World Health Organization

GUIDELINES FOR

DIAGNOSING, PREVENTING AND MANAGING CRYPTOCOCCAL DISEASE AMONG ADULTS, ADOLESCENTS AND CHILDREN LIVING WITH HIV

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Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV

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DEFINITION OF KEY TERMS

Age groups	The following definitions for adults, adolescents, children and infants are used in these guidelines for the purpose of implementing recommendations for specific age groups. Countries may have other definitions under national laws. • An adult is a person older than 19 years of age. • An adolescent is a person 10–19 years of age inclusive. • A child is a person one year to younger than 10 years of age. • An infant is a child younger than one year of age.
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 *(1)*. At presentation, all children living with HIV younger than five years should be considered as having advanced HIV disease.
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 impair normal body function, detected by abnormal clinical symptoms or signs.
Cryptococcal infection	Growth of *Cryptococcus* species in the body is 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 the 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*. *Cryptococcus gattii* also occurs in the context of HIV, and the resulting disease is indistinguishable from that caused by *C. neoformans*.
Meningeal disease	A disease presenting with nervous system signs or symptoms, specifically involving the meningeal layer surrounding the brain.
Microbiological culture-positive relapse	A new episode of active disease following resolution of the previous episode.
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 ≥25 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	Lack of clinical or mycological response among people who received suboptimal treatment or who received optimal treatment but failed to respond clinically.

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Guideline Development Group

Co-Chairs: Alexandra Calmy (Hôpitaux Universitaires de Genève, Switzerland) and **Nelesh Govender** (National Institute for Communicable Diseases and University of the Witwatersrand, South Africa).

Eduardo Arathoon (Hospital General San Juan de Dios, Guatemala), **Mohamed Chakroun** (Fattouma Bourguiba Teaching Hospital, Tunisia), **Rachel Burke** (Malawi Liverpool Wellcome Clinical Research Programme and London School of Hygiene & Tropical Medicine, Malawi), **Tom Chiller** (United States Centers for Disease Control and Prevention, United States of America (USA), **Brenda Crabtree Ramírez** (Departamento de Infectología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico), **Serge Eholie** (University Félix Houphouet-Boigny, Côte d'Ivoire), **Tom Ellman** (MSF Southern Africa, South Africa), **Andreas Jahn** (I-Tech, Malawi), **Thuy Le** (Oxford University Clinical Research Unit, Viet Nam), **Sayoki Mfinanga** (National Institute for Medical Research, united Republic of Tanzania), **Ni Ni Tun** (Myanmar Oxford Clinical Research Unit, Myanmar), **José E. Vidal** (Instituto de Infectologia Emílio Ribas and Faculdade de Medicina da Universidade de São Paulo, Brazil) and **Stephen Watiti** (Worldwide Hospice Palliative Care Alliance, Uganda).

Methodologist

Roger Chou (Oregon Health & Science University, USA).

External Review Group

Tihana Bicanic (Institute of Infection & Immunity, St George's University London, United Kingdom of Great Britain and Northern Ireland), **Yao-kai Chen** (Division of Infectious Diseases, Chongqing Public Health Medical Center, China), **Jeremy Day** (Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam), **Lisa Frigati** (Department of Paediatrics and Child Health, Tygerberg Children's Hospital and Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa), **Nagalingeswaran Kumarasamy** (VHS-Infectious Diseases Medical Centre, Voluntary Health Services, India), **Mathieu Nacher** (Centre Hospitalier de Cayenne, French Guiana), **Daniel O'Brien** (Department of Health and Human Services, Melbourne, Australia) and **Rita Oladele** (Department of Medical Microbiology & Parasitology, College of Medicine, University of Lagos, Nigeria).

External contributors

A number of people provided specific technical inputs to the guideline development meeting, relating to details of the randomized trial informing the new recommendations, the systematic assessment of the trial outcomes, and costing and ethical considerations. These individuals were not involved in the formulation of the recommendations.

WHO acknowledges the voluntary contributions of **Jessica Burry** (Médecins Sans Frontières, Geneva, Switzerland), **James Conroy** (Clinton Foundation HIV/AIDS Initiative, Uganda), **Thomas Harrison** (St George's University of London, United Kingdom), **Joe Jarvis** (London School of Hygiene & Tropical Medicine and Botswana Harvard AIDS Institute Partnership, Botswana), **David Lawrence** (London School of Hygiene & Tropical Medicine and Botswana Harvard AIDS Institute Partnership, Botswana), **Radha Rajasingham** (University of Minnesota, USA), **Theresa Rossouw** (University of Pretoria, South Africa), **Adrienne Shapiro** (University of Washington, USA) and **Mark Tenforde** (United States Centers for Disease Control and Prevention, USA).

Observers

Lee Abdelfadil (Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland), **Catherine Godfrey** (United States President's Emergency Plan for AIDS Relief (PEPFAR)), **Pamela Nawaggi** (Unitaid, Switzerland) and **Carmen Pérez Casas** (Unitaid, Switzerland).

Paediatric Antiretroviral Working Group

The Paediatric Antiretroviral Working Group is an established advisory group which provides technical advice to WHO during the formulation of ARV dosing guidance and other normative products. These individuals were not involved in the formulation of the recommendations and their contribution is voluntary. A dedicated terms of reference is in place and declarations of interest are collected every two years for all members of the group. The Paediatric Antiretroviral Working Group is composed of the following individuals:

Elaine Abrams (ICAP at Columbia University, USA), **Pauline Amuge** (Baylor College of Medicine Children's Foundation, Uganda), **Mo Archary** (University of Kwazulu-Natal, South Africa), **Adrie Bekker** (University of Stellenbosch, South Africa), **Brookie Best** (University of San Diego, USA), **David Burger** (Radboud University Nijmegen Medical Centre, Netherlands), **Esther Casas** (Médecins Sans Frontières, South Africa), **Luis Castaneda** (Hospital de Ninos Benjamin Bloom, El Salvador), **Diana Clarke** (Boston Medical Center, USA), **Polly Clayden** (HIV i-Base, United Kingdom), **Angela Colbers** (Radboud University Nijmegen Medical Centre, Netherlands), **Tim R. Cressey** (PHPT-IRD Research Unit, Chang Mai University, Thailand), **Roberto Delisa** (European Medicines Agency), **Paolo Denti** (University of Cape Town, South Africa), **Diana Gibb** (MRC Clinical Trials Unit at University College London, United Kingdom), **Rohan Hazra** (National Institute of Child Health and Human Development, USA), **Maria Kim** (Baylor International Pediatric AIDS Initiative, Malawi), **Shahin Lockman** (Harvard T.H. Chan School of Public Health, USA), **Fatima Mir** (Agha Khan University, Pakistan), **Mark H. Mirochnick** (Boston Medical Center, USA), **Elizabeth Obimbo** (University of Nairobi and Kenyatta National Hospital, Kenya), **Thanyawee Puthanakit** (Chulalongkorn University, Thailand), **Natella Rakhmanina** (Elizabeth Glaser Paediatric AIDS Foundation, USA), **Pablo Rojo** (Hospital de 12 Octubre, Madrid, Spain), **Vanessa Rouzier** (GHESIKO, Haiti), **Ted Ruel** (University of California, San Francisco, USA), **Nadia Sam-Agudu** (Institute of Human Virology, Nigeria), **Mariam Sylla** (EVA Network, Mali) and **Anna Turkova** (MRC Clinical Trials Unit at University College London, United Kingdom).

Paediatric Antiretroviral Working Group: Observers

Yodit Belew (United States Food and Drug Administration, USA), **Helen Bygrave** (Médecins Sans Frontières, South Africa), **Shaffiq Essajee** (UNICEF, USA), **Stephanie Hackett** (United States Centers for Disease Control and Prevention, USA), **Marc Lallemant** (PHPT Foundation, Thailand), **Linda Lewis** (Clinton Health Access Initiative, USA), **Lynne Mofenson** (Elizabeth Glaser Paediatric AIDS Foundation, USA), **Irene Mukui** (Drugs for Neglected Diseases initiative, Switzerland), **Sandra Nobre** (Medicines Patent Pool, Switzerland), **Mary Ojoo** (UNICEF, Denmark), **George Siberry** (United States Agency for International Development, USA), **Nandita Sugandhi** (ICAP at Columbia University, USA), **Marissa Vicari** (International AIDS Society, Switzerland), **Melynda Watkins** (Clinton Health Access Initiative, USA) and **Hilary Wolf** (Office of the United States Global AIDS Coordinator, Department of State, USA).

WHO staff and consultants

Nathan Ford and **Ajay Rangaraj** (Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes) coordinated the guideline development process under the leadership of **Meg Doherty** (Director, Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes). **Cadi Irvine** (Consultant, Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes) offered technical support for the development of this guideline.

WHO headquarters

The following WHO staff members in the Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes contributed to further developing and updating these guidelines: **Morkor Newman, Martina Penazzato**, **Marco Vitoria** and **Lara Vojnov**.

WHO regional offices

Frank Lule (WHO Regional Office for Africa), **Omar Sued** (Pan American Health Organization), **BB Rewari** and **Mukta Sharma** (WHO Regional Office for South-East Asia), **Elena Vovc** (WHO Regional Office for Europe) and **Chan Po-Lin** (WHO Regional Office for the Western Pacific).

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EXECUTIVE SUMMARY

Cryptococcal disease is one of the most common opportunistic infections among people living with advanced HIV disease and is a major contributor to illness, disability and mortality *(1)*.

By far the most common presentation is cryptococcal meningitis, which caused an estimated 223 100 incident cases and 181 100 deaths among people living with HIV in 2014 and accounted for 15% of all the people dying from HIV-related deaths globally *(2)*. Cryptococcal disease is uncommon among children with HIV.

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

These guidelines summarize recommendations that were first released in 2018 on diagnosing, preventing and managing cryptococcal disease. In response to important new evidence that became available in 2021, a new recommendation is provided on the preferred antifungal regimen for the induction phase of treatment.

