); **Sanjiv Lewin** (St. John's Medical College Hospital, India); **Tariro Azure Makadzange** (Massachusetts General Hospital, USA); **Barbara Marston** (United States Centers for Disease Control and Prevention, USA); **David Meya** (Infectious Diseases Institute, Uganda); **Romain Micol** (Institut Pasteur in Cambodia, Cambodia); **Yunus Moosa** (Nelson Mandela School of Medicine, South Africa); **Jeremy Penner** (University of California at

San Francisco and Kenya Medical Research Institute, Kenya); **Andrew Reid** (University of Zimbabwe School of Medicine, Zimbabwe); **Christine Ross** (United States Centers for Disease Control, USA); **Cao Thi Thanh Thuy** (National Hospital for Tropical Diseases, Viet Nam); **Snigdha Vallabheneni** (United States Centers for Disease Control, USA); **Joep van Oosterhout** (Queen Elizabeth Central Hospital, Malawi); **José E. Vidal** (Emílio Ribas Institute of Infectious Diseases and University of São Paulo, Brazil).

The following individuals are members of an expert group that provides advice to the WHO HIV department on clinical issues relating to paediatric HIV. They provided a perspective on the applicability of the evidence to paediatric populations:

Moherndran Archary (Department of Paediatrics and Children Health, King Edward VIII Hospital, University of KwaZulu-Natal, Durban, South Africa); **Andrew Prendergast** (Blizard Institute, Queen Mary University of London, London); **George Siberry** (Office of the US Global AIDS Coordinator, US Department of State, Washington, DC, USA); **Di Gibb** (MRC Clinical Trials Unit at UCL, London); **Emilia Rivadeneira** (CDC, Atlanta, United States); **Shaffiq Essajee** (UNICEF, New York, USA).

The following individuals contributed to the systematic reviews and supporting evidence:

Andrew T. Anglemyer (University of California at San Francisco, USA); **Nathan Ford** (HIV Department, WHO); **Andy Gray** (University of KwaZulu Natal, South Africa); **Mary Louise Lindegren** (Vanderbilt Institute for Global Health, USA); **Chantal Migone** (HIV Department, WHO); **Basile Njei** (University of Connecticut, USA); **George Rutherford**, University of California at San Francisco, USA); **Zara Shubber** (Imperial College London, UK); **Alicen Spaulding** (University of Minnesota, USA); **Mark Tenforde** (University of Washington, School of Public Health, Seattle, USA); **Ingrid Wilson** (Cochrane Evidence Based Health Care, Stellenbosch University, South Africa).

WHO staff and consultants

Philippa Easterbrook and Nathan Ford provided overall coordination for the development of these guidelines, under the direction of **Meg Doherty** and with the support of **Chantal Migone** (HIV Department, WHO); **Monica Roy** and **Snigdha Vallabheneni** (United States Centers for Disease Control and Prevention, USA) made a major contribution to the writing and research for these guidelines. The following WHO staff members contributed to further developing and updating these guidelines: **Rachel Beanland**, **Shaffiq Essajee**, **Martina Penazzato** and **Marco Vitoria** (HIV Department, WHO); **Masaya Kato** (WHO Country Office in Viet Nam); **Frank Lule** (WHO Regional Office for Africa); **Lulu Muhe** (Maternal, Child and Adolescent Health Department, WHO); **Omar Sued** (WHO Regional Office for the Americas).

Funding

The development of these guidelines was supported by funding to WHO, from the United States President's Emergency Plan for AIDS Relief through the United States Centers for Disease Control and Prevention cooperative agreement and the United States Agency for International Development.

1. EXECUTIVE SUMMARY

Cryptococcal disease is an opportunistic infection that occurs primarily among people with advanced HIV disease and is an important cause of morbidity and mortality. By far the most common presentation of cryptococcal disease is cryptococcal meningitis, which accounts for an estimated 15% of all AIDS-related deaths globally, three quarters of which are in sub-Saharan Africa. An estimated 223 100 cases of cryptococcal meningitis resulted in 181 100 deaths among people living with HIV in 2014. Less common presentations of cryptococcal disease include pulmonary disease and skin, lymph node and bone involvement. Cryptococcal disease is far less common among children with HIV, even in areas with a high disease burden among adults.

These guidelines provide recommendations and good practice guidance on 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 and recommendations on the timing of antiretroviral therapy (ART) initiation.

Recommendations in these guidelines were formulated during a series of Guideline Development Group meetings, informed by systematic evidence reviews. The GRADE approach was used for rating the certainty of the evidence. Additional considerations include resource use and cost implications of implementing the recommendations, and patient and provider values and preferences. Good practice principles were formulated by the Guideline Development Group based on their knowledge of the optimal approach to the clinical management of cryptococcal disease, taking into consideration the constraints of resource-limited settings.

The target audience for these guidelines includes HIV programme managers, policy-makers, national treatment advisory boards and health-care professionals providing care for people living with HIV in resource-limited settings with a high burden of cryptococcal disease. In addition, these recommendations are intended for partners supporting the implementation of HIV care and treatment services and organizations providing technical and financial support for HIV care and treatment programmes in low- and middle-income countries.

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)

The following diagnostic approaches are recommended, according to the context:

A. In settings with ready access to and no contraindication for lumbar puncture:

i) If both access to a cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) and rapid results (less than 24 hours) are available:

Lumbar puncture with rapid CSF cryptococcal antigen assay is the preferred diagnostic approach.

(Strong recommendation, moderate-certainty evidence for adults and adolescents; low-certainty evidence for children)

ii) If access to a cryptococcal antigen assay is not available and/or rapid results are not available:

Lumbar puncture with CSF India ink test examination is the preferred diagnostic approach.

(Strong recommendation, moderate-certainty evidence for adults and adolescents; low-certainty evidence for children)

B. In settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated:[a]

i) If both access to a cryptococcal antigen assay and rapid results (less than 24 hours) are available:

Rapid serum, plasma or whole-blood cryptococcal antigen assays are the preferred diagnostic approaches.

(Strong recommendation, moderate-certainty evidence for adults and adolescents; low-certainty evidence for children)

ii) If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured:

Prompt referral for further investigation and treatment as appropriate.

(Strong recommendation, moderate-certainty evidence for adults and adolescents; low-certainty evidence for children)

[a]Contraindications include significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs (excluding cranial nerve VI palsy) or recurrent seizures and, where possible, confirmed by computed tomography. Raised intracranial pressure does not contraindicate lumbar puncture in (suspected) cryptococcal meningitis. Other contraindications include major spinal deformity and patient refusal after fully informed consent was sought.

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/mm^3 *(strong recommendation; moderate-certainty evidence)* and may be considered at a higher CD4 cell count threshold of <200 cells/mm^3 *(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/mm^3 *(strong recommendation; moderate-certainty evidence)* and may be considered at a higher CD4 cell count threshold of < 200 cells/mm^3 *(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.

[a]**Good practice principal**: All 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 aand cryptococcal antigen assay (or India ink if cryptococcal antigen assay is not available) 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 (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day) 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 depending on drug availability:

- Two weeks of fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents) + flucytosine (100 mg/kg/day, divided into four doses per day) *(strong recommendation, moderate-certainty evidence).*

- Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) *(strong recommendation, moderate-certainty evidence).*

Consolidation

Fluconazole (800 mg daily for adults, 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 for adults, 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 should 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 for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 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)

Good practice principles

Preventing, monitoring and managing amphotericin B toxicity

Safe administration of amphotericin B should be given priority and may require referral to a centre with access to a minimum package of preventing, monitoring and managing toxicity. A minimum package of preventing, monitoring and managing toxicity should be provided to minimize the serious types of amphotericin B–related toxicity, especially hypokalaemia, nephrotoxicity and anaemia (Table 2).

Monitoring for and managing raised intracranial pressure

Monitoring for raised intracranial pressure

Adults, adolescents and children living with HIV with suspected cryptococcal meningitis should have an initial lumbar puncture and an 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

- Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient to reduce the CSF pressure to <20 cm H_20 or halving the baseline pressure baseline pressure if extremely high.[a]
- The persistence or recurrence of symptoms or signs of raised intracranial pressure should determine the frequency of repeat therapeutic lumbar puncture. For people with persistent symptoms of intracranial pressure, repeat daily therapeutic lumbar puncture (with measurement of CSF opening pressure where available) and CSF drainage, if required, are recommended until the symptoms resolve or the opening pressure is normal for at least two days.

[a]There are no data on the maximum volume of CSF that can be safely drained at one lumbar puncture. CSF opening pressure can be re-checked after every 10 ml removed. Usually 20–25 ml is enough to reduce the opening pressure sufficiently.

Monitoring treatment response

- Clinical response (including resolution or recurrence of fever, headache and symptoms or signs of raised intracranial pressure) should be assessed daily during the initial two weeks of induction therapy.
- Among people with evidence of a sustained clinical response, routine follow-up lumbar puncture after completing induction treatment to assess antifungal treatment response (CSF fungal culture and CSF cryptococcal antigen) or serum or plasma cryptococcal antigen is not advised in low- and middle-income countries.

Diagnostic approach to persistent or recurrent symptoms

The following diagnostic approach should be used for people with persistent or recurrent symptoms to establish potential underlying causes:

a. Review the patient history for evidence suggesting underlying treatment failure from (1) inadequate drug regimen, dose and duration, (2) poor adherence to fluconazole consolidation and maintenance treatment or (3) underlying fluconazole drug resistance among people with previous prolonged fluconazole therapy.

b. Perform a lumbar puncture with measurement of the opening pressure to establish the presence or absence of raised intracranial pressure and CSF examination with other relevant investigations to exclude concomitant illnesses.[b]

c. Consider paradoxical cryptococcal immune reconstitution inflammatory syndrome after excluding other causes of recurrent symptoms among people who have started ART.

d. Send or resend CSF for prolonged fungal culture (two weeks of incubation).

[a]Other diseases that can present with symptoms and signs similar to cryptococcal meningitis (such as viral, bacterial or tuberculous meningitis) should also be considered. Where possible, fluconazole susceptibility testing should be performed at a national reference laboratory when clinically suspected (culture-positive relapse despite fluconazole adherence).

Managing relapse

For people who present with cryptococcal meningitis relapse, the following steps are advised:

- Start or restart induction treatment according to the recommendations for induction treatment in section 3.3.
- Manage raised intracranial pressure with therapeutic lumbar puncture (see section 3.6.1).
- Reinforce adherence.
- If ART has not already started, initiating ART after 4–6 weeks of optimal antifungal therapy is recommended (see section 3.7 on recommendations on the timing of ART initiation).

2. BACKGROUND

Increasing access to ART has transformed the prognosis of people living with HIV in low- and middle-income countries. Expansion of testing and treatment of HIV has led to nearly 50% fewer people dying from HIV-related causes between 2005 and 2016 *(1)*. Despite this progress, up to half the people living with HIV present to care with advanced disease *(2–4)*, and many people continue to die from HIV-related opportunistic infections *(5,6)*.

Cryptococcal disease is one of the most important opportunistic infections among people living with advanced HIV disease and is a major contributor to mortality *(7–10)*. Cryptococcus, the causative agent of cryptococcal disease, is found in the environment worldwide. Exposure to the organism occurs through inhalation but rarely results in clinically significant invasive disease in the general population. Clinically significant invasive disease is thought to be primarily caused by reactivation of latent infection among immunocompromised individuals, such as people living with HIV, months to years after initial exposure *(11)*.

By far the most common presentation, representing 70–90% of HIV-related cryptococcal disease, is cryptococcal meningitis, which was responsible for an estimated 223 100 cases and 181 100 deaths among people living with HIV in 2014 and accounts for 15% of all the people dying from HIV-related deaths globally *(10)*. Other less common disease presentations include pulmonary disease and skin, lymph node and bone involvement *(12)*. Cryptococcal disease is less common among children with HIV *(13,14)*, even in areas with a high disease burden among adults *(15)*.

Mortality from cryptococcal meningitis remains highest in low-income countries. The estimated one-year mortality of people living with HIV who receive care for cryptococcal meningitis is 70% in low-income countries versus 20–30% for high-income countries *(10)*. A major reason for this high mortality is delay in diagnosis, largely as a result of limited access to lumbar puncture and rapid diagnostic assays. Further contributing factors are the limited availability and high cost of first-line antifungal drugs *(16)*. Another important contributor to mortality is the limited ability in low-income countries to monitor and manage treatment-limiting toxicities and the frequent complications of raised intracranial pressure as well as immune reconstitution inflammatory syndrome associated with cryptococcal meningitis and ART *(17–20)*.

A public health approach leading to prevention, earlier diagnosis and improved treatment of cryptococcal disease and its complications is critical to reduce the incidence and associated high mortality of cryptococcal meningitis in low- and middle-income countries.

WHO first published a rapid advice document for the diagnosis, prevention and management of cryptococcal disease in December 2011*(21)*. Since then, several recent advances provide opportunities for improving the prevention, diagnosis and management of cryptococcal disease in low- and middle-income countries, including:

- data supporting the efficacy of cryptococcal antigen screening to identify people living with HIV who could benefit from targeted pre-emptive fluconazole therapy to prevent invasive disease and death;
- evidence supporting the value of primary fluconazole prophylaxis in settings in which cryptococcal antigen screening is unavailable;

- data supporting the superiority of short-course amphotericin B and flucytosine as an induction regimen for treating cryptococcal meningitis in resource-limited settings;
- evidence supporting the superiority of flucytosine (compared to fluconazole) as the second drug of choice in combination with amphotericin B for treating cryptococcal meningitis;
- evidence on the optimal timing of ART for people with HIV-associated cryptococcal meningitis; and
- WHO recommendations that all people living with HIV start ART as soon as possible following a positive diagnosis and on managing advanced HIV disease.