These guidelines, which replace the 2018 guidelines, were developed in accordance with procedures established by the WHO Guideline Review Committee. All recommendations are based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to reviewing evidence, supported with information about acceptability, values and preferences, information on cost–effectiveness and feasibility. The guideline development process also identified key gaps in knowledge that will help to guide research.

The objective of these guidelines is to provide updated, evidence-informed recommendations for treating adults, adolescents and children living with HIV who have cryptococcal disease. These guidelines are aimed at HIV programme managers, policy-makers, health care professionals and people living with HIV.

Recommendations for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV

Summary of recommendations

Diagnosis of cryptococcal meningitis (2018 recommendations)

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 and low-certainty evidence for children

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

Settings with ready access to and no contraindication for lumbar puncture

1. 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.[a]
   Strong recommendation; moderate-certainty evidence for adults and adolescents and low-certainty evidence for children
2. 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 and low-certainty evidence for children

[a] For a first episode, CSF cryptococcal culture is also recommended in parallel with cryptococcal antigen testing if this is feasible.

Settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated[b]

1. 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 and low-certainty evidence for children
2. If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured, prompt referral for further investigation and treatment is appropriate.
   Strong recommendation; moderate-certainty evidence for adults and adolescents and low-certainty evidence for children

Note: Other diseases that can present with symptoms and signs similar to cryptococcal meningitis (such as viral, bacterial or tuberculous meningitis) should also be considered.

[b] 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 refusal by the patient after fully informed consent was sought.

Prevention and screening (2018 recommendations)

Overarching principle

Screening for plasma, serum or whole-blood 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 10 years and older presenting with advanced HIV disease.

Recommendations

Screening[c] 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 antiretroviral therapy (ART) for adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3.
Strong recommendation; moderate-certainty evidence
This may be considered at a higher CD4 cell count threshold of <200 cells/mm^3.
Conditional recommendation; moderate-certainty evidence

All people living with HIV with a positive cryptococcal antigen screening should be carefully evaluated for signs and symptoms of meningitis and undergo lumbar puncture, if feasible, with CSF examination and India ink or CSF cryptococcal antigen assay to exclude meningitis. India ink has low sensitivity and a negative result on India ink should be confirmed by CSF cryptococcal antigen testing or CSF culture.

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
This may be considered at a higher CD4 cell count threshold of <200 cells/mm^3.
Conditional recommendation; moderate-certainty evidence

[c] 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 meningitis.

Treating people with cryptococcal meningitis (2022 recommendations)

Induction therapy

A single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) should be used as the preferred induction regimen for treating people with cryptococcal meningitis.
Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children

Alternative induction regimens

If liposomal amphotericin is not available:
A seven-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by seven days of fluconazole (1200 mg daily for adults and 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).
Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children and adolescents

If no amphotericin formulation is available:
14 days of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) and flucytosine (100 mg/kg per day, divided into four doses per day).
Strong recommendation; moderate-certainty evidence

Note: fluconazole and flucytosine is the only recommended oral combination regimen and has been associated with lower mortality compared with amphotericin B deoxycholate and fluconazole *(3)*.

If flucytosine is not available:
14 days of liposomal amphotericin B (3–4 mg/kg per day) and fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).
Strong recommendation; moderate-certainty evidence

If liposomal amphotericin B and flucytosine are not available:
14 days of amphotericin B deoxycholate (1 mg/kg per day) and fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).
Strong recommendation; moderate-certainty evidence

Note: flucytosine-containing regimens are superior, and steps should be taken to ensure access to this drug.

Consolidation (2018 recommendation)

Fluconazole (800 mg daily for adults or 6–12 mg/kg per 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 (2018 recommendation)

Fluconazole (200 mg daily for adults or 6 mg/kg per day for adolescents and children) is recommended for the maintenance phase until immune reconstitution (CD4> 200 mm^3) and suppression of viral loads on ART.
Strong recommendation; high-certainty evidence

Use of adjunctive systemic corticosteroids in treating people with cryptococcal meningitis (2018 recommendations)

Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating adults, adolescents and children who have HIV-associated cryptococcal meningitis.
Strong recommendation; high-certainty evidence for adults and adolescents and moderate-certainty evidence for children

Timing of ART (2018 recommendations)

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

Good practice principles

Preventing, monitoring and managing amphotericin B toxicity (2022 good practice principles)

Infusion-related toxicity and side-effects from amphotericin B therapy are barriers to optimal induction treatment, especially 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 the recommended package of preventing, monitoring and managing toxicity.
- Liposomal amphotericin has fewer risks of drug toxicity than amphotericin B deoxycholate and requires a less intensive package for preventing, monitoring and managing toxicity.
- The recommended package of preventing, monitoring and managing toxicity should be provided to minimize the serious types of amphotericin B–related toxicity when using amphotericin B deoxycholate–based regimens, especially hypokalaemia, nephrotoxicity and anaemia. A single high dose (10 mg/kg) of liposomal amphotericin B and a seven-day amphotericin B deoxycholate regimen are better tolerated than a 14-day amphotericin B deoxycholate regimen, but these two regimens still require careful monitoring.

Monitoring for and managing raised intracranial pressure (2018 good practice principles)

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 sufficient volume to reduce the CSF pressure to <20 cm H_2O or to halve the baseline pressure if extremely high.[a]
- The persistence or recurrence of symptoms or signs of raised intracranial pressure (headache, blurred vision and vigilance disorders) 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, 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 rechecked after every 10 ml removed. Usually 20–30 ml is enough to reduce the opening pressure sufficiently.

Monitoring treatment response (2018 good practice principles)

- 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) is not advised in low- and middle-income countries. CSF, serum or plasma cryptococcal antigen testing is not recommended for monitoring response to treatment in any setting.

Diagnostic approach to persistent or recurrent symptoms (2018 good practice principles)

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).

[b] 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 (2018 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 therapy.
- Manage raised intracranial pressure with therapeutic lumbar puncture.
- Reinforce adherence.
- If ART has not already started, initiating ART after 4–6 weeks of optimal antifungal therapy is recommended.
- Consider fluconazole susceptibility testing if available .

1. BACKGROUND

Cryptococcal disease is one of the most important opportunistic infections among people living with advanced HIV disease and is a major contributor to illness, disability and mortality *(1–5)*. Clinically significant invasive disease is primarily caused by reactivation of latent infection among immunocompromised individuals, such as people living with HIV, months to years after initial exposure *(6)*.

By far the most common presentation, representing up to 90% of HIV-related cryptococcal disease, is cryptococcal meningitis, which caused an estimated 223 100 cases and 181 100 deaths among people living with HIV in 2014 and accounted for 15% of all the people dying from HIV-related deaths globally *(2)*. Other less common disease presentations include pulmonary disease and skin, lymph node and bone involvement *(7)*. Cryptococcal disease is uncommon among children with HIV *(8,9)*, even in areas with a high disease burden among adults *(10)*.

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 *(2)*. 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 currently recommended antifungal drugs *(11)* and intensive care. Another important contributor to mortality is the limited ability to monitor and manage treatment-limiting toxicity and the frequent complications of raised intracranial pressure as well as immune reconstitution inflammatory syndrome associated with cryptococcal meningitis and antiretroviral therapy (ART) *(12–15)*.

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.

These new guidelines were developed following the results of a randomized trial published in 2021 supporting the use of a single high-dose liposomal amphotericin B containing regimen as part of induction therapy.

1.1 Objectives and target audience

The objective of these guidelines is to provide updated, evidence-informed recommendations for treating adults, adolescents and children living with HIV who have cryptococcal disease. These guidelines are aimed at HIV programme managers, policy-makers, national treatment health care professionals and people living with HIV.

1.2 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 drugs along the continuum of HIV prevention, care and treatment.
- Rapid ART initiation regardless of CD4 cell count or immune status 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 among people living with HIV who have a positive cryptococcal antigen screening test result.[1]
- ART should be deferred by 4–6 weeks in cases of confirmed cryptococcal meningitis to reduce the risk of CNS IRIS and avert excess mortality.

Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, the burden of cryptococcal disease and the prevalence of other comorbidities.

Annex 1 summarizes the methods for developing these guidelines.

[1] 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.

2. RECOMMENDATIONS ON DIAGNOSING AND PREVENTING CRYPTOCOCCAL DISEASE

2.1 Diagnosing cryptococcal disease

The 2018 WHO recommendations for diagnosing cryptococcal disease remain unchanged *(16)*.

2.1.1 Background

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. National programmes 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. In addition, health-care professionals need to have a low threshold for suspecting cryptococcal meningitis.

Diagnosis of cryptococcal meningitis (2018 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 and low-certainty evidence for children

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

Settings with ready access to and no contraindication for lumbar puncture

1. 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.[a]
   Strong recommendation; moderate-certainty evidence for adults and adolescents and low-certainty evidence for children
2. 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 and low-certainty evidence for children

Settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated such as significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs or recurrent seizures[b]

1. 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 and low-certainty evidence for children
2. If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured, prompt referral for further investigation and treatment is appropriate.
   Strong recommendation; moderate-certainty evidence for adults and adolescents and low-certainty evidence for children

Note: Other diseases that can present with symptoms and signs similar to cryptococcal meningitis (such as viral, bacterial or tuberculous meningitis) should also be considered.

[a] For a first episode, CSF cryptococcal culture is also recommended in parallel with cryptococcal antigen testing if this is feasible.

[b] 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 refusal by the patient after fully informed consent was sought.

Summary of the diagnostic approach to cryptococcal meningitis

	Lumbar puncture available	Lumbar puncture not 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), treat immediately and refer for further investigation
No rapid cryptococcal antigen test available	CSF India ink	Prompt referral for further investigation

2.1.2 Rationale for the recommendations

Rapid cryptococcal antigen assay in CSF, serum, plasma or whole blood (depending on access to lumbar puncture) is preferred based on the much higher diagnostic accuracy of these rapid cryptococcal antigen assays versus the India ink test and the fact that these rapid assays depend less on the health-care provider's skills. Advantages of the lateral-flow assay over the latex agglutination assay include its rapid (<10 minutes) turnaround time, cost–effectiveness, minimal training requirements and laboratory infrastructure, no need for refrigerated storage and higher clinical and analytical sensitivity.