2.1 Objectives

The objectives of these guidelines are to provide updated, evidence-informed recommendations outlining a public health approach to preventing, diagnosing and managing cryptococcal disease among adults, adolescents and children living with HIV, focusing on settings with limited resources and a high burden of cryptococcal disease.

2.2 Target audience

These guidelines are aimed at HIV programme managers, policy-makers, national treatment advisory boards, implementing partners and health-care professionals providing care for people living with HIV in resource-limited settings with a high burden of cryptococcal disease.

2.3 Guiding principles

The following principles have informed the development of these guidelines and should guide the implementation of the recommendations:

- The guidelines are based on a public health approach to scaling up the use of antiretroviral (ARV) drugs along the continuum of HIV prevention, care and treatment.
- Early ART initiation regardless of CD4 count or immune status ("Treat All") is the most important preventive strategy to reduce the incidence of opportunistic infections.
- Early diagnosis and prompt initiation of optimal antifungal treatment is essential to improving survival and clinical and nervous system outcomes among people with HIV-associated cryptococcal meningitis.
- People should be promptly referred for HIV testing and care following diagnosis of cryptococcal disease to facilitate prompt HIV diagnosis, linkage to care and uptake of ART.
- ART initiation should be deferred for two weeks in people living with HIV who have a positive cryptococcal antigen screening test result.[†]
- ART should be deferred by 4-6 weeks in cases of confirmed cryptococcal meningitis to avert potentially life-threatening immune reconstitution inflammatory syndrome in the central nervous system.

The recommendations in these guidelines should be implemented informed by local context, including HIV epidemiology, the burden of cryptococcal disease, the prevalence of other comorbidities, access to laboratory assays for diagnosing and monitoring cryptococcal disease, access to drugs for treatment, the organization and capacity of the health system and anticipated cost–effectiveness.

Annex 1 summarizes the methods for developing these guidelines.

[†]All people living with HIV with a positive cryptococcal antigen test should have a careful evaluation for signs and symptoms of meningitis and a lumbar puncture if feasible to exclude cryptococcal meningitis.

3. KEY RECOMMENDATIONS, RATIONALE AND EVIDENCE SUMMARY

3.1 Diagnosing cryptococcal disease

Early diagnosis and treatment of cryptococcal meningitis is key to reducing mortality from cryptococcal disease. Health-care professionals should have a low threshold for suspecting cryptococcal meningitis among people with advanced HIV disease. Countries should give priority to reliable access to rapid diagnostic cryptococcal antigen assays, preferably lateral flow assays, for use in cerebrospinal fluid (CSF), serum, plasma or whole blood.

Recommendations

For adults, adolescents and children living with HIV suspected of having a first episode of cryptococcal meningitis, prompt lumbar puncture with measurement of 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)

The following diagnostic approaches are recommended, according to the context:

A. In settings with ready access to and no contraindication for lumbar puncture:

i) If both access to a cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) and rapid results (less than 24 hours) are available:

Lumbar puncture + rapid CSF cryptococcal antigen assay is the preferred diagnostic approach.

(Strong recommendation, moderate-certainty evidence for adults and adolescents; low-certainty evidence for children)

ii) If access to a cryptococcal antigen assay is not available and/or rapid results are not available:

Lumbar puncture + CSF India ink test examination is the preferred diagnostic approach.

(Strong recommendation, moderate-certainty evidence for adults and adolescents; low-certainty evidence for children)

B. In settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated:[a]

i) If both access to a cryptococcal antigen assay and rapid results (less than 24 hours) are available:

Rapid serum, plasma, or whole blood cryptococcal antigen assays are the preferred diagnostic approaches.

(Strong recommendation, moderate-certainty evidence for adults and adolescents; low-certainty evidence for children)

ii) If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured:

Prompt referral for further investigation and treatment as appropriate.

(Strong recommendation, moderate-certainty evidence for adults and adolescents; low-certainty evidence for children)

[a]Contraindications include significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs (excluding cranial nerve VI palsy) or recurrent seizures and, where possible, confirmed by computed tomography. Raised intracranial pressure does not contraindicate lumbar puncture in (suspected) cryptococcal meningitis. Other contraindications include major spinal deformity and patient refusal after fully informed consent was sought.

Table 1 Summary of the diagnostic approach to cryptococcal meningitis

	Lumbar puncture available	No lumbar puncture available or contraindicated
Rapid cryptococcal antigen test available	CSF cryptococcal antigen (preferably lateral flow assay)	Serum, plasma or whole blood, cryptococcal antigen (preferably lateral flow assay or latex agglutination assay for serum or CSF), treat immediately and refer for further investigation
No rapid cryptococcal antigen test available	CSF India ink	Prompt referral for further investigation

3.1.1 Background and rationale

The conventional approach to diagnosing cryptococcal meningitis requires a lumbar puncture with an India ink test, cryptococcal antigen test or culture. The Guideline Development Group reviewed evidence on the performance (sensitivity, specificity and predictive value) of three types of cryptococcal antigen assays (latex agglutination, enzyme immunoassay and lateral-flow assay) and CSF India ink test, compared with CSF culture or other cryptococcal antigen assays as the gold standard, among participants with either suspected or confirmed cryptococcal disease.

Annex 2 summarizes the sensitivity and specificity for all assays in different populations relative to various comparator assays.

3.1.2 Recommendations for adults and adolescents

The recommendation for the preferred use of a rapid cryptococcal antigen assay in CSF, serum, plasma or whole blood (depending on access to lumbar puncture) was based on the much higher sensitivity and specificity of these rapid cryptococcal antigen assays versus the India ink test and the fact that these rapid assays depend less on the health provider's skills. The enzyme immunoassay was not included as a recommended cryptococcal antigen assay because of cost and laboratory infrastructure requirements for its use. For rapid cryptococcal antigen assays, the lateral-flow assay has several advantages over the latex agglutination assay: it has a rapid (<10 minutes) turnaround time, requires little training for use and interpretation and can be performed with minimal laboratory infrastructure and without refrigerated storage. Data on the performance of the rapid cryptococcal antigen assay are currently more limited in some populations, such as children or people with isolated pulmonary disease.

A serum or plasma cryptococcal antigen test is recommended as an initial diagnostic option in settings where access to lumbar puncture is limited or contraindicated, to expedite diagnosis and prompt initiation of antifungal therapy. Serum, plasma or whole-blood cryptococcal antigen diagnosis should not replace the need for lumbar puncture with CSF examination and the important survival benefit of facilitating control of intracranial pressure *(22)*.

Using rapid low-cost assays in low- and middle-income countries that rely on limited technical skills and laboratory infrastructure facilitates prompt diagnosis and initiation of antifungal therapy. A high index of suspicion is needed for cryptococcal meningitis in regions with moderate to high HIV prevalence.

The cost of cryptococcal antigen assays needs to be reduced to make them more affordable in low- and middle-income countries. Countries should develop plans to improve access to rapid cryptococcal antigen assays, depending on the cryptococcal burden. Health-care infrastructure and available resources will determine the comprehensiveness of access.

3.1.3 Recommendations for children

Data on the accuracy of the diagnostic tests in children are limited, and the lateral-flow assay in particular has not been evaluated in children. However, limited data from retrospective observational cohorts suggest that diagnostic performance in children is similar to that of adults *(23,24)*. The recommendations for adults have therefore been extended to children.

3.2 Screening for and preventing cryptococcal disease

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/mm^3 *(strong recommendation; moderate-certainty evidence)* and may be considered at a higher CD4 cell count threshold of <200 cells/mm^3 *(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/mm^3 *(strong recommendation; moderate-certainty evidence)* and may be considered at a higher CD4 cell count threshold of <200 cells/mm^3 *(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.

[a]All 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 cryptococcal antigen assay (or India ink if cryptococcal antigen assay is not available) to exclude active cryptococcal disease.

3.2.1 Background and rationale

Early initiation of ART remains the most important preventive strategy to reduce the incidence of cryptococcal disease and associated high mortality. However, many people living with HIV continue to be diagnosed only when they have advanced HIV disease. Alternative approaches to preventing the development of cryptococcal disease are therefore an important component of the response to advanced HIV disease.

Previous WHO guidelines recommended screening for cryptococcal antigen among all people living with HIV who had a CD4 cell count <100 cells/mm^3 to identify patients at high risk of developing invasive cryptococcal disease. An alternative approach for these people –providing fluconazole primary prophylaxis – was not recommended except when a prolonged delay in ART initiation (or reinitiation) is likely.

A growing evidence base now supports the clinical benefit and cost–effectiveness of cryptococcal antigen screening. A trial in the United Republic of Tanzania and Zambia randomized 1999 ART-naive adults living with HIV with a CD4 cell count <200 cells/mm^3 to receive enhanced clinic-based care with cryptococcal antigen screening and pre-emptive antifungal treatment for those who were cryptococcal antigen–positive; importantly, additional community support, including ART delivery and adherence counselling, was provided to the intervention group. The trial reported a 28% reduction in mortality (13% versus 18%) among people receiving the intervention compared with standard care *(25)*. In a post hoc analysis, a statistically significant mortality decline was found among both people with a CD4 cell count <100 cells/mm^3 (mortality rate ratio 0.75, 95% confidence interval (CI) 0.58–0.95) and those with a CD4 cell count of 100–200 cells/mm^3 (mortality rate ratio 0.56, 95% CI 0.32–0.97) *(26)*.

A systematic review of 60 observational studies found that the pooled prevalence of cryptococcal antigen was 6.4% (95% CI 5.7–7.2%; 55 studies) among people with a CD4 cell count ≤100 cells/mm^3 and 2.0% (95% CI 1.2–2.7%; 21 studies) among people with a CD4 cell count of 100–200 cells/mm^3 *(26)*. Twenty-one studies provided sufficient information to compare cryptococcal antigen prevalence according to CD4 cell count strata; of the cryptococcal antigen–positive cases identified at a CD4 cell count ≤200 cells/mm^3 (n = 11 823), 18.6% (95% CI 15.4–22.2%) were identified among individuals with a CD4 cell count of 100–200 cells/mm^3. Among those with a CD4 cell count <100 cells/mm^3, cryptococcal antigen prevalence was higher among inpatients (9.8%, 95% CI 4.0–15.5%) than outpatients (6.3%, 95% CI 5.3–7.4%).

Several studies have evaluated the cost and cost benefit of cryptococcal antigen screening at the threshold of a CD4 cell count <100 cells/mm^3, including two South African studies reporting cost-benefit in settings with a prevalence of cryptococcal antigen positivity as low as 0.6% *(27)* and cost per result of between US$ 3.69 and US$ 6.03 *(28)*. A study in Malawi reported a cost per case detected of US$ 100.60 *(29)*. A study in Uganda found that the cost of detecting one person with asymptomatic cryptococcal antigenaemia with the lateral flow assay would be US$ 28.40, and the cost of saving one life would be US$ 39.70 *(30,31)*. A study in Viet Nam found that the incremental cost–effectiveness of cryptococcal antigen screening varied widely, from US$ 4 to US$ 296 per life year gained *(32)*. A study in Brazil found that, among inpatients screened at a CD4 cell count <200 cells/mm^3, the cost of cryptococcal antigen screening per life saved was US$ 326 (95% CI US$ 91–2685) *(33)*.

A systematic review assessing the benefits of providing routine fluconazole primary prophylaxis regardless of cryptococcal antigen status found no reduction in mortality overall but a 70% reduction in mortality from cryptococcal disease among people living with HIV with low CD4 cell counts (95% CI 12–89%). The study also found a 71% reduction in cryptococcal disease occurrence (95% CI 51–83%). The occurrence of serious adverse events did not differ (relative risk = 1.08, 95% CI 0.83–1.41), but there was some evidence of an increased risk of Candida infection resistant to fluconazole (relative risk = 1.25, 95% CI 1.00–1.55) *(34)*.

3.2.2 Recommendations for adults and adolescents

The Guideline Development Group recommended that all HIV positive adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3 be screened for cryptococcal antigen prior to ART initiation or reinitiation (strong recommendation; moderate-certainty evidence). Cryptococcal antigen screening may also be considered for adults and adolescents living with HIV who have a CD4 cell count <200 cells/mm^3 (conditional recommendation; moderate-certainty evidence). This recommendation was made in recognition of the higher prevalence of cryptococcal antigen observed at lower CD4 cell counts and the availability of cost–effectiveness data to support screening at this threshold.

All individuals screening positive for cryptococcal antigen should be given pre-emptive antifungal therapy (fluconazole 800 mg/day for adults, 12 mg/kg/day for adolescents, for two weeks), followed by consolidation and maintenance fluconazole therapy, as for treatment (see section 3.3).

Everyone testing positive for serum or plasma (or whole blood) cryptococcal antigen during screening should be carefully evaluated for signs and symptoms of meningitis. Everyone with signs or symptoms of meningitis should have a lumbar puncture and, where feasible, those without signs or symptoms of meningitis should also have lumbar puncture, with CSF examination and cryptococcal antigen assay (or India ink if cryptococcal antigen assay is not available) to exclude to exclude active cryptococcal disease.

To date no studies have specifically addressed the question of cryptococcal antigen screening or fluconazole prophylaxis among ART-experienced individuals who present after a period of disengagement from care with advanced HIV disease; however, the Guideline Development Group considered that these recommendations would apply equally to this group.

The Guideline Development Group placed high value on the benefits of cryptococcal antigen screening followed by pre-emptive therapy as the preferred approach to identify and intervene for people presenting with advanced HIV disease who are at risk of developing cryptococcal meningitis. This approach was preferred over providing fluconazole primary prophylaxis after considering cost, the potential for developing antifungal resistance and concerns about fetal safety among women of childbearing age without access to adequate contraception. Nevertheless, access to cryptococcal antigen testing remains limited in many settings, and although efforts are needed to improve access, fluconazole primary prophylaxis should be made available in settings in which cryptococcal antigen screening is not available or there may be prolonged delays in receiving the result. The importance of avoiding long delays in cryptococcal antigen testing was informed by data indicating that, among people presenting with a CD4 cell count <100 cells/mm^3, cryptococcal disease and mortality peak in the first four weeks *(35)*.

The duration of fluconazole primary prophylaxis differed in the randomized trials that support the clinical benefit of this intervention. In the REALITY trial conducted in Kenya, Malawi, Uganda and Zimbabwe, fluconazole (100 mg once daily) was discontinued after 12 weeks. In another trial conducted in Uganda in the era of ART, fluconazole (200 mg three times per week) was discontinued when participants' CD4 cell counts reached 200 cells/mm^3 *(36)*. National guidelines should determine the optimal duration of prophylaxis based on available resources.

3.2.3 Recommendations for children

These recommendations apply to adults and adolescents with advanced HIV disease. The decision not to extend these recommendations to children was based on the recognition that cryptococcal disease in this age group is rare, even in countries with high incidence *(15,37)*.

3.2.4 Implementation considerations

The relative advantage of various screening approaches should be considered according to context. Evidence from South Africa suggests that laboratory-based reflexive screening, in which cryptococcal antigen testing is routinely performed in the laboratory on any blood sample with a CD4 cell count threshold meeting the criteria for screening, can save time and resources when laboratory resources allow *(38,39)*.

In resource-limited settings with limited laboratory infrastructure, task shifting has been found to overcome human resource limitations. A study in Lesotho found that cryptococcal antigen screening by lay counsellors followed by pre-emptive fluconazole treatment for cryptococcal antigen–positive asymptomatic cases or referral to hospital for symptomatic cases was feasible *(40)*. This may be the preferred approach, especially when the point-of care CD4 cell count is available, allowing for same-day initiation of fluconazole among those who screen cryptococcal antigen–positive.

3.2.5 Future research

Further research is needed to assess the value of screening at CD4 cell count thresholds greater than 100 cells/mm^3, which has already been suggested to save costs if carried out in inpatient settings. Research is also needed to assess the value of cryptococcal antigen screening of ART-experienced patients with low CD4 cell counts.

High cryptococcal antigen titres have been found to predict subclinical meningitis, and it has been suggested that blood titres could be used in settings where lumbar puncture cannot be performed or where providing lumbar puncture for everyone screening cryptococcal antigen–positive is operationally challenging; the feasibility of this approach should be further investigated in a diversity of settings *(41)*. Second-generation cryptococcal antigen lateral-flow assays that can give a high or low cryptococcal antigen titre result need to be evaluated as part of this approach.

WHO recommends a package of interventions for people presenting with advanced HIV disease, and implementation science research is encouraged on the feasibility and impact of cryptococcal antigen screening delivered together with other components of an advanced ART package (such as tuberculosis (TB) lipoarabinomannan assay and TB prophylaxis).

3.3 Induction, consolidation and maintenance antifungal treatment regimens

Recommendations

Induction

- For adults, adolescents and children, a short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day) 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 for adults, 12 mg/kg/day for children and adolescents) + flucytosine (100 mg/kg/day, divided into four doses per day) *(strong recommendation, moderate-certainty evidence).*
- Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) *(strong recommendation, moderate-certainty evidence)*.

Consolidation

Fluconazole (800 mg daily for adults, 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 for adults, 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 should be provided to minimize treatment toxicity related to amphotericin B and flucytosine.

3.3.1 Background and rationale

Recent studies in resource-limited settings, notably the recently completed ACTA trial, have aimed to shorten the induction phase of treatment for cryptococcal meningitis, with the aim of limiting the costs and toxicity of treatment while maintaining efficacy *(42)*. A systematic review of randomized trials comparing antifungal induction therapies used for treating the first episode of HIV-associated cryptococcal meningitis identified 13 eligible studies (2426 participants) that compared 21 interventions *(43)*. These interventions were compared directly and also ranked through network meta-analysis. In the direct comparisons, amphotericin B deoxycholate and flucytosine for one week, followed by fluconazole on days 8–14, reduced mortality at 10-week follow-up by 51% compared with one week of amphotericin B deoxycholate and fluconazole (95% CI 28–66%). The one-week amphotericin B deoxycholate and flucytosine induction regimen reduced mortality by 38% compared with two weeks of amphotericin B deoxycholate and flucytosine (95% CI 7–58%) and by 32% compared with two weeks of flucytosine and fluconazole (95% CI 1–53%). The shortened one-week amphotericin B deoxycholate and flucytosine regimen has superior efficacy and a 69% (95% CI 10–84%) lower risk of grade 3 or 4 anaemia compared with two weeks of amphotericin B deoxycholate and flucytosine. The evidence was of moderate certainty for each of these comparisons. The network meta-analysis supports one week of amphotericin B deoxycholate and flucytosine as the best induction regimen; the superiority of the shorter course of treatment likely results from a lower risk of toxicity and nosocomial sepsis.

3.3.2 Recommendations

Based on this evidence, one week of amphotericin B deoxycholate and flucytosine-based therapy (followed by one week of fluconazole 1200 mg) is the preferred antifungal regimen for the induction phase of treatment of HIV-associated cryptococcal meningitis. If flucytosine is not available, two weeks of amphotericin B deoxycholate + fluconazole is recommended. If amphotericin B deoxycholate is not available, an oral two-week regimen of flucytosine and fluconazole is recommended.[‡] These recommendations apply to all age groups and settings, and while the systematic review found no randomized studies among children, observational data support the use of amphotericin B and flucytosine among children *(13,24)*. The recommendations for children are therefore based on extrapolation from evidence for adults and in the absence of specific contraindication for this age group.

Liposomal amphotericin B is preferred over amphotericin B deoxycholate, since liposomal amphotericin B has demonstrated equivalent efficacy and better safety compared with the conventional form of amphotericin B deoxycholate *(44,45)*. However, access to liposomal amphotericin B remains extremely limited in low- and middle-income countries because of its high cost.

[‡]Flucytosine and fluconazole can be administered naso-gastrically to people who cannot take medicines orally because of altered mental status.

3.3.3 Consolidation regimens

Two trials compared eight weeks of fluconazole (400 or 600 mg/day) as consolidation therapy with itraconazole *(46,47)*. Itraconazole has the potential for interactions with several commonly used ARV drugs (including efavirenz, darunavir, lopinavir and ritonavir). The Guideline Development Group therefore recommended fluconazole at 800 mg/day for 8 weeks following one week of an amphotericin B–based induction regimen. These recommendations were based primarily on expert opinion.

3.3.4 Maintenance treatment

Maintenance or secondary prophylaxis until evidence exists of sustained ART-related immune reconstitution is an integral part of managing cryptococcal meningitis. Among ART-naive people, fluconazole was effective at preventing relapse in one randomized controlled trial, with no relapses in the fluconazole arm *(48)*. Fluconazole was also superior as a maintenance treatment to weekly amphotericin B and itraconazole *(49,50)*.

3.3.5 Implementation considerations

Access to essential antifungal drugs remains inadequate, and drug toxicity and laboratory monitoring costs continue to be important barriers. Lack of local manufacturers, lack of in-country registration and high costs are the main barriers *(51,52)*. Liposomal amphotericin B is included in the 2015 WHO List of Essential Medicines and WHO Prequalification Expression of Interest list. Although liposomal amphotericin B has been off patent since 2016, the current price of liposomal amphotericin B per vial remains substantially higher than that of amphotericin B deoxycholate. The originator manufacturer has reduced the cost of liposomal amphotericin B for managing visceral leishmaniasis in some countries; however, preferential pricing has not yet been consistently applied to cryptococcal meningitis.

Fluconazole is widely registered and is available in low- and middle-income countries. However, several countries have not included fluconazole in their national list of essential medicines. The average cost of fluconazole at treatment dosage (800 mg/day) is US$ 26 per day, and the daily treatment price varies from US$ 1 to US$ 31.

Flucytosine has just three manufacturers in 2017 and is not registered in any African country. Although registering standard formulations of flucytosine is the current priority, 100 mg/kg/day dosages of flucytosine given four times a day are problematic in resource-limited settings, and WHO has issued a Prequalification Expression of Interest for slow-release formulations of flucytosine that may permit twice-daily dosing.

3.3.6 Future research

Recent Phase 2 clinical trial results show that liposomal amphotericin B could potentially be used as a high-dose, one-time injection in combination with high-dose fluconazole (1200 mg daily) and flucytosine for the induction phase of cryptococcal meningitis treatment, with good results *(53)*. A Phase 3 trial is ongoing to further evaluate the safety and efficacy of this approach *(54)*.

3.3.7 Treatment for localized non-meningeal disease

No clinical trial data have evaluated the optimal treatment of localized non-meningeal disease. Treatment with fluconazole 800 mg/day for two weeks followed by 400 mg/day for eight weeks followed by fluconazole 200-mg/day maintenance therapy is suggested based on expert opinion.

No clinical trial data have evaluated the optimal treatment of cryptococcoma. Published data on managing cryptococcoma are limited to case reports. The following treatment regimen is suggested based on expert opinion: intravenous amphotericin B and oral flucytosine for at least six weeks, followed by consolidation and maintenance therapy with fluconazole (all doses similar to those used for cryptococcal meningitis). Corticosteroids or surgical intervention may be considered for intracranial lesions with evidence of mass effect. Data on the treatment of other forms of cerebral parenchymal involvement caused by cryptococcosis are also scarce, but the management approach may be similar to those described for cryptococcoma.

3.3.8 Treatment for pregnant women

Amphotericin B therapy can be given to pregnant women with meningeal and non-meningeal disease. Exposure to flucytosine and fluconazole during pregnancy has been associated with an increased risk of birth defects in animal studies and some uncontrolled human studies. The use of flucytosine and fluconazole for treating cryptococcal disease in pregnant women should be evaluated on an individual basis, considering the benefits and potential harm.

3.4 Adjunctive corticosteroids in treating HIV-associated cryptococcal meningitis

Recommendation

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).*

3.4.1 Background and rationale

Despite the high mortality and disability associated with HIV-associated cryptococcal meningitis, treatment options are limited and relatively few new treatment strategies exist. Adjuvant corticosteroids reduce the inflammatory response to infection and have been shown to improve outcomes in the treatment of other central nervous system infections such as bacterial and TB meningitis in adolescents and adults in some settings *(55,56)*.

A systematic review assessed whether adjuvant systemic corticosteroids in the treatment of HIV-associated cryptococcal meningitis improved outcomes compared with standard care. The review identified one study of adjunctive therapy with dexamethasone in HIV-associated cryptococcal meningitis *(57)*; this was a double-blind, randomized, placebo-controlled trial of adults living with HIV who had clinical and laboratory-confirmed cryptococcal meningitis. The study was carried out in hospitals in Indonesia, the Lao People's Democratic Republic, Malawi, Thailand, Uganda and Viet Nam *(57)*.

The participants (n = 451) were randomized to receive dexamethasone for six weeks or placebo in addition to antifungal therapy with amphotericin B and fluconazole, co-trimoxazole prophylaxis and ART. No difference in mortality was identified between the two groups at 10 weeks (hazard ratio of death in the dexamethasone group 1.11, 95% CI 0.84–1.47) or at six months (hazard ratio of death in the dexamethasone group, 1.18, 95% CI, 0.91–1.53). The disability outcome at 10 weeks was worse in the dexamethasone group: 13% of the participants in the dexamethasone group had a positive outcome (no death or disability) at 10 weeks compared with 25% in the placebo group. Serious adverse events were more common in the dexamethasone group, including grade 3 or 4 infections, cardiac, renal and gastrointestinal disorders and biochemical abnormalities. The rate of fungal clearance in the CSF in the first two weeks of treatment was slower in the dexamethasone group than in the placebo group. The certainty of the evidence was rated as high.

3.4.2 Recommendation

The recommendation against the routine use of adjunctive corticosteroid therapy in the induction phase of treatment for HIV-associated cryptococcal meningitis among adults and adolescents is supported by high-quality evidence for adults and adolescents.

A paediatric advisory group was convened to advise the Guideline Development Group on specific considerations for children. This group advised that there was no rationale as to why recommendations on the use of adjuvant corticosteroids in treating HIV-associated cryptococcal meningitis should be different for children. The Guideline Development Group therefore strongly recommended against the routine use of adjuvant corticosteroids in the induction phase of

treatment of cryptococcal meningitis among children; however, the Guideline Development Group considered that the evidence for children was indirect, since the randomized controlled trial did not include children, and the certainty of the evidence was therefore rated as moderate.