A serum, plasma or whole-blood cryptococcal antigen test is recommended as an initial diagnostic option in settings in which access to lumbar puncture is limited or contraindicated. The use of serum, plasma or whole-blood cryptococcal antigen diagnosis does not replace the need for lumbar puncture with CSF examination where this is feasible, considering also the important survival benefit of facilitating control of intracranial pressure *(17)*.

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

Limited data from retrospective cohorts suggest that diagnostic performance among children is similar to that of adults *(18,19)*. The recommendations for adults have therefore been extended to children.

2.2 Preventing and screening for cryptococcal disease

The 2018 WHO recommendations for prevention and screening for cryptococcal disease remain unchanged *(16)*.

2.2.1 Background

Early diagnosis and initiation of antiretroviral therapy remains the most important preventive strategy to reduce the incidence of cryptococcal disease among people living with HIV and the associated high mortality.[2] Screening for cryptococcal antigenaemia is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying infection when managing people aged 10 years or older presenting with advanced HIV disease *(20)*. There remains a role for fluconazole primary prophylaxis in settings in which cryptococcal antigen screening is not available.

[2] ART initiation among people who have cryptococcal meningitis should be deferred by 4–6 weeks from the initiation of antifungal treatment because of the risk of increased mortality.

Prevention and screening (2018 recommendations)

Screening[a] for cryptococcal antigen followed by pre-emptive antifungal therapy *(21)*[3] 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 count <100 cells/mm^3.
Strong recommendation; moderate-certainty evidence
This may be considered at a higher CD4 cell count threshold of <200 cells/mm^3.
Conditional recommendation; moderate-certainty evidence

All people living with HIV with a positive cryptococcal antigen screening should be carefully evaluated for signs and symptoms of meningitis and undergo lumbar puncture, if feasible, with CSF examination and India ink or CSF cryptococcal antigen assay to exclude meningitis. India ink has low sensitivity, and a negative result on India ink should be confirmed by CSF cryptococcal antigen testing or CSF culture.

When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3 *(23)*.
Strong recommendation; moderate-certainty evidence
This may be considered at a higher CD4 cell count threshold of <200 cells/mm^3.
Conditional recommendation; moderate-certainty evidence

[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 meningitis.

2.2.2 Rationale for the recommendations

Since 2018, WHO guidelines have recommended that all adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3 be screened for cryptococcal antigen before ART initiation or reinitiation; cryptococcal antigen screening may also be considered for adults and adolescents living with HIV who have a CD4 cell count <200 cells/mm^3. These recommendations were supported by evidence favouring the clinical benefit and cost–effectiveness of cryptococcal antigen screening *(20,22,24–30)*. All individuals screening positive for cryptococcal antigen should be given pre-emptive antifungal therapy (fluconazole 800–1200 mg/day for adults and 12 mg/kg per day for adolescents for two weeks), followed by consolidation and maintenance fluconazole therapy, as for treatment. The 2019 guidelines from the Southern African HIV Clinicians Society recommend 1200 mg for first 2 weeks given safety and concerns over breakthrough infection *(21)*.

Everyone testing positive for serum, 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 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 cryptococcal meningitis.

These recommendations would apply equally to people who present to care again after a period of disengagement from care with advanced HIV disease.

Cryptococcal antigen screening followed by pre-emptive therapy is 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. 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 since cryptococcal disease and mortality peak in the first four weeks among people presenting with a CD4 cell count <100 cells/mm^3 *(31)*.

[3] The Southern African HIV Clinicians' Society recommends starting ART two weeks after starting fluconazole, and consideration is given to starting ART immediately if lumbar puncture excludes cryptococcal meningitis among people who test positive for whole-blood cryptococcal antigen.

This recommendation is based on a systematic review that found a 70% reduction in mortality from cryptococcal disease among people living with HIV with low CD4 cell counts (95% confidence interval (CI) 12–89%); the review also found a 71% reduction in cryptococcal disease incidence; the incidence of serious adverse events did not differ, but some evidence indicated an increased risk of fluconazole-resistant *Candida* infection *(23)*.

National guidelines should determine the optimal duration of prophylaxis based on available resources. 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 *(31)*. 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 *(32)*.

2.2.3 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 *(4,10)*.

3. RECOMMENDATIONS ON INDUCTION, CONSOLIDATION AND MAINTENANCE ANTIFUNGAL TREATMENT REGIMENS

These 2022 guidelines provide a new recommendation for the preferred antifungal regimen for the induction phase of treatment.

3.1 Background

The 2018 WHO guidelines recommended seven days of amphotericin B deoxycholate and flucytosine-based therapy (followed by seven days of fluconazole 1200 mg) as the preferred antifungal regimen for the induction phase of treatment of HIV-associated cryptococcal meningitis. This was a strong recommendation based on moderate-certainty evidence for adults and low-certainty evidence for children and adolescents *(3)*. Liposomal amphotericin B is preferred over amphotericin B deoxycholate because of better tolerability. The guidelines recommended the following as alternative options considering availability of treatment: if flucytosine is not available, 14 days of amphotericin B deoxycholate + fluconazole is recommended; if amphotericin B deoxycholate is not available, an oral 14-day regimen of flucytosine and fluconazole is recommended.

These recommendations applied to all age groups and settings, and although the systematic review found no randomized studies among children, observational data support the use of amphotericin B and flucytosine among children *(9,19)*. The recommendations for children were therefore based on extrapolation from evidence for adults and in the absence of specific contraindication for this age group.

Amphotericin B deoxycholate has been known to be associated with several side-effects such as anaemia, nausea, vomiting, rigors, fever, hypertension or hypotension, hypoxia, metabolic derangements such as hypokalaemia, hypomagnesaemia and nephrotoxicity *(33–35)*. The 2018 WHO guidelines noted that liposomal amphotericin B was preferred as a formulation over amphotericin B deoxycholate, considering equivalent efficacy and better safety. However, access to liposomal amphotericin B remains extremely limited in low- and middle-income countries mainly because of its high price, lack of registration and limited number of quality-assured manufacturers as well as the need for close monitoring for seven to 14 doses through intravenous infusion, similar to amphotericin B deoxycholate. The development and testing in a large Phase III trial of a single high-dose liposomal amphotericin B–based regimen offers an additional option.

Flucytosine accessibility, affordability and registration is also very limited in low-and middle-income countries. Despite these access challenges, the use of high-dose fluconazole monotherapy is not recommended, considering the limited evidence of improved patient survival with this option *(36,37)*.

In 2022, WHO held a guideline development meeting to consider including a single high-dose liposomal amphotericin B–based regimen with 14 days of flucytosine and fluconazole as the preferred induction therapy for managing cryptococcal meningitis.

3.2 Induction therapy

Induction therapy (2022 recommendations)

A single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) should be used as the preferred induction regimen for treating people with cryptococcal meningitis.
Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children

Alternative induction regimens

If liposomal amphotericin B is not available:
A seven-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by seven days of fluconazole (1200 mg daily for adults and 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).
Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children and adolescents

If no amphotericin B formulations are available:
14 days of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) + flucytosine (100 mg/kg per day, divided into four doses per day).
Strong recommendation; moderate-certainty evidence

Note: fluconazole + flucytosine is the only recommended oral combination regimen and has been associated with lower mortality compared with amphotericin B deoxycholate + fluconazole *(3)*.

If flucytosine is not available:
14 days of liposomal amphotericin (3–4 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).
Strong recommendation; moderate-certainty evidence for adults

If liposomal amphotericin B and flucytosine are not available:
14 days of amphotericin B deoxycholate (1 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).
Strong recommendation; moderate-certainty evidence

Note: flucytosine-containing regimens are superior, and steps should be taken to ensure access to this drug.

3.2.1 Rationale for the recommendations

A systematic review from 2022 identified one randomized trial comparing a single high dose of liposomal amphotericin B, combined with oral flucytosine and fluconazole for 14 days, compared with the preferred induction therapy recommended by WHO in 2018 *(38)*.

The trial, conducted in Botswana, Malawi, South Africa, Uganda and Zimbabwe, enrolled 844 individuals with HIV-associated cryptococcal meningitis who were randomized 1:1 to either single, high-dose liposomal amphotericin B 10 mg/kg given with 14 days of flucytosine 100 mg/kg per day and fluconazole 1200 mg/day (liposomal amphotericin B group) or the 2018 WHO-recommended treatment of seven daily doses of amphotericin B deoxycholate (1 mg/kg per day) plus flucytosine (100 mg/kg per day), followed by seven days of fluconazole 1200 mg/day (control group). The primary endpoint was all-cause mortality at 10 weeks, with the trial powered to show non-inferiority at a 10% margin.

In the primary intention-to-treat analysis, 10-week mortality was 24.8% (101 of 407; 95% CI 20.7–29.3%) in the liposomal amphotericin B group and 28.7% (117 of 407; 95% CI 24.4–33.4%) in the control group. The risk difference in the liposomal amphotericin B group compared with the control group was –3.9 percentage points (95% CI –10.0 to 2.2 percentage points). In a prespecified superiority analysis, mortality risk was significantly lower in the liposomal amphotericin B group compared with the control group after adjusting for covariates associated with cryptococcal mortality with a risk difference of –5.7 percentage points (95% CI –11.4 to –0.04 percentage points).

Fewer participants experienced grade 3 or 4 adverse events in the liposomal amphotericin B group than in the control group (50% [210 of 420] versus 62% [263 of 422], $P = 0.0003$). Potentially life-threatening (grade 4) adverse events occurred in fewer participants in the liposomal amphotericin B group than the control group (22% [91 of 420] versus 30% [127 of 422]. Grade 3 or 4 anaemia developed in 13% (56 of 420) of participants in the liposomal amphotericin B group versus 39% (165 of 422) in the control group ($P < 0.0001$). The mean decrease in haemoglobin over the seven days of the induction period was lower in the liposomal amphotericin B group (0.3 g/dL) than in the control group (1.9 g/dL), resulting in fewer transfusions (7.6% versus 18.0%).