The study did not include participants with clinical conditions among which corticosteroids may have a role, such as in the treatment of cryptococcoma with mass effect or adult respiratory distress syndrome; in these situations, clinical management may include the use of corticosteroids, but the protocols are not well defined. The recommendation against the use of adjuvant corticosteroids therefore applies specifically to the routine use during the induction phase of treatment of cryptococcal meningitis. If people have a clinical condition for which treatment with systemic corticosteroids is indicated, they should be used if this is clinically appropriate.

3.5 Preventing, monitoring and managing amphotericin B toxicity

3.5.1 Good practice principles

Drug toxicity and side-effects from amphotericin B therapy, especially hypokalaemia, nephrotoxicity and anaemia, are barriers to optimal induction treatment, particularly in low- and middle-income countries.

- Safe administration of amphotericin B should be given priority and may require referral to a centre with access to a minimum package of preventing, monitoring and managing toxicity.
- A minimum package of preventing, monitoring and managing toxicity should be provided to minimize the serious types of amphotericin B–related toxicity, especially hypokalaemia, nephrotoxicity and anaemia (Table 2).

3.5.2 Background and rationale

In a review of 60 studies of cryptococcal meningitis treatment, the rates of hypokalaemia ranged from 0% to 35% and the rates of nephrotoxicity from 1% to 38%. The pooled incidence of amphotericin B deoxycholate–associated nephrotoxicity was 33.2% (95% CI: 30.8–36.0%), and discontinuation because of nephrotoxicity occurred among 4.8% (95% CI: 4.3–6.3%) of the people monitored *(58)*. Another important concern is anaemia: an analysis of data from six randomized trials of people receiving amphotericin B deoxycholate–based induction therapy found that one third developed grade 3 or 4 anaemia; haemoglobin levels dropped by a mean of 1.5 g/dl following seven days of amphotericin B and by a mean of 2.3 g/dl after 14 days *(59)*.

A protocol for twice-weekly monitoring of potassium, magnesium (where available) and creatinine and weekly haemoglobin monitoring is advised, together with a simplified protocol for pre-hydration and electrolyte replacement before each amphotericin B infusion, based on evidence from a pooled analysis of data from two randomized controlled trials and two observational studies that this approach can substantially reduce the incidence of these types of toxicity *(60–63)*.

For flucytosine, regularly monitoring full blood count should be considered (Table 2). The dose of flucytosine may need to be adjusted among people with renal impairment.

Table 2 Minimum package for preventing, monitoring and managing amphotericin B toxicity

Pre-emptive hydration and electrolyte supplementation	
Adults and adolescents	One litre of normal saline solution with 20 mEq of potassium chloride (KCl) over two hours before each controlled infusion of amphotericin B and one to two 8-mEq KCl tablets orally twice daily. An additional 8-mEq KCl tablet twice daily may be added during the second week. If available, magnesium supplementation should also be provided (two 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily, or magnesium chloride 4 mEq twice daily).
Monitoring (adults, adolescents and children)	
Serum potassium	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Serum creatinine	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Haemoglobin	Baseline and weekly
Management (adults, adolescents and children)	
Hypokalaemia	If hypokalaemia is significant (K <3.3 mol/l), increase potassium supplementation to 40 mEq KCl by intravenous injection and/or one to two 8-mEq KCl tablets orally three times daily. Monitor potassium daily.
Elevated creatinine	If creatinine increases by ≥2 fold from the baseline value, increase pre-hydration to 1 L every eight hours and consider temporarily omitting a dose of amphotericin B. Once creatinine improves, restart amphotericin B at 0.7 mg/kg/day and consider alternate-day amphotericin B. If creatinine continues to rise, consider discontinuing amphotericin B and continuing with fluconazole at 1200 mg/day, especially if seven doses of amphotericin have been received. Monitor creatinine daily.
Severe anaemia	Transfusion should be undertaken if possible for severe amphotericin B–related anaemia (anaemia may also be a reason to discontinue amphotericin B prematurely in the second week of a planned two-week induction course of amphotericin B with fluconazole)

Additional notes:

- Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia.
- Careful attention should be given to monitoring of intake and output of fluid and daily weight, especially among children.
- Flucytosine – because of concerns about bone marrow suppression, regular monitoring of full blood counts should be considered.
- The incidence of renal dysfunction and electrolyte disturbance is much less with liposomal amphotericin preparations, but renal function and electrolytes still need to be monitored.

3.6 Monitoring and managing people with cryptococcal meningitis

3.6.1 Monitoring for and managing raised intracranial pressure

Initial measurement of intracranial pressure and management of raised intracranial pressure is an essential part of cryptococcal meningitis management to prevent death and serious nervous system complications. Raised intracranial pressure is a frequent and potentially life-threatening complication, occurring in up to 80% of people with HIV-associated cryptococcal meningitis *(17,19,20)*. Intracranial pressure may be raised even in the absence of symptoms *(19,20,22)*. Raised intracranial pressure at baseline has been associated with increased mortality in some *(20)* but not all *(19)* observational studies. The limitations of using clinical symptoms or signs to identify people suspected of having raised intracranial pressure requiring repeat therapeutic lumbar puncture has been recognized *(20)*.

Reduction of raised CSF pressure is associated with clinical improvement *(20,64–66)* and survival benefit, regardless of initial opening pressure *(22,67)*. Conversely, failure to reduce CSF pressure is associated with poor nervous system outcome and increased mortality *(22,68)*. Adults, adolescents and children living with HIV with suspected cryptococcal meningitis should have an initial lumbar puncture and an 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; clinicians could consider doing more than one repeat lumbar puncture even in the absence of symptoms of raised intracranial pressure (such as third lumbar puncture on day 3). For people with initial intracranial pressure of 20 cm H_20 or more or subsequent development or recurrence of symptoms or signs of raised intracranial pressure, repeat therapeutic lumbar puncture[§] should be carried out.

People with raised intracranial pressure at baseline and those who develop symptoms or signs of raised intracranial pressure (Box 1) should be given priority for follow-up lumbar puncture in low- and middle-income countries.

Box 1. Common symptoms and signs of raised intracranial pressure

Symptoms

- Headache
- Nausea with or without vomiting
- Changes in vision or hearing (such as double vision, blindness or deafness)

Signs

- Change in mental status (ranging from confusion to lethargy to coma)
- Papilloedema
- Seizures
- Cranial nerve palsies (such as eye movement problems, particularly cranial nerve VI)
- Other focal neurological nervous system deficits

[§]Therapeutic lumbar puncture is defined as a lumbar puncture performed to remove CSF to decrease intracranial pressure.

Good practice principles

The following steps are advised for managing raised intracranial pressure:

- Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient to reduce the CSF pressure to less than 20 cm H_20 or halving the baseline pressure baseline pressure if extremely high.**
- The persistence or recurrence of symptoms or signs of raised intracranial pressure should determine the frequency of repeat therapeutic lumbar puncture. For people with persistent symptoms of raised intracranial pressure, repeat daily therapeutic lumbar puncture (with measurement of CSF opening pressure where available) and CSF drainage if required until the symptoms resolve or the opening pressure is normal for at least two days is advised.

Using drugs (mannitol, acetazolamide, furosemide or steroids) for managing raised intracranial pressure is not recommended because there is no evidence that indicates that using these drugs improves outcomes in managing cryptococcal meningitis–associated raised intracranial pressure, and some evidence indicates that using them may be harmful *(20,57,69–71)*.

No clinical trials have evaluated the optimal frequency and quantity of CSF drainage required to improve clinical outcomes among people with raised intracranial pressure or whether this can be guided by clinical symptoms alone or requires measuring opening or closing pressure. The experience of the Guideline Development Group suggests that, on average, 20–25 ml may need to be drained. Access to manometers is a challenge to reliably measuring and monitoring intracranial pressure in low- and middle-income countries, and therapeutic lumbar puncture with drainage of CSF may need to be undertaken even in the absence of reliable measurement of intracranial pressure.

3.6.2 Monitoring for and managing raised intracranial pressure

Regular and careful monitoring of clinical symptoms and signs is the most important and most feasible strategy to evaluate response to antifungal treatment in low- and middle-income countries. CSF or serum or plasma cryptococcal antigen is of little or no value in predicting treatment failure or relapse among people living with HIV who have cryptococcal meningitis *(72–76)*. Routine monitoring using CSF culture requires a prolonged time to obtain results and is not feasible in most low- and middle-income settings.

Good practice principles: monitoring treatment response

- Clinical response (including resolution or recurrence of fever, headache and symptoms or signs of raised intracranial pressure) should be assessed daily during the initial two weeks of induction therapy.
- Among people with evidence of a sustained clinical response, routine follow-up lumbar puncture after completing induction treatment to assess antifungal treatment response (CSF fungal culture and CSF cryptococcal antigen) or serum or plasma cryptococcal antigen is not advised in low- and middle-income countries.

**There are no data on the maximum volume of CSF that can be safely drained at one lumbar puncture. CSF opening pressure can be re-checked after every 10 ml is removed. Usually 20–25 ml is enough to reduce the opening pressure sufficiently

3.6.3 Diagnostic approach for persistent or recurrent symptoms

Many people with cryptococcal meningitis experience persistent (failing to resolve after two weeks of antifungal treatment) or recurrent symptoms (reappearing after initial resolution following treatment for an episode of cryptococcal meningitis). Among people receiving optimal induction therapy, the most common causes of recurrence of symptoms are raised intracranial pressure, non-adherence to fluconazole and immune reconstitution inflammatory syndrome (Box 2).

Box 2. Main causes of persistent and recurrent symptoms among people with cryptococcal meningitis

Persistent symptoms

- Raised intracranial pressure
- Treatment failure caused by suboptimal induction treatment
- Inadequate drug regimen, dose or duration
- Fluconazole drug resistance (rare)
- Other concomitant illness (such as viral, bacterial, or tuberculous meningitis)

Recurrent symptoms

- Raised intracranial pressure
- Treatment failure due to suboptimal induction, consolidation or maintenance treatment
- Inadequate drug regimen, dose or duration
- Failure to prescribe or to adhere to fluconazole consolidation or maintenance treatment
- Fluconazole drug resistance (rare)
- Cryptococcal immune reconstitution inflammatory syndrome (IRIS) following ART initiation
- Other concomitant illness (such as viral, bacterial or tuberculous meningitis)

Good practice principles: diagnostic approach to persistent or recurrent symptoms

The following diagnostic approach should be used for people with persistent or recurrent symptoms to establish potential underlying causes:

- Review the patient's history for evidence suggesting underlying treatment failure from (1) inadequate drug regimen, dose and duration, (2) poor adherence to fluconazole consolidation and maintenance treatment or (3) underlying fluconazole drug resistance among people with previous prolonged fluconazole therapy.

- Perform lumbar puncture with measurement of the opening pressure to establish the presence or absence of raised intracranial pressure and CSF examination with other relevant investigations to exclude concomitant illnesses.††
- Consider paradoxical cryptococcal immune reconstitution inflammatory syndrome after excluding other causes of recurrent symptoms among people who have started ART.
- Resend CSF for prolonged fungal culture (two weeks of incubation).

3.6.4 Managing relapse

In case of persistent or recurrent symptoms resulting from treatment failure or relapse, induction therapy should be restarted according to the recommendations for treatment in section 3.3. Particular attention should be paid to reinforcing adherence to therapy. If ART has not yet been started, initiation should be deferred by four weeks in accordance with the recommendation in section 3.7.

Good practice principles

For people who present with cryptococcal meningitis relapse, the following steps are advised:

- Start or restart induction treatment according to the recommendations for induction treatment in section 3.3.
- Manage raised intracranial pressure with therapeutic lumbar puncture (see section 3.6.1).
- Reinforce adherence.
- If ART has not already started, initiating ART after 4-6 weeks of optimal antifungal therapy is recommended (see section 3.7 on the timing of ART initiation).

3.6.5 Managing cryptococcal immune reconstitution inflammatory syndrome

Paradoxical cryptococcal immune reconstitution inflammatory syndrome occurs among 10–50% of people with cryptococcal disease initiating ART *(77)* and is associated with high mortality in some studies *(18)*. The median time to onset in reported cohort studies ranges from 1 to 10 months but typically is 3–12 weeks after initiating ART *(77)*.

Raised intracranial pressure is a common feature of cryptococcal immune reconstitution inflammatory syndrome and an important contributor to high mortality *(78)*. Multiple repeat lumbar puncture may be necessary. Optimizing antifungal therapy and reinduction with an amphotericin-based regimen is important if suboptimal antifungal treatment is considered to contribute to developing immune reconstitution inflammatory syndrome.

††Other diseases that can present with symptoms and signs similar to cryptococcal meningitis (such as viral, bacterial or tuberculous meningitis) should also be considered. Where possible, fluconazole susceptibility testing should be performed at a national reference laboratory when clinically suspected (culture-positive relapse despite fluconazole adherence).

The following steps are advised for managing cryptococcal immune reconstitution inflammatory syndrome:

1. Continue ART.
2. Promptly manage raised intracranial pressure.
3. Optimize antifungal therapy and consider restarting induction therapy according to the recommendations for treatment in section 3.3 as appropriate.
4. Short-course oral steroid[‡‡] therapy, although not recommended for routine use in treating cryptococcal meningitis (see section 4.3), may be considered if there is continued deterioration and/or the development of life-threatening complications (such as intracranial space-occupying lesions with mass effect or extracranial disease impinging on vital structures) despite the above measures.

3.7 Timing of ART initiation

Recommendation

Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 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)

3.7.1 Background and rationale

WHO guidelines published in 2017 *(2)* recommend initiating ART within seven days after HIV diagnosis and that people with advanced HIV disease be given priority for assessment and ART initiation; the guidelines further recommend that ART initiation should be offered on the same day to people who are ready to start *(2)*. However, people presenting for the first time or those returning to care should undergo history and clinical examination to evaluate for significant opportunistic infections (such as signs and symptoms of TB and signs and symptoms suggesting cryptococcal meningitis) before rapid ART initiation is offered. Immediate ART initiation is contraindicated among people living with HIV who have cryptococcal meningitis because of the increased mortality presumed to be caused by immune reconstitution inflammatory syndrome in the central nervous system.

The optimal timing of ART after cryptococcal meningitis was informed by a systematic review that identified four relevant randomized controlled trials *(79–82)*. Overall, early ART initiation increased mortality compared with delaying ART initiation (pooled relative risk for mortality at 6–12 months, 1.42, 95% CI 1.02–1.97). Immediately initiating ART is therefore not recommended among people with cryptococcal meningitis because of the potentially high risk of life-threatening intracranial immune reconstitution inflammatory syndrome.

[‡‡]Prednisolone 1 mg/kg/day or dexamethasone at equivalent doses for at least one week or until clinical improvement, with tapering over 2–6 weeks. Longer treatment may be required depending on the symptom response.

3.7.2 Recommendation

WHO strongly recommends deferring ART initiation for four weeks following an amphotericin B–based induction regimen or 4–6 weeks following a fluconazole + flucytosine induction regimen (based on a slower rate and longer time to achieve CSF fungal clearance with fluconazole versus amphotericin B) *(83)*. This recommendation applies across all age groups and also applies to ART-experienced people who develop cryptococcal meningitis following ART treatment failure who may need to switch to second-line ART and to people reinitiating after interruption. Although clear data are lacking, the consensus of the Guideline Development Group was that, for ART-experienced people, ART switches should be similarly deferred by four weeks following an amphotericin B–based induction regimen or 4–6 weeks following a fluconazole-based induction regimen.

No prospective evidence supports decisions about when to start ART among asymptomatic people with cryptococcal antigenaemia after initiation of pre-emptive antifungal therapy. Guidelines from the Southern African HIV Clinicians' Society recommend starting ART two weeks after starting fluconazole, and consideration is being given to starting ART immediately if lumbar puncture excludes cryptococcal meningitis among people who test positive for whole-blood cryptococcal antigen *(84)*.

3.7.3 Implementation considerations

ART-experienced people who develop cryptococcal meningitis should be evaluated for potential underlying ART treatment failure, ideally through confirmation with an HIV viral load. ART switches should be deferred by four weeks following an amphotericin B–based induction regimen or 4–6 weeks following a fluconazole-based induction regimen.

3.8 Discontinuing fluconazole maintenance treatment (secondary prophylaxis)

Among adults, adolescents and children older than five years living with HIV who have successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuing antifungal maintenance treatment is advised based on the following criteria:

If HIV viral load monitoring is available:

- The person is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥100 cells/mm^3 and a fully suppressed viral load.

If HIV viral load monitoring is not available:

- The person is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥200 cells/mm^3.

For children living with HIV who are 2–5 years old and have successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuing antifungal treatment maintenance is recommended if the child is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count percentage greater than 25% or an absolute count >750 cells/mm^3.

Maintenance treatment for cryptococcal disease should not be discontinued for children younger than two years.

Secondary prophylaxis for cryptococcal disease should be restarted if the CD4 count drops to <100 cells/mm^3 or less for adults, adolescents and children older than five years living with HIV (or CD4 cell count ≤25% or ≤750 cells/mm^3 for children 2–5 years old) or if a WHO stage 4 clinical event occurs, regardless of age.

Although CD4 cell count monitoring is no longer recommended for monitoring the response to ART in settings in which viral load is available, it remains important in guiding decisions about when to discontinue fluconazole maintenance therapy.

Few studies have evaluated the risk of recurrent disease after maintenance treatment is discontinued. A systematic review identified five single-arm trials and one observational study *(85–90)*. Only four of 185 adults who discontinued maintenance treatment at a CD4 count >100 cells/mm^3 relapsed or experienced recurrent disease, and 106 adults had no deaths after discontinuation. In the only study from a low- or middle-income country – a randomized controlled trial in Thailand *(91)* – there were no cases of recurrent disease among 20 people, 48 weeks after discontinuation, at a CD4 count >100 cells/mm^3 and an undetectable HIV viral load for 3 months.

The advice for discontinuing prophylaxis is therefore based on the very low risk of recurrence when people have successfully completed initial induction and consolidation antifungal therapy and have had a sustained increase in their CD4 count on ART to greater than 200 cells/mm^3. This more conservative, higher CD4 cell count threshold for discontinuing prophylaxis takes into account the widespread use of the less-effective oral fluconazole monotherapy induction treatment, limitations in access to viral load, and less frequent CD4 count monitoring in low- and middle-income countries. Discontinuation at a lower threshold of CD4 >100 cells/mm^3 is advised if viral load monitoring is available and confirms a suppressed viral load on ART.

No studies have evaluated the optimal timing for discontinuing maintenance treatment among people with localized non-meningeal disease (such as pulmonary disease) or isolated serum cryptococcal antigen positivity. The optimal regimen and timing for discontinuing maintenance treatment for these populations remains to be determined.

Only one of the six studies evaluating the timing of the discontinuation of maintenance treatment reported data on adolescents, and no study reported data on children. Despite the limited evidence base, the same principles of establishing sustained ART-related immune reconstitution before discontinuing antifungal treatment should apply equally to children.

4. IMPLEMENTATION CHALLENGES AND CONSIDERATIONS

4.1 Overview

As part of the guideline development process, a country-level feasibility assessment was undertaken among health-care providers in 16 countries across Africa, Asia and Latin America to determine the current availability of diagnostic tests and antifungal drugs for treating cryptococcal disease and barriers to access. Drug costing information was also obtained and taken into account in developing the treatment recommendations.

The results of the access survey highlighted implementation challenges in four key areas: (1) limited access to rapid diagnostics, (2) limited access to optimal antifungal treatment, (3) administration and monitoring the toxicity of amphotericin B treatment and (4) the education and training of health-care providers.

Survey respondents consistently highlighted the inability to diagnose cryptococcal meningitis rapidly and the lack of essential medicines as key gaps. India ink was the primary diagnostic test available in most countries, and the turnaround time for test results varied from a few hours to three days. Rapid cryptococcal antigen tests (lateral flow assay or latex agglutination assay) were often unavailable or prohibitively expensive.

Lack of appropriate medications in Africa was attributed to several factors: high drug costs, especially of amphotericin B, limited access to flucytosine despite being included in several national guidelines, frequent drug stock-outs because of poor forecasting and distribution and variation in approaches to funding of both amphotericin B and fluconazole, with many countries having user fees for drug costs. In Asia, generic amphotericin B and fluconazole, produced by regional manufacturers, are more widely available, and flucytosine and liposomal amphotericin B can also be accessed; national governments generally provide drugs for treating cryptococcal meningitis, including amphotericin B, free of user fees.

Lumbar puncture is performed with variable frequency, 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.

Amphotericin B toxicity monitoring and management practices vary widely, but pre-emptive hydration and electrolyte replacement are rare. In addition, financial barriers and the burden placed on family members limit referral to centres with monitoring capabilities. Lack of provider education and awareness about cryptococcal disease has also been identified as a cause of suboptimal management.

As a result of these issues, fluconazole monotherapy without managing raised intracranial pressure is common in low- and middle-income countries, resulting in unacceptably high mortality rates. Successfully implementing the recommendations in these guidelines requires that countries identify and respond to these implementation challenges.

4.2 Access to diagnostics

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 *(52)*.

4.3 Access to medicines

Lack of appropriate drug forecasting and monitoring often results in both unused stock and drug stock-outs of fluconazole and amphotericin B. Lack of clinician awareness about the proper indications for use and education on the safe administration of amphotericin B and flucytosine has also contributed to fluctuating levels of demand *(52)*.

Flucytosine is not registered and largely unavailable in most low- and middle-income countries, especially in sub-Saharan Africa *(16)*. The cost of registration in many countries is an additional disincentive to using flucytosine. Advocacy is required to reduce the cost of flucytosine and simplify drug registration procedures. The induction regimen given priority in these recommendations, based on the best-performing arms in the ACTA trial, contains flucytosine. A combination flucytosine and fluconazole induction regimen is an alternative regimen if amphotericin B is not available (section 3.3). These regimens can potentially reduce mortality by half compared with using fluconazole monotherapy.

Antifungal medications for treating cryptococcal meningitis are increasingly more affordable, and barriers to access 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 included in WHO Model List of Essential Medicines *(92)*);
- ensuring adequate supply chains at the national level; and
- developing proper drug-forecasting and -monitoring systems *(52)*.

4.4 Educating and training health-care providers

Gaps in educating health-care providers on appropriately managing cryptococcal meningitis in low- and middle-income countries have contributed to the use of suboptimal induction treatment regimens and failure to diagnose and appropriately manage the complications of cryptococcal meningitis, such as raised intracranial pressure. In the outpatient setting, relapse of cryptococcal meningitis commonly results from lack of fluconazole maintenance therapy, either because health-care workers fail to prescribe, people are lost to follow-up because of poor linkage to care or adherence is poor. Greater efforts need to be made to educate health-care providers and to provide policy guidance at the national level on managing cryptococcal disease. Effectively implementing guidelines also requires supportive supervision systems and prescribing decision-making aids *(52)*.

5. DISSEMINATING, ADAPTING AND IMPLEMENTING THE GUIDELINES

These guidelines will be launched as a web-based product for dissemination and will be supported by peer-reviewed publication of the systematic reviews on which these recommendations are based. These guidelines will also be incorporated into the next full update of the WHO consolidated ARV guidelines planned for 2019. The consolidated ARV guidelines are planned to be reviewed and updated every 2-3 years. The technical update of each section is reviewed as the evidence base and users' needs change.

WHO will work closely with WHO regional and country offices, national health ministries of health and implementing partners to plan for rapidly disseminating, adapting and implementing the new recommendations. Key steps in the dissemination include: presenting the recommendations at international conferences; workshops to support country adaptation; rapidly developing adaptation tools to assist countries in setting priorities among limited resources to facilitate full implementation over time; and carrying out briefings and joint planning for dissemination with international and national implementing partners. An evaluation process will be conducted in 2020 to assess the uptake of the recommendations in national guidelines.

REFERENCES

1. UNAIDS data 2017. Geneva: UNAIDS; 2017(http://www.unaids.org/en/resources/documents/2017/2017_data_book, accessed 17 January 2018).

2. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Health Organization; 2017 (http://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en, accessed 17 January 2018).

3. Waldrop G, Doherty M, Vitoria M, Ford N. Stable patients and patients with advanced disease: consensus definitions to support sustained scale up of antiretroviral therapy. Trop Med Int Health. 2016;21:1124–30.

4. IeDEA and COHERE Cohort Collaborations. Global Trends in CD4 Cell Count at the Start of Antiretroviral Therapy: Collaborative Study of Treatment Programs. Clin Infect Dis. 2018 Jan 25.

5. May M, Boulle A, Phiri S, Messou E, Myer L, Wood R et al. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. Lancet. 2010;376:449–57.

6. 2012 report on the global AIDS epidemic. Geneva: UNAIDS; 2012 (http://www.unaids.org/en/resources/campaigns/20121120_globalreport2012/globalreport, accessed 17 January 2018).

7. Lawn SD, Bekker LG, Myer L, Orrell C, Wood R. Cryptococcocal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. AIDS. 2005;19:2050–2.

8. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS. 2008;22:1897–908.

9. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS. 2009;23:525–30.

10. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017;17:873–81.

11. Garcia-Hermoso D, Janbon G, Dromer F. Epidemiological evidence for dormant Cryptococcus neoformans infection. J Clin Microbiol. 1999;37:3204–9.

12. Mitchell TG, Perfect JR. Cryptococcosis in the era of AIDS – 100 years after the discovery of Cryptococcus neoformans. Clin Microbiol Rev. 1995;8:515–48.

13. Gonzalez CE, Shetty D, Lewis LL, Mueller BU, Pizzo PA, Walsh TJ. Cryptococcosis in human immunodeficiency virus–infected children. Pediatr Infect Dis J. 1996;15:796–800.

14. Speed BR, Kaldor J. Rarity of cryptococcal infection in children. Pediatr Infect Dis J. 1997;16:536–7.

15. Meiring ST, Quan VC, Cohen C, Dawood H, Karstaedt AS, McCarthy KM et al. A comparison of cases of paediatric-onset and adult-onset cryptococcosis detected through population-based surveillance, 2005–2007. AIDS. 2012;26:2307–14.

16. Loyse A, Dromer F, Day J, Lortholary O, Harrison TS. Flucytosine and cryptococcosis: time

to urgently address the worldwide accessibility of a 50-year-old antifungal. J Antimicrob Chemother. 2013;68:2435–44.