There was moderate certainty regarding reduction in harm and low certainty regarding reduction in mortality. Because both of these favour single high-dose therapy, the overall certainty was judged as moderate.

For children, the WHO-convened Paediatric Antiretroviral Working Group confirmed that the evidence supporting the use of a single high dose (10 mg/kg) of liposomal amphotericin B could be extrapolated to children *(39)*; the certainty of the evidence was downgraded to low because no direct evidence is available for children *(40)*.

The Guideline Development Group judged that the recommendation should be strong for both adults and children. The certainty of the evidence for reduction in mortality with liposomal amphotericin B was low due to imprecision (confidence interval crosses zero) and inconsistency (unable to assess, due to a single trial). However, the evidence on reduction in harms with liposomal amphotericin B was moderate. Both of these outcomes (reduced mortality and reduced toxicity) favored liposomal amphotericin B. As the evidence is already moderate for reduction in harms, additional evidence for reduction in mortality strengthens the overall evidence favoring liposomal amphotericin B. Additionally, the strong recommendation is supported by similar cost, improved feasibility (in particular with respect to reduced monitoring requirements), greater acceptability and favourable ethical and equity considerations.

The previously recommended alternative regimens remain valid. However, the Guideline Development Group noted that fluconazole + flucytosine is associated with lower mortality than amphotericin B deoxycholate + fluconazole *(3)*, and efforts should be made to ensure access to a flucytosine-containing regimen.

Liposomal, deoxycholate and lipid complex amphotericin B formulations are not interchangeable

Various formulations of amphotericin B are available commercially, including liposomal, deoxycholate and lipid complex formulations. These formulations are not interchangeable. For the indication of cryptococcal meningitis, only amphotericin B deoxycholate and liposomal amphotericin B have been recommended. In health-care settings in which both amphotericin B deoxycholate and liposomal amphotericin B are available, health-care providers must be cautious to avoid mixing up these products since the doses are different and significant adverse events have been reported when the deoxycholate formulation was given at a higher dose than recommended *(41)*.

Feasibility and acceptability

Qualitative data from a purposively selected group of participants, surrogate decision-makers and researchers working at the AMBITION trial sites in Botswana and Uganda identified a clear preference regarding the administration and tolerability of the single-dose liposomal amphotericin B–containing regimen *(42)*.

There was a general preference for the single-dose liposomal amphotericin B regimen because it was associated with fewer intravenous doses. The single intravenous dose took longer to prepare on the first day of treatment, but the entire regimen was less time-consuming to administer over the course of the induction therapy. In addition, the single dose of liposomal amphotericin B can be infused over two hours, whereas each amphotericin B deoxycholate

infusion must run over four hours. Fewer intravenous doses of liposomal amphotericin B resulted in a reduced need for essential pre- and post-hydration and oral electrolyte supplementation aimed at preventing toxicity. The single high-dose intravenous regimen may enable rapid hospital discharge for people with good clinical status.

The favourable safety profile of the single-dose liposomal amphotericin B–containing regimen with a lower risk of anaemia and hypokalaemia reduced the intensity of monitoring and managing drug-related toxicity (Tables 1 and 2). In the single-dose liposomal amphotericin B–containing regimen, flucytosine is given four times a day for 14 days, but participants broadly accepted this as an important part of their treatment and adhered to it.

Cost and cost–effectiveness

A detailed costing and cost–effectiveness analysis performed as part of the AMBITION trial calculated that the mean total costs per person (using Malawi as a reference case) were US$ 1369 in the liposomal amphotericin B group and US$ 1237 in the control group. The difference between groups was US$ 132 (95% CI US$ 53–211) and the incremental cost–effectiveness ratio was US$ 128 (95% CI US$ 59–257) per life-year saved. Excluding protocol-driven cost, using a real-world toxicity monitoring schedule, the cost per life-year saved declined to US$ 80 (95% CI US$ 15–275). Cost–effectiveness was robust in sensitivity analysis, including those assuming higher drug costs.

Despite the substantial difference in the actual cost of liposomal amphotericin B between countries, the overall cost difference between groups and the incremental cost–effectiveness ratio were similar in all settings. Only a few suppliers have received regulatory approval, and although a preferential pricing agreement has been negotiated with the manufacturer of the originator product, uptake has been low. As generic manufacturers of liposomal amphotericin B begin to enter the market, access is anticipated to improve. Another important barrier to liposomal amphotericin B is that, although it is included in the WHO Model List of Essential Medicines *(43)*, it is seldom included in national guidelines and national essential medicines lists, and this is also a concern for access to flucytosine *(44)*.

Ethics and equity

An ethical perspective requires that, as far as possible, the benefits and burdens and risks of public health programmes should be distributed fairly and, when this cannot be achieved, such unequal distributions should be justified with data. The benefits and burdens or risks of any new intervention should be carefully assessed, which includes examining whether the expected benefits justify the identified burdens within a human rights framework.

Liposomal amphotericin B has the benefit of single-dose administration and, combined with flucytosine and fluconazole, is at least as effective as amphotericin B deoxycholate–based combination treatment. It also has a better side-effect profile, with fewer risks related to drug toxicity. Although a single high-dose liposomal amphotericin B-containing regimen requires 14 days to administer flucytosine, this is well tolerated and accepted by participants in a clinical trial setting. Implementing the single high-dose liposomal amphotericin B–containing regimen could increase access to effective treatment for HIV-associated cryptococcal meningitis for people at health-care facilities unable to procure and/or safely administer seven or more days of amphotericin B deoxycholate treatment. As such, the use of single high-dose liposomal amphotericin B would likely increase equity if the drug is made available at an affordable price that does not detract resources from the overall health budget. The reduced time burden on human resources will also free health-care provider time, which can then be directed elsewhere in the health system.

3.3 Preventing, monitoring and managing amphotericin B deoxycholate toxicity

Managing toxicity (2022 good practice principles)

Infusion-related toxicity and side-effects from amphotericin B therapy are barriers to optimal induction treatment, especially 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 the recommended package of preventing, monitoring and managing toxicity.
- Liposomal amphotericin B has fewer risks of drug toxicity than amphotericin B deoxycholate and requires a less intensive package for preventing, monitoring and managing toxicity.
- The recommended package of preventing, monitoring and managing toxicity should be provided to minimize the serious types of amphotericin B–related toxicity when using amphotericin B deoxycholate–based regimens, especially hypokalaemia, nephrotoxicity and anaemia. A single 10 mg/kg dose of liposomal amphotericin B and the seven-day amphotericin B deoxycholate regimen is better tolerated than a 14-day amphotericin deoxycholate regimen, but these regimens still require careful monitoring.

Adverse events associated with amphotericin B deoxycholate include hypokalaemia, nephrotoxicity and anaemia *(33–35)*. A protocol for monitoring of potassium, magnesium (if 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.

Dose adjustment is needed for people with significant renal impairment.

Table 1 Monitoring amphotericin B–related toxicity

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Single high-dose liposomal amphotericin B														
Pre-emptive hydration and electrolyte supplementation (adults and adolescents)														
1 litre of normal saline solution with 20 mEq KCl over two hours before infusion	X													
8-mEq KCl tablets orally (twice daily)	X	X	X											
Magnesium supplementation if available[a]	X	X	X											
Monitoring (adults, adolescents and children)														
Serum potassium	X		X											
Serum creatinine	X		X											
Haemoglobin	X						X[b]							

[a] 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily or magnesium chloride 4 mEq twice daily.
[b] If still in hospital.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Amphotericin B deoxycholate: seven days														
Pre-emptive hydration and electrolyte supplementation (adults and adolescents)														
1 litre of normal saline solution with 20 mEq KCl over two hours before each controlled infusion	X	X	X	X	X	X	X							
2 times 8-mEq KCl tablet (twice daily)	X	X	X	X	X	X	X							
Magnesium supplementation if available[a]	X	X	X	X	X	X	X							
Monitoring (adults, adolescents and children)														
Serum potassium	X		X		X		X		X[b]					
Serum creatinine	X		X		X		X							
Haemoglobin	X						X							
Amphotericin B deoxycholate: 14 days														
Pre-emptive hydration and electrolyte supplementation (adults and adolescents)														
1 litre of normal saline solution with 20 mEq KCl over two hours before each controlled infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2 times 8-mEq KCl tablet (twice daily)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
1 times 8-mEq KCl tablet (twice daily)								X	X	X	X	X	X	X
Magnesium supplementation if available[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitoring (adults, adolescents and children)														
Serum potassium	X		X		X		X		X		X		X	
Serum creatinine	X		X		X		X		X		X		X	
Haemoglobin	X						X							X

Additional notes:

- Amphotericin B is incompatible with normal saline.
- Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia.
- Careful attention should be given to monitoring the 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; guidelines from the Southern African HIV Clinicians Society recommend monitoring full blood counts at baseline and at least weekly for as long as the person is taking flucytosine *(21)*.

If standard dose liposomal amphotericin B is being given for 14 days with fluconazole, the incidence of renal dysfunction and electrolyte disturbance is lower than with amphotericin B deoxycholate, but renal function and electrolytes still need to be monitored. In such cases, follow the standard recommendations for amphotericin B deoxycholate.

[a] 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily or magnesium chloride 4 mEq twice daily.
[b] if still in hospital.