17. Lightowler JV, Cooke GS, Mutevedzi P, Lessells RJ, Newell ML, Dedicoat M. Treatment of cryptococcal meningitis in KwaZulu-Natal, South Africa. PLoS One. 2010;5:e8630.

18. Kambugu A, Meya DB, Rhein J, O'Brien M, Janoff EN, Ronald AR et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. Clin Infect Dis. 2008;46:1694–1701.

19. Bicanic T, Brouwer AE, Meintjes G, Rebe K, Limmathurotsakul D, Chierakul W et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. AIDS. 2009;23:701–6.

20. Graybill JR, Sobel J, Saag M, van Der Horst C, Powderly W, Cloud G et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. Clin Infect Dis. 2000;30:47–54.

21. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization; 2011 (http://www.who.int/hiv/pub/cryptococcal_disease2011/en/, accessed 17 January 2018).

22. Rolfes MA, Hullsiek KH, Rhein J, Nabeta HW, Taseera K, Schutz C et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. Clin Infect Dis. 2014;59:1607–14.

23. Likasitwattanakul S, Poneprasert B, Sirisanthana V. Cryptococcosis in HIV infected children. Southeast Asian J Trop Med Public Health. 2004;34:935–9.

24. Abadi J, Nachman S, Kressel AB, Pirofski L. Cryptococcosis in children with AIDS. Clin Infect Dis. 1999;28:309–13.

25. Mfinanga S, Chanda D, Kivuyo SL, Guinness L, Bottomley C, Simms V et al. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. Lancet. 2015;385:2173–82.

26. Ford N, Shubber Z, Jarvis J, Chiller T, Greene G, Migone C et al. CD4 cell count threshold for cryptococcal antigen screening of HIV-infected individuals. Clin Infect Dis. In press.

27. Jarvis JN, Harrison TS, Lawn SD, Meintjes G, Wood R, Cleary S. Cost effectiveness of cryptococcal antigen screening as a strategy to prevent HIV-associated cryptococcal meningitis in South Africa. PLoS One. 2013;8:e69288.

28. Cassim N, Schnippel K, Coetzee LM, Glencross DK. Establishing a cost-per-result of laboratory-based, reflex cryptococcal antigenaemia screening (CrAg) in HIV+ patients with CD4 counts less than 100 cells/µl using a lateral flow assay (LFA) at a typical busy CD4 laboratory in South Africa. PLoS One. 2017;12:e0171675.

29. Chipungu C, Veltman JA, Jansen P, Chiliko P, Lossa C, Namarika D et al. Feasibility and acceptability of cryptococcal antigen screening and prevalence of cryptococcemia in patients attending a resource-limited HIV/AIDS clinic in Malawi. J Int Assoc Provid AIDS Care. 2015;14:387–90.

30. Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A et al. Cost–effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count ≤100 cells/µL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010;51:448–55.

31. Rajasingham R, Meya DB, Boulware DR. Integrating cryptococcal antigen screening and pre-emptive treatment into routine HIV care. J Acquir Immune Defic Syndr. 2012;59:e85–91.

32. Smith RM, Nguyen TA, Ha HT, Thang PH, Thuy C, Lien TX et al. Prevalence of cryptococcal antigenemia and cost–effectiveness of a cryptococcal antigen screening program – Vietnam. PLoS One. 2013;8:e62213.

33. Vidal JE, Toniolo C, Paulino A, Colombo A, Dos Anjos Martins M, da Silva Meira C et al. Asymptomatic cryptococcal antigen prevalence detected by lateral flow assay in hospitalised HIV-infected patients in Sao Paulo, Brazil. Trop Med Int Health. 2016;21:1539–44.

34. Awotiwon A, Johnson S, Rutherford G, Meintjes G, Eshun-Wilson I. Preventing cryptococcal infection in people living with HIV. Cochrane Database Syst Rev. In press.

35. Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C et al. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. N Engl J Med. 2017;377:233–45.

36. Parkes-Ratanshi R, Wakeham K, Levin J, Namusoke D, Whitworth J, Coutinho A et al. Primary prophylaxis of cryptococcal disease with fluconazole in HIV-positive Ugandan adults: a double-blind, randomised, placebo-controlled trial. Lancet Infect Dis. 2011;11:933–41.

37. Ford N, Shubber Z, Meintjes G, Grinsztejn B, Eholie S, Mills EJ et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. Lancet HIV. 2015;2:e438-444.

38. Larson BA, Rockers PC, Bonawitz R, Sriruttan C, Glencross DK, Cassim N et al. Screening HIV-infected patients with low CD4 counts for cryptococcal antigenemia prior to initiation of antiretroviral therapy: cost effectiveness of alternative screening strategies in South Africa. PLoS One. 2016;11:e0158986.

39. Vallabhaneni S, Longley N, Smith M, Smith R, Osler M, Kelly N et al. Implementation and operational research: evaluation of a public-sector, provider-initiated cryptococcal antigen screening and treatment program, Western Cape, South Africa. J Acquir Immune Defic Syndr. 2016;72:e37–42.

40. Rick F, Niyibizi AA, Shroufi A, Onami K, Steele SJ, Kuleile M et al. Cryptococcal antigen screening by lay cadres using a rapid test at the point of care: a feasibility study in rural Lesotho. PLoS One. 2017;12:e0183656.

41. Wake RM, Britz E, Sriruttan C, Rukasha I, Omar T, Spencer DC et al. High cryptococcal antigen titers in blood are predictive of subclinical cryptococcal meningitis among HIV-infected patients. Clin Infect Dis. 2017. Epub ahead of print.

42. Molloy S, Kanyama C, Heyderman R, Loyse A, Kouanfack C, Chanda D, Mfinanga S, et al. A randomized controlled trial for the treatment of HIV-associated cryptococcal meningitis in Africa: oral fluconazole plus flucytosine or one week amphotericin-based therapy vs two weeks amphotericin-based therapy. The ACTA Trial. 9th IAS Conference on HIV Science. Paris 23-26 July, 2017. Abstract 5573.

43. Tenforde M, Shapiro A, Rouse B, Jarvis J, Li T, Eshun-Wilson I et al. Treatment for HIV-associated cryptococcal meningitis: a systematic review and network meta-analysis. Cochrane Database Syst Rev. In press.

44. Leenders AC, Reiss P, Portegies P, Clezy K, Hop WC, Hoy J et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. AIDS. 1997;11:1463–71.

45. Hamill RJ, Sobel JD, El-Sadr W, Johnson PC, Graybill JR, Javaly K et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment

of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. Clin Infect Dis. 2010;51:225–32.

46. Mootsikapun P, Chetchotisakd P, Anunnatsiri S, Choksawadphinyo K. The efficacy of fluconazole 600 mg/day versus itraconazole 600 mg/day as consolidation therapy of cryptococcal meningitis in AIDS patients. J Med Assoc Thai. 2003;86:293–8.

47. van der Horst CM, Saag MS, Cloud GA, Hamill RJ, Graybill JR, Sobel JD et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. N Engl J Med. 1997;337:15–21.

48. Bozzette SA, Larsen RA, Chiu J, Leal MA, Tilles JG, Richman DD et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. N Engl J Med. 1991;324:580–4.

49. Saag MS, Cloud GA, Graybill JR, Sobel JD, Tuazon CU, Johnson PC et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Clin Infect Dis. 1999;28:291–6.

50. Powderly WG, Saag MS, Cloud GA, Robinson P, Meyer RD, Jacobson JM et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. N Engl J Med. 1992;326:793–8.

51. Antifungal drug maps [website]. Geneva: Global Action Fund for Fungal Infections; 2018 (http://www.gaffi.org/antifungal-drug-maps, accessed 17 January 2018).

52. Loyse A, Thangaraj H, Easterbrook P, Ford N, Roy M, Chiller T et al. Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries. Lancet Infect Dis. 2013;13:629–37.

53. Jarvis J, Leeme T, Chofle A, Bidwell G, Molefi M, Tsholo K et al. Ambition-CM: high dose liposomal amphotericin for HIV-related cryptococcal meningitis. Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, 13–16 February 2017. Abstract 82.

54. AMBITION-CM. AMBIsome therapy induction optimization - intermittent high dose AmBisome® on a high dose fluconazole backbone for cryptococcal meningitis induction therapy in sub-Saharan Africa. Berlin: ISRCTN Registry; 2017 (http://www.isrctn.com/ISRCTN10248064, accessed 17 January 2018).

55. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2015;9:CD004405.

56. Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2016;4:CD002244.

57. Beardsley J, Wolbers M, Kibengo FM, Ggayi AB, Kamali A, Cuc NT et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. N Engl J Med. 2016;374:542–54.

58. Girois S, Chapuis F, Decullier E, Revol B. Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis. Eur J Clin Microbiol Infect Dis. 2006;25:138–49.

59. Bicanic T, Bottomley C, Loyse A, Brouwer AE, Muzoora C, Taseera K et al. Toxicity of amphotericin B deoxycholate-based induction therapy in patients with HIV-associated cryptococcal meningitis. Antimicrob Agents Chemother. 2015;59:7224–31.

60. Bahr NC, Rolfes MA, Musubire A, Nabeta H, Williams DA, Rhein J et al. Standardized electrolyte supplementation and fluid management improves survival during amphotericin therapy for cryptococcal meningitis in resource-limited settings. Open Forum Infect Dis. 2014;1:ofu070.

61. Echevarria J, Seas C, Cruz M, Chávez E, Campos M, Cieza J et al. Oral rehydration solution to prevent nephrotoxicity of amphotericin B. Am J Trop Med Hyg. 2006;75:1108–12.

62. Girmenia C, Cimino G, Di Cristofano F, Micozzi A, Gentile G, Martino P. Effects of hydration with salt repletion on renal toxicity of conventional amphotericin B empirical therapy: a prospective study in patients with hematological malignancies. Support Care Cancer. 2005;13:987–92.

63. Thakur CP, Kumar A, Mitra DK, Roy A, Sinha AK, Ranjan A. Improving outcome of treatment of kala-azar by supplementation of amphotericin B with physiologic saline and potassium chloride. Am J Trop Med Hyg. 2010;83:1040–3.

64. Park MK, Hospenthal DR, Bennett JE. Treatment of hydrocephalus secondary to cryptococcal meningitis by use of shunting. Clin Infect Dis. 1999;28:629–33.

65. Sun HY, Hung CC, Chang SC. Management of cryptococcal meningitis with extremely high intracranial pressure in HIV-infected patients. Clin Infect Dis. 2004;38:1790–2.

66. Yuchong C, Jianghan C, Hai W, Julin G. Lumbar puncture drainage with intrathecal injection of amphotericin B for control of cryptococcal meningitis. Mycoses. 2011;54:e248–51.

67. Meda J, Kalluvya S, Downs JA, Chofle AA, Seni J, Kidenya B et al. Cryptococcal meningitis management in Tanzania with strict schedule of serial lumber punctures using intravenous tubing sets: an operational research study. J Acquir Immune Defic Syndr. 2014;66:e31–6.

68. Shoham S, Cover C, Donegan N, Fulnecky E, Kumar P. Cryptococcus neoformans meningitis at 2 hospitals in Washington, D.C.: adherence of health care providers to published practice guidelines for the management of cryptococcal disease. Clin Infect Dis. 2005;40:477–9.

69. Newton PN, Thai le H, Tip NQ, Short JM, Chierakul W, Rajanuwong A et al. A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. Clin Infect Dis. 2002;35:769–72.

70. Orem J, Tindyebwa L, Twinoweitu O, Mukasa B, Tomberland M, Mbidde EK. Feasibility study of serial lumbar puncture and acetazolamide combination in the management of elevated cerebrospinal fluid pressure in AIDS patients with cryptococcal meningitis in Uganda. Trop Doct. 2005;35:19–21.

71. Rex JH, Larsen RA, Dismukes WE, Cloud GA, Bennett JE. Catastrophic visual loss due to Cryptococcus neoformans meningitis. Medicine (Baltimore). 1993;72:207–24.

72. Antinori S, Radice A, Galimberti L, Magni C, Fasan M, Parravicini C. The role of cryptococcal antigen assay in diagnosis and monitoring of cryptococcal meningitis. J Clin Microbiol. 2005;43:5828–9.

73. Lu H, Zhou Y, Yin Y, Pan X, Weng X. Cryptococcal antigen test revisited: significance for cryptococcal meningitis therapy monitoring in a tertiary Chinese hospital. J Clin Microbiol. 2005;43:2989–90.

74. Dismukes WE, Cloud G, Gallis HA, Kerkering TM, Medoff G, Craven PC et al. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. N Engl J Med. 1987;317:334–41.

75. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis. Clin Infect Dis. 1994;18:789–92.

76. Zuger A, Louie E, Holzman RS, Simberkoff MS, Rahal JJ. Cryptococcal disease in patients with the acquired immunodeficiency syndrome. Diagnostic features and outcome of treatment. Ann Intern Med. 1986;104:234–40.

77. Haddow LJ, Colebunders R, Meintjes G, Lawn SD, Elliot JH, Manbe YC et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infect Dis. 2010;11:791–802.

78. Shelburne SA 3rd, Darcourt J, White AC Jr, Greenberg SB, Hamill RJ, Atmar RL et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. Clin Infect Dis. 2005;40:1049–52.

79. Bisson GP, Molefi M, Bellamy S, Thakur R, Steenhoff A, Tamuhla N et al. Early versus delayed antiretroviral therapy and cerebrospinal fluid fungal clearance in adults with HIV and cryptococcal meningitis. Clin Infect Dis. 2013;56:1165–73.

80. Boulware DR, Meya DB, Muzoora C, Rolfes MA, Huppler Hullsiek K, Musubire A et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med. 2014;370:2487–98.

81. Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. Clin Infect Dis. 2010;50:1532–8.

82. Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One. 2009;4:e5575.

83. Bicanic T, Meintjes G, Wood R, Hayes M, Rebe K, Bekker LG et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with amphotericin B or fluconazole. Clin Infect Dis. 2007;45:76–80.

84. Southern African HIV Clinicians Society. Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update. S Afr J HIV Med. 2013;14:2.

85. Aberg JA, Price RW, Heeren DM, Bredt B. A pilot study of the discontinuation of antifungal therapy for disseminated cryptococcal disease in patients with acquired immunodeficiency syndrome, following immunologic response to antiretroviral therapy. J Infect Dis. 2002;185:1179–82.

86. Kirk O, Reiss P, Uberti-Foppa C, Bickel M, Gerstoft J, Pradier C et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. Ann Intern Med. 2002;137:239–50.

87. Martínez E, García-Viejo MA, Marcos MA, Pérez-Cuevas JB, Blanco JL, Mallolas J et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in HIV-infected patients responding to highly active antiretroviral therapy. AIDS. 2000;14:2615–7.

88. Mussini C, Pezzotti P, Miró JM, Martinez E, de Quiros JC, Cinque P et al. Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with highly active antiretroviral therapy: an international observational study. Clin Infect Dis. 2004;38:565–71.

89. Rollot F, Bossi P, Tubiana R, Caumes E, Zeller V, Katlama C et al. Discontinuation of secondary prophylaxis against cryptococcosis in patients with AIDS receiving highly active antiretroviral therapy. AIDS. 2001;15:1448–9.

90. Sheng WH, Hung CC, Chen MY, Hsieh SM, Chang SC. Successful discontinuation of fluconazole as secondary prophylaxis for cryptococcosis in AIDS patients responding to highly active antiretroviral therapy. Int J STD AIDS. 2002;13:702–5.

91. Vibhagool A, Sungkanuparph S, Mootsikapun P, Chetchotisakd P, Tansuphaswaswadikul S, Bowonwatanuwong C et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study. Clin Infect Dis. 2003;36:1329–31.

92. Model List of Essential Medicines. Geneva: World Health Organization; 2017 (http://www.who.int/medicines/publications/essentialmedicines/en, accessed 17 January 2018).

ANNEXES

ANNEX 1. PROCESS OF DEVELOPING THE GUIDELINES

Methods for synthesizing evidence

WHO first published a rapid advice document for the diagnosis, prevention and management of cryptococcal disease in December 2011. In order to update this rapid advice, a series of virtual Guideline Development Group meetings were convened between 2012 and 2014. A further Guideline Development Group was convened in 2017 to assess new evidence relating to preventing, screening and treating cryptococcal disease. This group met virtually via teleconference in October and November 2017.

The following table summarizes the timelines for developing the recommendations contained in this guideline.

Recommendation	Recommended in 2012	Updated in 2017
Diagnosis		
Diagnosing suspected cryptococcal meningitis	√	
Screening for and preventing cryptococcal disease		
Using serum or plasma cryptococcal antigen screening (using lateral flow assay or latex agglutination assay) followed by pre-emptive antifungal therapy if a person is cryptococcal antigen–positive at different CD4 cell thresholds	√	√
Primary antifungal prophylaxis for cryptococcal disease for people living with HIV		√
Induction, consolidation and maintenance antifungal treatment regimens for cryptococcal meningitis		
Induction phase	√	√
Consolidation phase	√	
Maintenance phase	√	
Discontinuing maintenance treatment	√	
Other treatment		
Adjuvant therapy with systemic corticosteroids in the induction phase		√
Timing of ART		
Timing of ART initiation	√	√

Retrieving, summarizing and presenting the evidence

Quantitative evidence synthesis and evidence to recommendations

The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) method was used to rate the quality of the evidence and determine the strength of the recommendations. The GRADE approach to developing recommendations, which WHO has adopted, defines the quality of evidence as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The strength of a recommendation reflects the degree to which the Guideline Development Group is confident that the desirable effects (potential benefits) of the recommendation outweigh the undesirable effects (potential harm). Desirable effects may include beneficial health outcomes (such as reduced morbidity and mortality), reduction of burden on the individual and/or health services and potential cost savings. Undesirable effects include those affecting individuals, families, communities or health services. Additional considerations include the resource use and cost implications of implementing the recommendations and clinical outcomes (such as drug resistance and drug toxicity). All systematic reviews followed the PRISMA guidelines for reporting systematic reviews and meta-analyses.

Feasibility and acceptability

A review was undertaken to study and compare current recommendations on managing cryptococcal disease in guidelines from 31 low- and middle-income countries. At the same time, a country-level feasibility assessment was undertaken through a semistructured telephone interview with 30 health-care providers in 16 countries across Africa, Asia and Latin America to determine the current availability of diagnostic tests, anticryptococcal drugs and barriers to access. In 2016, an online survey of health-care workers, HIV programme managers and people living with HIV was carried out to assess the feasibility and acceptability of strategies to manage advanced HIV disease, and the results of this survey were used to inform the acceptability and feasibility of cryptococcal antigen screening and pre-emptive fluconazole therapy.

Cost

Costing information for the key cryptococcal drugs (amphotericin B, liposomal amphotericin, fluconazole and flucytosine) in various countries was prepared from pricing information contained in key databases *(http://mshpriceguide.org/en/home/)*. Updated evidence of the cost and availability of cryptococcal antigen testing assays, as well as antifungal drugs, was conducted with input from the United States Centers for Disease Control and Prevention, the United States Agency for International Development and the Global Action Fund for Fungal Infections (GAFFI). Consultations were conducted with two organizations that had experience with drug donation programmes, and the findings were summarized.

Guideline Development Group meeting

The Guideline Development Group met for a series of face-to-face meetings and teleconferences between 2012 and 2014. For the updated recommendations in 2017, the Guideline Development Group met virtually via Webex teleconferencing on 16–17 October and 14 November 2017. All recommendations were made through unanimous agreement. Voting was not required but the group agreed at the start of the meeting that 60% of votes would be required for a decision.

Good practice principles were formulated by the Guideline Development Group based on their knowledge of the optimal approach to the clinical management of cryptococcal disease, taking into consideration the constraints of resource-limited settings.

Peer review

The draft guidelines were circulated for review to members of the Guideline Development Group and the External Review Group. The WHO Guideline Steering Group reviewed the comments and incorporated them into the final document with due consideration of any conflicts of interest of External Review Group members.

Declarations of interest

All external contributors to the guidelines, including members of the Guideline Development Group and the external peer review group completed a WHO declaration of interests form in accordance with WHO policy for experts. A brief biography of each Guideline Development Group member was published on the WHO HIV website for a period of 14 days before the first meeting of the Guideline Development Group with a description of the objectives of the meeting. No public comments or objections were received. The responsible technical officer reviewed the declaration of interests forms as well as the results of the web-based search for each member of the Guideline Development Group. The results were shared with the WHO Guideline Steering Group, which reviewed the results, and a management plan was agreed and recorded for each individual. At the start of the guideline development meeting, all conflicts of interest identified and the management plan for any conflicts of interest were shared with the meeting participants. For the 2017 Guideline Development Group, in accordance with the revised WHO policy for experts, a web-based search was conducted of Guideline Development Group members to identify any potential competing interest. The WHO Guideline Steering Group recorded and reviewed the results of the web-based search to identify any potential competing interest.

All members of the Guideline development group verbally declared any conflicts of interest at the start of the Guideline Development Group meeting. Two members of the 2017 Guideline Development Group were principal investigators or co-investigators in key clinical trials relevant to the recommendations on treatment. They were excluded from voting on these specific recommendations. One member of the Guideline Development Group had received a significant research grant award relevant to the recommendations and was excluded from voting from the related. No other conflicts of interest warranted exclusion from the discussion of specific recommendations.

External Review Group

The responsible technical officers reviewed the declaration of interest forms from members of the External Review Group in accordance with WHO guideline development policy, and the results were shared with the WHO Guideline Steering Group. Any conflicts of interest identified were considered when interpreting comments from External Review Group members during the external review process.

ANNEX 2. SUMMARY OF THE PERFORMANCE OF DIAGNOSTIC ASSAYS

Cerebrospinal fluid

Latex agglutination

Sixteen studies *(1–16)* compared the performance of CSF latex agglutination to CSF culture and microscopy. The pooled sensitivity of latex agglutination versus culture and microscopy in these 16 studies was 98.2% (95% CI: 97.6–98.7%), and the specificity was 96.8% (95% CI: 96.1–97.5%).

Enzyme immunoassay

CSF enzyme immunoassay versus CSF culture had a pooled sensitivity of 100% (95% CI: 95.0–100.0%) and specificity of 98.3% (95% CI: 95.1–99.6%) *(15)*; CSF enzyme immunoassay versus CSF latex agglutination had a pooled sensitivity of 98.1% (95% CI: 89.7–100.0%) and specificity of 98.8% (95% CI: 96.6–99.8%) *(17–19)*.

Lateral-flow assay

Five studies *(20–24)* have evaluated CSF lateral-flow assay performance versus CSF culture as well as latex agglutination and enzyme immunoassay. The pooled sensitivity ranged from 94.0% to 100%. The performance of CSF India ink test was compared with that of CSF culture and microscopy in nine studies *(1,5,6,8,10,11,25,26)* rated as low-quality evidence: eight of the nine studies were excluded from the pooled estimates for specificity and predictive value because of missing data, and four of the nine studies estimated lower sensitivity than the other five studies; the pooled sensitivity was 90.3% (95% CI: 89.3–91.3%).

Serum and plasma

The performance of the cryptococcal antigen test in serum versus CSF culture and microscopy was evaluated for latex agglutination *(1,2,4,6–8,12,14,15,27,28)*, enzyme immunoassay *(12,15,29)* and lateral-flow assay *(29)*. The performance of the serum antigen test was slightly lower than that of the CSF antigen test versus CSF culture and microscopy. For latex agglutination, the sensitivity was 96.8% (95% CI: 94.8–98.2%), the specificity was 98.6% (95% CI: 97.9–99.1%), the positive predictive value was 92.4% (95% CI: 80.7–100.0) and negative predictive value was 99.2% (95% CI: 97.2–100.0%). The test performance was similar for enzyme immunoassay. The serum lateral-flow assay had 100% sensitivity, specificity, positive predictive value and negative predictive value versus CSF culture and microscopy. Recent data also shows excellent concordance between lateral-flow assay performed using whole blood compared to serum and plasma, and the assay is therefore now approved for use in whole blood *(30)*. However, in urine, its diagnostic accuracy is poor with a high rate of false positives *(31)*.

Cryptococcal pneumonia

There were limited data evaluating test performance among people with isolated pulmonary disease. Serum lateral flow assay had a pooled sensitivity of 100% when compared with blood culture and of 95.6% when compared to serum enzyme immunoassay *(32)*. Pooled sensitivity of serum latex agglutination when compared to pulmonary culture was 37.3%, (95% CI 26.4-49.3) *(2,33,34)*. Pooled sensitivity of serum enzyme immunoassay compared with blood culture was 88.9% (95% CI 70.8-97.6) (9,32) (Annex 2).

Non-meningeal and non-pulmonary cryptococcal disease

For adults, adolescents and children living with HIV with suspected non-meningeal and non-pulmonary cryptococcal disease, serum, plasma or whole blood testing with cryptococcal antigen assay can be used in conjunction with histopathological examination and/or culture of appropriate tissue or body fluid samples and exclusion of other diagnoses. India ink microscopy examination or a cryptococcal antigen assay in appropriate tissue or body fluid samples may also be used.