Table 2 Managing amphotericin B–related toxicity (adults, adolescents and children)

	Single 10 mg/kg liposomal amphotericin B	Amphotericin B deoxycholate
Hypokalaemia	If hypokalaemia is significant (K <3.3 mol/l), increase potassium supplementation to 40 mEq KCl by intravenous infusion and/or one to two 8-mEq KCl tablets orally three times daily. Monitor potassium daily.	
Elevated creatinine	Ensure adequate hydration and discontinue concurrent nephrotoxic drugs if possible. Adjust fluconazole and flucytosine doses appropriately if renal impairment is significant. Note that renal function often improves initially following rehydration.	If serum creatinine doubles from baseline, one dose of amphotericin B deoxycholate may be omitted and/or prehydration may be increased to 1 L of normal saline every eight hours; serum creatinine should then be monitored daily. If serum creatinine improves, amphotericin B may be restarted at a dose of 0.7 mg/kg per day, and/or alternate-day treatment could be considered. If creatinine remains elevated or repeatedly rises, liposomal amphotericin B should be substituted if available, or amphotericin B deoxycholate should be stopped and an alternative regimen should be used.
Severe anaemia	Transfusion if possible for severe (grade 4 and clinically symptomatic) liposomal amphotericin B–related anaemia	Transfusion if possible for severe (grade 4 and clinically symptomatic) amphotericin B deoxycholate–related anaemia. If severe anaemia develops during the second week of a planned 14-day induction course of amphotericin B deoxycholate and blood transfusion is not possible, the benefits of continuing amphotericin B deoxycholate need to be carefully balanced against the risks of severe anaemia.

3.4 Drug interactions

Drug interactions in the context of concurrent use of amphotericin, flucytosine and fluconazole alongside ART regimens have not been well documented *(45)*.

However, individuals receiving tenofovir disoproxil fumarate (TDF)–based regimens who are receiving amphotericin or recently received amphotericin B preparations should be closely monitored for nephrotoxicity. Liposomal preparations of amphotericin B are considered to be safer *(46)* than deoxycholate but would still require close follow-up. The dose of TDF should be adjusted for renal function.

Flucytosine, following its absorption and metabolism, is converted to fluorouracil and then dihydropyrimidine dehydrogenase, which is involved in the metabolic pathway of pyrimidine analogues and could potentially cause blood toxicity. Haematological parameters should be monitored, and the dose of TDF should be adjusted in individuals with reduced renal function who are also receiving amphotericin *(47)*.

Fluconazole induces CYP3A4 and P-gp *(47)*. No dose adjustment of ART is required.

3.5 Consolidation and maintenance treatment

The 2018 WHO recommendations for consolidation and maintenance treatment for cryptococcal disease remain unchanged *(16)*.

Consolidation (2018 recommendation)
Recommendation Fluconazole (800 mg daily for adults, 6–12 mg/kg per 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 (2018 recommendation)
Fluconazole (200 mg daily for adults, 6 mg/kg per day for adolescents and children) is recommended for the maintenance phase until immune reconstitution (CD4 >200 cells/mm^3) and suppression of viral loads on ART. *Strong recommendation; high-certainty evidence*

3.5.1 Rationale for the recommendations

WHO recommends fluconazole at 800 mg/day for eight weeks following an amphotericin B deoxycholate–based induction regimen; these recommendations were based primarily on expert opinion, considering the limited evidence from two trials that compared itraconazole versus fluconazole at lower doses *(48,49)*. Recent guidelines from the European AIDS Clinical Society recommend 400 mg for eight weeks after a single loading dose of 800 mg on the first day of therapy *(50)*. Maintenance or secondary prophylaxis until there is evidence 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 *(51)* and was superior to weekly amphotericin B or itraconazole *(52,53)*.

3.6 Treatment for localized non-meningeal disease and disseminated cryptococcal disease other than meningitis

No clinical trial has evaluated the optimal treatment of localized non-meningeal disease. The following treatment regimen is suggested based on expert opinion: fluconazole 800 mg/day for two weeks followed by 400 mg/day for eight weeks followed by fluconazole 200-mg/day maintenance therapy.

If available, neuroimaging (preferably magnetic resonance imaging) should be performed before lumbar puncture. However, neuroimaging should not cause significant delay in performing lumbar puncture. Published data on managing cryptococcoma and other forms of cerebral parenchymal involvement caused by cryptococcosis (such as gelatinous pseudocysts) are scarce *(54–56)*. However, these findings seem to affect the outcome of HIV-associated cryptococcal meningitis *(57–59)*. The following treatment regimen is suggested based on expert opinion: intravenous amphotericin B (liposomal formulation if possible) 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 except for high-dose liposomal amphotericin B 10 mg/kg dosing). 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.

The treatment of disseminated cryptococcal disease other than meningitis (diagnosed by a positive culture of *Cryptococcus* from blood) should be the same as for meningitis, based on expert opinion.

3.7 Treatment for pregnant women

Amphotericin B therapy can be given to pregnant women with meningeal and non-meningeal disease when the benefits outweigh the harm. Liposomal amphotericin B is considered as a pregnancy category B drug and although animal reproduction studies have failed to demonstrate a risk, an increase in spontaneous abortions was noted at higher doses. 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 *(60)*. The use of flucytosine and fluconazole for treating cryptococcal disease among pregnant women should be evaluated on an individual basis, considering the benefits and potential harm.

3.8 Adjunctive corticosteroids in treating HIV-associated cryptococcal meningitis

Adjunctive corticosteroids (2018 recommendation)
Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating adults, adolescents and children who have HIV-associated cryptococcal meningitis. *Strong recommendation; high-certainty evidence for adults and adolescents and moderate-certainty evidence for children*

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 trial evidence for adults and adolescents *(61)*. The trial found no difference in mortality but increased disability and serious adverse events among people receiving dexamethasone. 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.

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 recommendation against the use of adjuvant corticosteroids applies specifically to the routine use during the induction phase of treatment of cryptococcal meningitis. Systemic corticosteroids should be used for other conditions when clinically indicated.

3.9 Timing of ART initiation

Timing of ART (2018 recommendations)

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

Strong recommendation; low-certainty evidence for adults and very-low-certainty evidence for children and adolescents

3.9.1 Rationale for the recommendation

The optimal timing of ART after cryptococcal meningitis was informed by a systematic review that identified four randomized controlled trials *(62)*. 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.

WHO strongly recommends deferring ART initiation for four weeks following an amphotericin B–based induction regimen or 4–6 weeks following a fluconazole and flucytosine induction regimen (based on a slower rate and longer time to achieve CSF fungal clearance with fluconazole versus amphotericin B). This recommendation applies across all age groups and 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.

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 immediately among ART-naïve people who are blood cryptococcal antigen–positive on screening and have a lumbar puncture that excludes cryptococcal meningitis. Asymptomatic cryptococcal antigen–positive people who decline consent for lumbar puncture or for whom lumbar puncture is contraindicated should start ART after at least two weeks of antifungal treatment *(21)*.

3.9.2 Implementation considerations

ART-experienced people who develop cryptococcal meningitis should be evaluated for potential underlying ART treatment failure, ideally through confirmation by 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.

3.10 Monitoring and managing people with cryptococcal meningitis

3.10.1 Raised intracranial pressure

Initial measurement of intracranial pressure and management of raised intracranial pressure are 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. 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 *(15)*.

Reduction of raised CSF pressure is associated with clinical improvement *(63)* and survival benefit, regardless of initial opening pressure *(64)*. Adults, adolescents and children living with HIV with suspected cryptococcal meningitis should have an initial diagnostic 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 a third lumbar puncture on day 3). For people with initial intracranial pressure of 25 cm H_2O or more *(65)* or subsequent development or recurrence of symptoms or signs of raised intracranial pressure, repeat therapeutic lumbar puncture[4] should be carried out. People in low- and middle-income countries 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.

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, especially cranial nerve VI)
- Other focal nervous system deficits

[4] 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 monitoring and managing 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.
- Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient to reduce the CSF pressure to less than 20 cm H_2O (preferably) or halving the baseline pressure baseline pressure if extremely high (alternatively).[5]
- 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, two therapeutic lumbar punctures (such as 12 hours apart) may be necessary. 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. If available, lumbar or ventricular shunts should be placed only if the person is receiving or has received appropriate antifungal therapy and if therapeutic lumbar punctures have failed to control raised intracranial pressure. Using drugs (mannitol, acetazolamide, furosemide or steroids) for managing raised intracranial pressure is not recommended because no evidence indicates that using these drugs improves outcomes and some evidence indicates that using them may be harmful *(15,61,66)*.

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, 20–30 ml may need to be drained with every therapeutic lumbar puncture. 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.

[5] There are no data on the maximum volume of CSF that can be safely drained at one lumbar puncture. CSF opening pressure can be rechecked after every 10 ml is removed. Usually 20–30 ml is enough to reduce the opening pressure sufficiently.

3.10.2 Cryptococcal immune reconstitution inflammatory syndrome

Paradoxical cryptococcal immune reconstitution inflammatory syndrome is associated with high mortality *(13)*. The median time to onset in reported cohort studies is typically 3–12 weeks after initiating ART *(67)*. Raised intracranial pressure is a common feature of cryptococcal immune reconstitution inflammatory syndrome and an important contributor to high mortality *(68)*. Multiple repeat lumbar puncture may be necessary. Optimizing antifungal therapy and reinduction with an amphotericin B–based regimen is important if suboptimal antifungal treatment is considered to contribute to developing immune reconstitution inflammatory syndrome.

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.
4. Short-course oral steroid therapy,[6] although not recommended for routine use in treating cryptococcal meningitis, 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. This is not supported by direct evidence and is based on expert opinion.

[6] 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.

4. IMPLEMENTATION CONSIDERATIONS

Diagnosis

Diagnosis is key to improving mortality from cryptococcal disease, and national programmes 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.

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.

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 *(69,70)*.

In resource-limited settings with limited laboratory infrastructure, task sharing 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 *(71)*. This may be the preferred approach, especially when point-of care CD4 cell count is available, enabling same-day initiation of fluconazole among those who screen cryptococcal antigen–positive.

Treatment

Access to essential antifungal drugs remains inadequate, and drug toxicity and laboratory monitoring costs continue to be important barriers. Lack of local generic manufacturers, lack of in-country registration and high prices are some of the main barriers *(72,73)*.

Liposomal amphotericin B is included in the 2021 WHO List of Essential Medicines and WHO Prequalification Expression of Interest list. Although liposomal amphotericin B has been off patent since 2016, and despite preferential pricing from the originator for some countries, the current price of liposomal amphotericin B remains substantially higher than that of amphotericin B deoxycholate in most countries. Lack of registration and inclusion in national essential medicines lists and national treatment guidelines can also be barriers to access. For example, as of February 2022, liposomal amphotericin B was only registered in two countries in sub-Saharan Africa (Ethiopia and South Africa).

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. Flucytosine is not widely registered nor available in most low- and middle-income countries. Although registering standard formulations of flucytosine is the current priority, 100 mg/kg per day dosages of flucytosine given four times a day are problematic.

Antifungal medications for treating cryptococcal meningitis are increasingly more affordable, and barriers to access can be overcome by:

- increasing advocacy for reducing drug prices and promoting generic production, especially for liposomal 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 deoxycholate, liposomal amphotericin B, flucytosine and fluconazole are included in the WHO Model List of Essential Medicines);
- ensuring adequate supply chains at the national level;
- developing proper drug-forecasting and -monitoring systems; and
- improving access to liposomal amphotericin B by integrating it in the national package of drugs to treat severe fungal diseases.

The new 10 mg/kg liposomal amphotericin B–based induction regimen could enable people to be discharged from hospital earlier since intravenous treatment is not required after the initial dose and the need for toxicity monitoring is reduced. However, because of the severity of illness of many people with advanced HIV disease and cryptococcal meningitis, very early discharge (before day seven) should only be considered for clinically stable individuals, with provisions in place for outpatient follow-up and management of raised intracranial pressure if required.

In exceptional circumstances, the single high-dose liposomal amphotericin B induction regimen could be administered to ambulatory patients in outpatient settings, but this should only be considered when no option for safe inpatient treatment is available.

Monitoring

The recommended package for preventing, monitoring and managing amphotericin B toxicity sets the standard that should be followed when resources permit. However, in settings in which applying all monitoring requirements is not possible, this should not limit provision of amphotericin B since the benefits of treatment will still outweigh the toxicity risks. The monitoring package should be informed by resource availability, local data and clinical experience.

5. RESEARCH NEEDS

Further research is needed to assess the value of cryptococcal antigen screening at CD4 cell count thresholds between 100 and 200 cells/mm^3, which has been suggested to save costs if carried out in inpatient settings.

High cryptococcal antigen titres (>160) in blood have been found to predict subclinical meningitis. It has been suggested that blood titres could be used to predict meningitis in settings in which lumbar puncture cannot be performed or in which 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. Second-generation cryptococcal antigen lateral-flow assays that can give a high or low cryptococcal antigen result need to be evaluated as part of this approach.

Research could help improve the understanding of how to manage relapse or treatment non-response in public health settings, since the current course of action would be referral to a tertiary care centre. In tertiary care settings, intrathecal and intraventricular administration of amphotericin B have been attempted successfully, but further research is needed to establish safety and tolerability *(74)*. Managing space-occupying lesions among people with a positive serum cryptococcal antigen test, the concurrent treatment of HIV-associated TB and cryptococcal meningitis and the best approach for treating immune reconstitution inflammatory syndrome are other research needs.

WHO has issued a Prequalification Expression of Interest for sustained-release flucytosine to simplify inpatient and outpatient treatment of cryptococcal infections. The role of azoles other than fluconazole, notably voriconazole and isavuconazole, as well as novel oral antifungal agents (such as oral encochleated amphotericin B) for the treatment and prophylaxis of cryptococcosis could benefit from further study.

There remains a need to better understand the prevalence of cryptococcal disease among children and the best diagnostic approach to enable the timely identification of disease.

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 lipoarabinomannan assay and tuberculosis prophylaxis).

6. UPDATING AND DISSEMINATION

These guidelines will be launched as a web-based product for dissemination and will be supported by peer-reviewed publications of the systematic review and other evidence on which these recommendations are based. These guidelines will also be incorporated into the periodic updates of the WHO consolidated guidelines on HIV *(75)*. The consolidated guidelines on HIV will be updated in full or in part based on regular scoping exercises of available evidence and experience from country implementation that will guide and trigger the need for new guidance. As the evidence base or user needs change, consideration will be given to producing technical updates on specific areas.

WHO will work closely with WHO regional and country offices, national health ministries 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.

To monitor uptake, data will be made available within the WHO country intelligence database, which is updated every six months to reflect both change in policy and implementation diffusion for all low- and middle-income countries and selected high-income countries *(76)*.

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ANNEX 1. PROCESS FOR DEVELOPING THE GUIDELINES

WHO first published a rapid advice document on the diagnosis, prevention and management of cryptococcal disease in December 2011.

In 2018, WHO published guidelines in response to new evidence relating to preventing, screening and treating cryptococcal disease. In 2021, new evidence on induction therapy was published that triggered a review of the evidence and a WHO guideline development process. A Guideline Development Group meeting was held in February 2022 to review the evidence and formulate a recommendation on the preferred induction regimen for treating people with cryptococcal meningitis.

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

Recommendation	Recommended in 2012	Updated in 2018	Updated in 2022
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 certainty of the evidence and determine the strength of the recommendations. The GRADE approach to developing recommendations, which WHO has adopted, defines the certainty 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.

To inform the update of these guidelines, a systematic review of the treatment of cryptococcal meningitis was conducted under the leadership of Adrienne Shapiro at the Division of Allergy and Infectious Diseases, University of Washington School of Medicine, Seattle, USA. The technical lead at WHO and the guideline methodologist were responsible for overseeing the collection, review and grading of evidence.

Acceptability, feasibility and cost

Acceptability, values and preferences were assessed in a qualitative study within the randomized trial included in the systematic review *(1,2)*. Since this is the first clinical use of this treatment option, there are no other sources of information to inform this question.

Information on cost–effectiveness and feasibility was assessed as a substudy of the AMBITION Trial with data from Botswana, Malawi, South Africa, Uganda and Zimbabwe, and this information was presented to the Guideline Development Group.

Costing information for the key cryptococcal drugs (amphotericin B deoxycholate, liposomal amphotericin B, fluconazole and flucytosine) in various countries was prepared from pricing information from the Clinton Health Access Initiative. Additional costing data and implementation experience were shared by Médecins Sans Frontières *(3)*.

Guideline Development Group meeting

The Guideline Development Group met virtually on the 2 February 2022. The recommendation was made through consensus and the methodologist facilitated discussion. Voting was not required, but the Group agreed at the start of the meeting that two thirds of the votes would be required for a decision.

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 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 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.

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 responsible technical officer reviewed the declaration of interests forms and the results of the web-based search for each member of the Guideline Development Group. A management plan for each declared conflict was agreed and recorded in advance of the meeting. Members of the Guideline Development Group were also asked to declare any undeclared and/or new conflicts of interest at the start of the Guideline Development Group meeting.

All declaration of interests forms are on electronic file at the WHO Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes and will be maintained for 10 years.

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.

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ANNEX 2. DECLARATIONS OF INTEREST FOR THE GUIDELINE DEVELOPMENT GROUP AND EXTERNAL PEER REVIEW GROUP

Guideline Development Group members (*n* = 15)

Sex	Percentage
Male	53%
Female	47%

Region	Percentage
African Region	47%
Region of the Americas	27%
European Region	6%
Eastern Mediterranean Region	6%
South-East Asia Region	6%
Western Pacific Region	6%

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Additional information	7. Tobacco products	Conflicts and management plan
Eduardo Arathoon, (Hospital General San Juan de Dios, Guatemala)	0	0	0	0	0	0	0	Full participation
Rachael Burke (Liverpool Wellcome Clinical Research Programme and London School of Hygiene & Tropical Medicine, Malawi)	0	0	0	0	0	0	0	Full participation
Alexandra Calmy (Hôpitaux Universitaires de Genève, Switzerland)	0	0	0	0	0	0	0	Full participation
Mohamed Chakroun (Fattouma Bourguiba Teaching Hospital, Tunisia)	0	0	0	0	0	0	0	Full participation
Tom Chiller (United States Centers for Disease Control and Prevention)	0	0	0	0	0	0	0	Full participation

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Additional information	7. Tobacco products	Conflicts and management plan
Brenda Crabtree (Departamento de Infectología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico)	0	0	0	0	0	0	0	Full participation
Tom Ellman (MSF, Johannesburg, South Africa)	0	0	0	0	0	0	0	Full participation
Serge Eholie (University Félix Houphouet-Boigny, Côte d'Ivoire)	0	0	0	0	0	0	0	Full participation
Nelesh Govender (National Institute for Communicable Diseases and University of the Witwatersrand, South Africa)	0	Non-monetary support (2b): provision of cryptococcal antigen test reagents for a retesting quality improvement project (2018) and a national survey (2020); IMMY; does not belong to individual; approximately 35 000 cryptococcal antigen LFA test strips; reagents were provided directly to my organization; 2018 and 2020	0	0	0	0	0	Full participation
Andreas Jahn, (I-Tech, Malawi)	0	0	0	0	0	0	0	Full participation
Thuy Le (Oxford University Clinical Research Unit, Viet Nam)	0	Investigator-initiated research grant from Gilead, belongs to Duke University, US$ 749 000	0	0	0	0	0	Full participation
Sayoki Mfinanga (National Institute for Medical Research, United Republic of Tanzania)	0	0	0	0	0	0	0	Full participation

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Additional information	7. Tobacco products	Conflicts and management plan
Ni Ni Tun (Myanmar Oxford Clinical Research Unit, Myanmar)	0	0	0	0	0	0	0	Full participation
Jose Vidal (Instituto de Infectologia Emílio Ribas and Faculdade de Medicina da Universidade de São Paulo, Brazil)	Board meeting (once) and speaker (once); United Medical and Gilead; does not belong individual; US$ 1500; no current interest	Donation of diagnostics kits for research (2017 to the present); principal investigator; IMMY; does not belong to individual; approximately 10 kits (each with 50 tests); ongoing	0	0	Author of the institutional protocol on management of cryptococcosis among people living with HIV at Instituto de Infectologia Emilio Ribas and Universidade de São Paulo, both in São Paulo, Brazil; author of the Brazilian guidelines on management of cryptococcosis among people living with HIV; member of the Technical Group on Systemic Mycoses of Brazil's Ministry of Health	0	0	Full participation
Stephen Watiti (Worldwide Hospice Palliative Care Alliance, Uganda)	0	0	0	0	0	Survivor of cryptococcal meningitis in 1999–2000 and was successfully treated using amphotericin B and fluconazole; as a person living with HIV, at risk of developing cryptococcal meningitis in the future	0	Full participation