Sensitivity and specificity for diagnostic assays in different populations relative to comparator assays

Sample type	Test evaluated	Compared with	Studies	Pooled sensitivity (%) (95% CI)	Pooled specificity (%) (95% CI)	Pooled Positive predictive value (%) (95% CI)	Pooled Negative predictive value (%) (95% CI)
Suspected cryptococcal meningitis							
CSF	CSF latex agglutination	CSF culture and microscopy for people with suspected cryptococcal meningitis	*(1–16)*	98.2 (97.6–98.7)	96.8 (96.1–97.5)	96.5 (96.0–97.0)	98.4 (98.0–98.8)
			Pooled estimates (3,7,12–15)	98.7 (98.3–99.1)	96.8 (96.2–97.4)	86.6 (85.4–87.8)	99.7 (99.5–99.9)
	CSF enzyme immunoassay	CSF culture for people with suspected cryptococcal meningitis	*(12,15)*	100.0 (95.0–100.0)	98.3 (95.1–99.6)	96.1 (93.6–98.4)	100.0 (100.0–100.0)
	CSF lateral-flow assay	CSF latex agglutination for people with suspected cryptococcal meningitis	*(20–22)*	*94.1 (91.8–96.4)*	*97.1 (95.4–98.8)*	*97.7 (96.2–99.2)*	*92.7 (90.1–95.3)*
	CSF enzyme immunoassay	CSF latex agglutination for people with suspected cryptococcal meningitis	*(17–19,23,24)*	98.5 (97.6–99.4)	99.2 (98.6–99.9)	92.9 (91.0–94.8)	99.8 (99.5–100.0)
	CSF lateral-flow assay	CSF enzyme immunoassay for people with suspected cryptococcal meningitis	*(23)*	100.0 (100.0–100.0)	99.8 (99.4–100.0)	97.2 (95.7–98.7)	100.0 (100.0–100.0)

Sample type	Test evaluated	Compared with	Studies	Pooled sensitivity (%) (95% CI)	Pooled specificity (%) (95% CI)	Pooled Positive predictive value (%) (95% CI)	Pooled Negative predictive value (%) (95% CI)
Suspected cryptococcal meningitis							
CSF	CSF India ink	CSF culture and microscopy for people with suspected cryptococcosis	*1,5,6,8,10–12,24–26)*	90.3 (89.3–91.3)			
			Pooled estimates (12)	93.5 (93.5)	100.0 (100.0)	100.0 (100.0)	90.9 (90.9)
Serum	Serum latex agglutination	CSF culture and microscopy or clinical disease for people with suspected cryptococcal meningitis	*(1,2,4,6–8,12,14,15,27,28)*	96.1 (95.3–100.0)			
			Pooled estimates (7,12,14,15,27,28)	95.2 (94.3–96.1)	98.6 (98.1–99.1)	90.5 (89.2–91.8)	99.3 (98.9–99.7)
	Serum enzyme immunoassay	CSF culture and microscopy for people with suspected cryptococcal meningitis	*(12,15,29,35)*	98.4 (96.7–100.0)			
			Pooled estimates (12,15)	96.8 (94.0–99.6)	97.7 (95.3–100.0)	96.8 (94.0–99.6)	97.7 (95.3–100.0)
	Serum latex agglutination	Serum enzyme immunoassay for people with suspected cryptococcal meningitis	*(17–19,21,36)*	97.2 (96.5–97.9)	99.3 (95.7–100.0)	94.9 (93.8–95.8)	99.6 (99.3–99.9)
	Serum lateral-flow assay	Serum latex agglutination for people with suspect cryptococcal meningitis	*(37)*	100.0 (97.4–100.0)	96.8 (93.7–98.6)	95.7 (91.4–98.0)	100.0 (98.1–100.0)
	Serum lateral-flow assay	CSF culture and microscopy for people with suspected cryptococcal meningitis	*(29,35)*	100.0 (97.6–100.0)	100.0 (100.0)	100.0 (100.0)	100.0 (100.0)
	Serum lateral-flow assay	Serum enzyme immunoassay for people with suspected cryptococcal meningitis	*(20–22,24,36,37)*	92.8 (91.7–94.0)	99.4 (99.0–99.8)	97.4 (96.7–98.1)	98.3 (97.8–98.9)
	Serum lateral-flow assay	Serum enzyme immunoassay for people with suspected cryptococcosis (mixed cryptococcal meningitis and pneumonia)	*(23)*	100.0 (100.0)	96.2 (96.2)	66.1 (66.1)	100.0 (100.0)

Sample type	Test evaluated	Compared with	Studies	Pooled sensitivity (%) (95% CI)	Pooled specificity (%) (95% CI)	Pooled Positive predictive value (%) (95% CI)	Pooled Negative predictive value (%) (95% CI)
Diagnosis of cryptococcal pneumonia							
Serum	Serum latex agglutination	Pulmonary culture for people with cryptococcal pneumonia	*(2,33,34)*	37.3 (26.4–49.3)			
	Serum enzyme immunoassay	Blood culture for people with cryptococcal pneumonia	*(9,32)*	88.9 (70.8–97.6)			
	Serum lateral-flow assay	Culture for people with respiratory disease	*(32)*	100.0 (100.0)			
	Serum lateral-flow assay	Serum enzyme immunoassay for people with respiratory disease (five-minute incubation)	*(32)*	90.1 (90.1)	99.5 (99.5)	97.6 (97.6)	97.6 (97.6)
Suspected cryptococcal meningitis							
Serum	Serum lateral-flow assay	Serum enzyme immunoassay for people with respiratory disease (15-minute incubation)	*(32)*	95.6 (95.6)	99.5 (99.5)	97.8 (97.8)	98.9 (98.9)

Pooled estimates are available from the studies that reported sensitivity, specificity, positive predictive value and negative predictive value.

REFERENCES

1. Antinori S, Galimberti L, Magni C, Casella A, Vago L, Manini F et al. Cryptococcus neoformans infection in a cohort of Italian AIDS patients: natural history and autopsy findings. Eur J Clin Microbiol Infect Dis. 2001;20:711–7.

2. Batungwanayo J, Taelman H, Bogaerts J, Allen S, Lucas S, Kagame A et al. Pulmonary cryptococcosis associated with HIV-1 infection in Rwanda: a retrospective study of 37 cases. AIDS. 1994;8:1271–6.

3. Bogaerts J, Rouvroy D, Taelman H, Kagame A, Aziz MA, Swinne D et al. AIDS-associated cryptococcal meningitis in Rwanda (1983–1992): epidemiologic and diagnostic features. J Infect. 1999;39:32–7.

4. Calvo B, Fischman O, Castelo Filho A, Reis Filho J, Del Bianco R, Barbosa RM et al. [Detection of capsular polysaccharide antigen of Cryptococcus neoformans in patients with AIDS and neurocryptococcosis in São Paulo, Brazil]. Rev Inst Med Trop Sao Paulo. 1991;33:485–90.

5. Chen S, Sorrell T, Nimmo G, Speed B, Currie B, Ellis D et al. Epidemiology and host- and variety-dependent characteristics of infection due to Cryptococcus neoformans in Australia and New Zealand. Australasian Cryptococcal Study Group. Clin Infect Dis. 2000;31:499–508.

6. Chuck SL, Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. N Engl J Med. 1989;321:794–9.

7. Desmet P, Kayembe KD, De Vroey C. The value of cryptococcal serum antigen screening among HIV-positive/AIDS patients in Kinshasa, Zaire. AIDS. 1989;3:77–8.

8. Likasitwattanakul S, Poneprasert B, Sirisanthana V. Cryptococcosis in HIV infected children. Southeast Asian J Trop Med Public Health. 2004;34:935–9.

9. Lin TY, Yeh KM, Lin JC, Wang NC, Peng MY, Chang FY. Cryptococcal disease in patients with or without human immunodeficiency virus: clinical presentation and monitoring of serum cryptococcal antigen titers. J Microbiol Immunol Infect. 2009;42:220–6.

10. McCarthy KM, Morgan J, Wannemuehler KA, Mirza SA, Gould SM, Mhlongo N et al. Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence. AIDS. 2006;20:2199–206.

11. Rozenbaum R, Goncalves AJ. Clinical epidemiological study of 171 cases of cryptococcosis. Clin Infect Dis. 1994;18:369–80.

12. Saha DC, Xess I, Biswas A, Bhowmik DM, Padma MV. Detection of Cryptococcus by conventional, serological and molecular methods. J Med Microbiol. 2009;58(Pt 8):1098–105.

13. Sekhon AS, Garg AK, Kaufman L, Kobayashi GS, Hamir Z, Jalbert M et al. Evaluation of a commercial enzyme immunoassay for the detection of cryptococcal antigen. Mycoses. 1993;36:31–4.

14. Swinne D, Bogaerts J, Van de Perre P, Batungwanayo J, Taelman H. Evaluation of the cryptococcal antigen test as a diagnostic tool of AIDS-associated cryptococcosis in Rwanda. Ann Soc Belg Med Trop. 1992;72:283–8.

15. Tanner DC WM, Fedorciw B, Joho KL, Thorpe JJ, Reller LB. Comparison of commercial kits for detection of cryptococcal antigen. J Clin Microbiol. 1994;32:1680–4.

16. Wadhwa A, Kaur R, Bhalla P. Profile of central nervous system disease in HIV/AIDS patients with special reference to cryptococcal infections. Neurologist. 2008;14:247–51.

17. Frank UK, Nishimura SL, Li NC, Sugai K, Yajko DM, Hadley WK et al. Evaluation of an enzyme immunoassay for detection of cryptococcal capsular polysaccharide antigen in serum and cerebrospinal fluid. J Clin Microbiol. 1993;31:97–101.

18. Gade W, Hinnefeld SW, Babcock LS, Gilligan P, Kelly W, Wait K et al. Comparison of the PREMIER cryptococcal antigen enzyme immunoassay and the latex agglutination assay for detection of cryptococcal antigens. J Clin Microbiol. 1991;29:1616–9.

19. Knight FR. New enzyme immunoassay for detecting cryptococcal antigen. J Clin Pathol. 1992;45:836–7.

20. Rolfes M, Butler E, von Hohenberg M, Nabeta H, Kwizera R, Rajasingham R et al. Evaluation of a novel point-of-care lateral flow assay to detect cryptococcal antigen in plasma and CSF. 19th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA, 5–8 March 2012.

21. Clarke S, Gibb R. Evaluation of the IMMY cryptococcal antigen lateral flow assay for detection of cryptococcal antigen. Australian Society for Microbiology 2012 Annual Scientific Meeting, Brisbane, Australia,. 1–5 July 2012.

22. Vijayan T , Bauman S, Chiller T, Klausner J. Test performance of a novel lateral-flow assay to detect cryptococcal disease. Infectious Disease Week, San Diego, CA, USA, 16–21 October 2012.

23. Hansen J, Slechta ES, Gates-Hollingsworth MA, Neary B, Barker AP, Bauman S et al. Large-scale evaluation of the immuno-mycologics lateral flow and enzyme-linked immunoassays for detection of cryptococcal antigen in serum and cerebrospinal fluid. Clin Vaccine Immunol. 2013;20:52–5.

24. CrAg LFA (cryptococcal antigen lateral flow assay). Norman (OK): IMMY Diagnostics; 2018 (http://www.immy.com/products/lateral-flow-assays/crag-lfa/#1473450453921-a2843b7f-7b86, accessed 17 January 2018).

25. Jarvis JN, Meintjes G, Williams A, Brown Y, Crede T, Harrison TS. Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases. BMC Infect Dis. 2010;10:67.

26. Sathyanarayanan V, Razak A, Chakraborty J. Clinical profile of disseminated cryptococcal infection – a case series. Asian Pacific Trop Med. 2010;3:818–20.

27. French N, Gray K, Watera C, Nakiyingi J, Lugada E, Moore M et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS. 2002;16:1031–8.

28. Nelson MR, Bower M, Smith D, Reed C, Shanson D, Gazzard B. The value of serum cryptococcal antigen in the diagnosis of cryptococcal infection in patients infected with the human immunodeficiency virus. J Infect. 1990;21:175–81.

29. Jarvis JN, Percival A, Bauman S, Pelfrey J, Meintjes G, Williams GN et al. Evaluation of a novel point-of-care cryptococcal antigen test on serum, plasma, and urine from patients with HIV-associated cryptococcal meningitis. Clin Infect Dis. 2011;53:1019–23.

30. Williams DA, Kiiza T, Kwizera R, Kiggundu R, Velamakanni S, Meya DB et al. Evaluation of fingerstick cryptococcal antigen lateral flow assay in HIV-infected persons: a diagnostic accuracy study. Clin Infect Dis. 2015;61:464–7.

31. Longley N, Jarvis JN, Meintjes G, Boulle A, Cross A, Kelly N et al. Cryptococcal antigen screening in patients initiating ART in South Africa: a prospective cohort study. Clin Infect Dis. 2016;62:581–7.

32. Lindsley MD, Mekha N, Baggett HC, Surinthong Y, Autthateinchai R, Sawatwong P et al. Evaluation of a newly developed lateral flow immunoassay for the diagnosis of cryptococcosis. Clin Infect Dis. 2011;53:321–5.

33. Helou S, Robles AM, Arechavala AI, Bianchi MH, Negroni R. [Respiratory cryptococcosis in HIV positive patients.]. Rev Iberoam Micol. 1999;16:126–9.

34. Taelman H, Bogaerts J, Batungwanayo J, Van de Perre P, Lucas S, Allen S. Failure of the cryptococcal serum antigen test to detect primary pulmonary cryptococcosis in patients infected with human immunodeficiency virus. Clin Infect Dis. 1994;18:119–20.

35. Boulware DR, Rolfes MA, Rajasingham R, von Hohenberg M, Qin Z, Taseera K et al. Multisite validation of cryptococcal antigen lateral flow assay and quantification by laser thermal contrast. Emerg Infect Dis. 2014;20:45–53.

36. Binnicker MJ, Jespersen DJ, Bestrom JE, Rollins LO. Comparison of four assays for the detection of cryptococcal antigen. Clin Vaccine Immunol. 2012;19:1988–90.

37. Boulware DR, Meya D, Longley N, Govender N, Jarvis J, Neary B et al. Multicenter evaluation of a novel POC assay for the detection of cryptococcal antigen in HIV-infected persons with and without cryptococcal meningitis. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 9–12 September 2012.

For more information, contact:

World Health Organization
Department of HIV/AIDS
20, avenue Appia
1211 Geneva 27
Switzerland

Email: hiv-aids@who.int

www.who.int/hiv

ISBN 978-92-4-155027-7