External Peer Review Group (*n* = 8)

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Additional information	7. Tobacco products
Tihana Bicanic (Institute of Infection & Immunity, St George's University London, United Kingdom)	0	In 2020–2022, received research fellowships and speaker advisory board from Gilead Sciences Inc., unrelated to cryptococcal meningitis work; role as principal investigator; £200 000 research fellowship and three £800 speaker advisory board fees; research grant current	0	0	0	0	0
Yao-kai Chen (Division of Infectious Diseases, Chongqing Public Health Medical Center, China)	0	0	0	0	0	0	0
Jeremy Day (Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam)	0	0	0	0	0	0	0
Lisa Frigati (Department of Paediatrics and Child Health, Tygerberg Children's Hospital and Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa)	WHO consultant in 2020, contract concluded	0	0	0	0	0	0
Daniel O'Brien (Department of Health and Human, Melbourne, Australia)	0	0	0	0	0	0	0
Rita Oladele (Department of Medical Microbiology & Parasitology, College of Medicine, University of Lagos, Nigeria)	0	Research grant on cryptococcal antigenemia, CCD Foundation, US$ 28 paid to medical mycology society in Nigeria, 2019	0	0	Advisory board member March 2022, Pfizer Pharmaceuticals, US$ 1000	0	0
Nagalingeswaran Kumarasamy (VHS-Infectious Diseases Medical Centre, Voluntary Health Services, India)	0	0	0	0	0	0	0
Mathieu Nacher (Centre Hospitalier de Cayenne, French Guiana)	0	0	0	0	0	0	0

ANNEX 3. SYSTEMATIC REVIEW AND GRADE EVIDENCE PROFILE ON TREATMENT STRATEGIES FOR HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS

Adrienne E. Shapiro[1], Mark W. Tenforde[2], Tom M. Chiller[2], Nathan Ford[3], Radha Rajasingham[4]

[1] Departments of Global Health & Medicine, University of Washington, Seattle, WA, USA

[2] United States Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[3] Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, World Health Organization, Geneva, Switzerland

[4] Division of Infectious Diseases & International Medicine, Department of Medicine, University of Minnesota, Minneapolis, USA

Abstract

Objective: The purpose of this systematic review is to provide updated evidence on the preferred induction therapy for treating people with HIV-associated cryptococcal meningitis, considering the most recent evidence available, to inform the need for updates to WHO guidelines.

Design: Systematic review.

Methods: We searched Medline via PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov for published or completed randomized clinical trials that evaluated induction treatment of first-episode HIV-associated cryptococcal meningitis from 9 July 2018 (date of last search) through 1 September 2021.

Results: One randomized clinical trial of 844 people with HIV-associated cryptococcal meningitis met the inclusion criteria. The participants were randomized to: (1) amphotericin deoxycholate for seven days, with flucytosine and fluconazole (control); or (2) a single dose of liposomal amphotericin 10 mg/kg with flucytosine and fluconazole (intervention).

In the intention-to-treat analysis, 10-week mortality was 24.8% (95% confidence interval (CI) 20.7–29.3%) in the single-dose liposomal amphotericin group versus 28.7% (95% CI 24.4–33.4%) in the control group. The absolute difference in 10-week mortality was –3.9 percentage points, with an upper one-sided 95% CI of 1.2 percentage points, within the 10% pre-specified non-inferiority margin. Fewer participants had grade 3 and 4 adverse events in the intervention arm than in the control arm (50.0% versus 62.3%, $P < 0.001$).

Conclusions: In the single study included in this systematic review, single high-dose liposomal amphotericin B with flucytosine and fluconazole was non-inferior to the WHO-recommended standard-of-care induction therapy for HIV-associated cryptococcal meningitis, with significantly fewer adverse events.

Background

Cryptococcal meningitis is a leading cause of HIV-related mortality globally *(1)*. A systematic review and network meta-analysis published in 2018 *(2)* provided evidence that, in resource-limited settings, one-week intravenous amphotericin B deoxycholate and oral flucytosine induction therapy was superior to other regimens that had been evaluated in clinical trials, and this formed the basis for guidelines published by WHO *(3)*. Despite this highly effective antifungal regimen, 10-week mortality in clinical trials is estimated to be about 35% (95% confidence interval (CI) 29–42%) and higher outside clinical trial settings; this regimen is also associated with important drug-related adverse events and associated toxicity-monitoring requirements *(4,5)*. There is a critical need to identify novel therapies to treat cryptococcal meningitis that are highly effective, more feasible to administer in resource-limited settings and cost-effective.

Since the last review in 2018, the results of a randomized trial conducted in five countries across southern and eastern Africa – Botswana, Malawi, Uganda, South Africa and Zimbabwe – have shown that a single high-dose of liposomal amphotericin B paired with two oral antifungals, fluconazole and flucytosine, is as effective as therapy based on seven-day amphotericin-B deoxycholate in reducing deaths *(6)*.

The purpose of this systematic review is to provide updated evidence on the preferred induction therapy for treating people with HIV-associated cryptococcal meningitis, considering the most recent evidence available, to inform the revision of WHO guidelines.

Methods

Eligibility criteria

We included randomized controlled trials among people living with HIV with a first episode of cryptococcal meningitis evaluating induction regimens for treating people with cryptococcal meningitis not currently recommended by WHO guidelines. The standard-of-care arm had to include an induction regimen recommended by the WHO guidelines, either one week of amphotericin deoxycholate with flucytosine or two weeks of flucytosine plus fluconazole.

We excluded non-randomized studies. Additional exclusion criteria were laboratory or animal studies, trials that did not evaluate cryptococcal meningitis induction treatment, secondary analyses of randomized clinical trials, diagnostic studies and cryptococcal prevention trials.

Outcomes

The primary outcomes of interest were mortality at two weeks and 10 weeks; the secondary outcomes included early fungicidal activity – the mean rate of fungal clearance from the cerebrospinal fluid – and laboratory grade 3 and 4 serious drug-related adverse events as defined by the Division of AIDS criteria *(7)*. Specifically, we evaluated the incidence of anaemia, neutropaenia, thrombocytopaenia, hypokalaemia and alanine aminotransferase elevation.

Search strategy

We sought to identify all published and unpublished studies regardless of language between 9 July 2018 (date of last search) and 1 September 2021. We searched the following electronic databases: Medline via PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov. The specific search terms used are included in the Appendix. Briefly, the search strategy included terms for HIV infection, cryptococcal meningitis and antifungal therapies.

We also searched conference abstracts and presentations from 1 January 2018 to 1 June 2021 for the following HIV-related conferences: the International AIDS Society and Conference on Retroviruses and Opportunistic Infections. After reviewing ClinicalTrials.gov and conference abstracts, we contacted lead researchers to identify unpublished data from clinical trials.

Study selection

The articles yielded from the search strategy were collected using Covidence systematic review software *(8)*. Two reviewers (RR and AES) independently screened the abstracts and titles and for those that potentially met inclusion criteria; the same two reviewers independently screened the full text. Each reviewer completed a template with the specified selection criteria to document reasons for exclusion; any discrepancies regarding the eligibility criteria were discussed; no additional adjudication was needed. The reviewers contacted the study authors as needed. Fig. 1 highlights the screening and eligibility criteria in a flow diagram.

Data collection

The same reviewers collected outcome data from each included report using a standardized extraction template. The following variables of interest were collected: two-week mortality, 10-week mortality, two-week rate of cerebrospinal fluid clearance (log10 colony-forming units [CFU]/mL/day), number of grade 3 or 4 adverse events, number of participants who dropped out after randomization and number lost to follow-up.

Study risk of bias assessment

One author (AES) assessed the methodological quality for randomized controlled trials using the Cochrane Risk of Bias Tool. Studies were graded as low, high or unclear risk based on the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

Effect measures

Point estimates and 95% confidence intervals (CI) were calculated for the main outcomes for each study. For pairwise comparisons, we present risk ratios with the associated 95% CI, and the risk difference between the intervention and control arms. Early fungicidal activity is presented as a mean difference with the associated 95% CI.

Certainty assessment

The GRADE approach was used to assess the overall certainty of the evidence, considering risk of bias, inconsistency, indirectness, imprecision and publication bias *(9)*. Four levels of certainty ratings were possible: very low, low, moderate and high.

Results

Study selection

We identified 301 publications through database searches and one additional publication in press arising from an abstract from other sources (Fig. 1). After de-duplication, 276 records were available for reviewing titles and abstracts. Of these 276 records, 267 were excluded since they were not randomized clinical trials involving humans with results available. Nine records were available for full text review, of which eight were excluded; four did not use flucytosine in the comparator arm, three had been previously included in the previous systematic review and one was conducted in a population without HIV infection. As a result, this review included one randomized clinical trial.

Study characteristics

The included study was a randomized controlled trial of 844 participants with HIV-associated cryptococcal meningitis from five countries in sub-Saharan Africa: Botswana, Malawi, South Africa, Uganda and Zimbabwe. The study design was a non-inferiority design. The participants were 18 years or older with confirmed cryptococcal meningitis (either with positive cerebrospinal fluid India ink or cryptococcal antigen test). Pregnant or breastfeeding people were excluded, as were people with a history of previous cryptococcal meningitis, previous adverse reactions to study drugs, previous receipt of >48 hours of antifungal therapy and people who were unable to consent.

Participants were randomized to: (1) WHO-recommended induction therapy of amphotericin deoxycholate 1 mg/kg/day + flucytosine 100 mg/kg/day for seven days, followed by fluconazole 1200 mg/day for seven days; or (2) the intervention of a single dose of liposomal amphotericin 10 mg/kg + flucytosine 100 mg/kg/day and fluconazole 1200 mg/day for 14 days. Consolidation therapy for both arms was fluconazole 800 mg/day for eight weeks followed by fluconazole 200 mg/day for maintenance therapy.

The primary outcome was mortality at 10 weeks. The secondary outcomes were early fungicidal activity and the proportion of participants in each arm with grade 3 and 4 adverse events.

Study results

In the intention-to-treat analysis, 10-week mortality was 24.8% (95% CI 20.7–29.3%) in the single-dose liposomal amphotericin group versus 28.7% (95% CI 24.4–33.4%) in the control group. The absolute difference in 10-week mortality was –3.9 percentage points, with an upper one-sided 95% confidence interval of 1.2 percentage points, within the 10% prespecified non-inferiority margin. The rate of fungal clearance, measured as early fungicidal activity, was higher in the control arm than in the intervention arm (–0.42 log10 CFU/mL/day versus –0.40 log10 CFU/mL/day, respectively), although not statistically significant. Fewer participants had grade 3 and 4 adverse events in the intervention arm than in the control arm (50.0% versus 62.3%, $P < 0.001$). Grade 4 adverse events, grade 3 or 4 anaemia and thrombophlebitis were significantly less common in the intervention group than in the control group.

Risk of bias

The study design was a randomized controlled trial; thus, the risk of bias was deemed not serious. We were unable to assess consistency since the data are from a single study. Imprecision was downgraded one level to serious for mortality and early fungicidal activity outcomes, because the data are from a single study with wide CI around the point estimate of effect, noting that the CI fell within the prespecified non-inferiority limit for the primary analysis. The indirectness was deemed not serious. The certainty of evidence was graded as low for the primary outcome, low for early fungicidal activity and moderate for grade 3 and 4 adverse events. Publication bias was not detected.

Discussion

This updated review identified one study of 844 participants comparing a novel induction strategy for treating people with a first episode of HIV-associated cryptococcal meningitis. In the single study included in this systematic review, single high-dose (10 mg/kg) liposomal amphotericin B with flucytosine and fluconazole was non-inferior to the WHO-recommended standard-of-care induction therapy for HIV-associated cryptococcal meningitis, with significantly fewer adverse events. Based on low-certainty evidence from one study, mortality within 10 weeks may be lower with single-dose liposomal amphotericin B with flucytosine and fluconazole than the WHO-preferred induction regimen. Based on moderate-certainty evidence, single-dose liposomal amphotericin B has less toxicity associated with treatment. In the context of existing WHO recommendations, a regimen that is non-inferior with respect to mortality, has fewer adverse events and may potentially lead to shorter hospitalization could be considered a preferred regimen.

The limitations of this review are related to only one study meeting the selection criteria, which also precluded further synthesis or meta-analysis. The single study that met our selection criteria excluded children and pregnant and breastfeeding women, and no study data came from high-income country settings. We excluded randomized controlled trials that did not use a WHO-recommended regimen containing flucytosine as a comparator from our review, although the majority of health-care centres in sub-Saharan Africa, Asia and Latin America do not have access to flucytosine-based induction regimens *(10)*. Additional implementation science studies are warranted to confirm the effectiveness of single-dose liposomal amphotericin and to evaluate implementation in routine clinical settings in which standard-of-care pharmacy capacity, laboratory monitoring capacity, performance of therapeutic lumbar punctures and management of adverse events may differ from those provided in the context of a clinical trial.

Informed by these findings, WHO published updated guidelines in March 2022 to strongly recommend single-dose liposomal amphotericin B with flucytosine and fluconazole as preferred induction therapy. To provide this highly effective regimen, there is urgent need to expand access to liposomal amphotericin and flucytosine in resource-limited settings where HIV-associated cryptococcal meningitis is most common.

Acknowledgements

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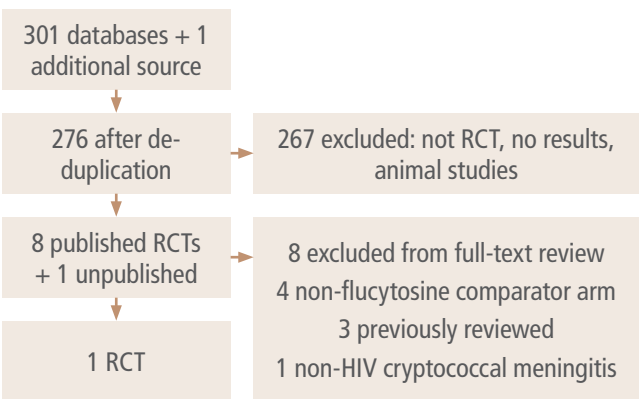
Fig. A1. Study selection



Supplemental Fig. 1. Risk of bias summary

Jarvis 2022

Appendix. Search strategy: utility and impact review

The following search terms were used:

1. Search (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab]OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immunodeficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immunodeficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab])).
1. Search ("Meningitis, Cryptococcal"[11] OR cryptococcal meningitis[tiab] OR cryptococcal meningitis[tiab] OR cryptococcal meningitides[tiab] OR cerebral cryptococcosis[tiab] OR cerebral cryptococcoses[tiab] OR toruloma*[tiab] OR cryptococcus neoforman[mh] OR cryptococcus neoforman[tiab] OR ((cryptococcal[tiab] OR cryptococcal[tiab] OR cyptococcosis[tiab] OR cryptococcoses[tiab] OR Cryptococcus[tiab]) AND (meningitis[tiab])).
1. Search (Antifungal agents[mh] OR azole*[tiab] OR fluconazole[tiab] OR amphotericin[tiab] OR flucytosine[tiab] OR sertraline[tiab] OR dexamethasone[tiab] OR voriconazole[tiab] OR acetazolamide[tiab] OR diflucan[tiab] OR itraconazole[tiab] OR rifampin[tiab] OR 5-FC[tiab]).
1. Search (#1 AND #2 AND #3).

GRADE evidence profile on updated systematic review of HIV-associated cryptococcal meningitis treatment strategies

Certainty assessment							Summary of findings					
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients in intervention	Number of patients in control	Relative effect (95% CI)	Absolute effect (95% CI)	Certainty	Importance
10-week mortality												
1	Randomized trial	Not serious	Serious[a]	Not serious	Serious[b]	None	101/407 (24.8%)	117/407 (28.7%)	RR 0.863 (0.690 to 1.080)	39 fewer per 1000 (89 fewer to 23 more)	Low	Critical
Early fungicidal activity												
1	Randomized trial	Not serious	Serious[a]	Not serious	Serious[b]	None	363	381	–	MD 0.017 log10 CFU/mL/day higher (0.001 lower to 0.036 higher)	Low	Important
Grade 3 or 4 adverse events												
1	Randomized trial	Not serious	Serious[a]	Not serious	Not serious	None	210/420 (50.0%)	263/422 (62.3%)	RR 0.80 (0.71 to 0.91)	125 fewer per 1,000 (181 fwwer to 56 fewer)	Moderate	Critical

a Unable to assess inconsistency with a single study.

b Downgraded one level for precision given wide confidence intervals and a single study; of note, the study design was non-inferiority and the confidence interval was within the prespecified non-inferiority limit for mortality.

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ANNEX 4. EVIDENCE-TO-DECISION-MAKING TABLE

Summary of judgements

Question	Judgement
1. Is the problem a priority?	Yes
2. How substantial are the benefits?	Large
3. How substantial is the harm?	Large to moderate
4. What is the overall certainty of evidence?	Moderate
5. What is the balance between benefits and harm?	Favours intervention
6. Is there important variability or uncertainty in patient preferences regarding the key outcomes?	No important uncertainty or variability
7. How large are the resource requirements (costs)?	Varies
8. What is the certainty of evidence for the costs?	Low
9. Is the intervention cost-effective?	Probably favours intervention
10. What would the impact be on health equity?	Probably increased
11. Is the intervention acceptable to all stakeholders?	Yes
12. Is the intervention feasible to implement?	Probably yes
Recommendation	In favour of single high-dose liposomal amphotericin for induction therapy as part of management of cryptococcal disease
Strength	Strong

Detailed evidence-to-decision-making table

Factor	Explanation and evidence	Judgement
Certainty of evidence	A systematic review found one randomized controlled trial, and the evidence was considered to be of moderate certainty.	Moderate
Balance of benefits versus harm	The evidence indicated that the single high-dose liposomal amphotericin regimen was non-inferior in terms of 10-week mortality to the current WHO-recommended treatment of seven daily doses of amphotericin B deoxycholate (1 mg/kg/day) plus flucytosine (100 mg/kg/day) followed by seven days of fluconazole 1200 mg/day and that the liposomal amphotericin regimen was associated with significantly fewer adverse events.	Benefits outweighs harm, with benefits being considered large, and reduction in harm being large to moderate in relation to the comparator.

Factor	Explanation and evidence	Judgement
Values and preferences	Qualitative data from a purposively selected group of participants, surrogate decision-makers and researchers working at the sites in Gaborone, Botswana and Kampala, Uganda identified a clear preference with regards to the administration and tolerability of the single-dose liposomal amphotericin regimen. The liposomal amphotericin regimen was favoured because it involved a single intravenous dose which, despite taking longer to prepare on the first day of treatment (20–40 minutes versus 5–10 minutes for amphotericin B deoxycholate), was less time consuming over the course of the induction therapy. In addition, liposomal amphotericin can be administered over two hours, whereas amphotericin B deoxycholate must run over four hours. Fewer intravenous doses of amphotericin resulted in a reduced need for essential pre- and post-hydration and oral electrolyte supplementation aimed at preventing toxicity. Liposomal amphotericin was subjectively observed to result in fewer and less severe infusion-related rigours, but this was not objectively measured within the trial.	No important uncertainty or variability of preferences.
Acceptability	Qualitative data from a purposively selected group of participants, surrogate decision-makers and researchers working at the AMBITION trial sites in Gaborone, Botswana and Kampala, Uganda (LEOPARD study) identified a clear preference regarding the administration and tolerability of the single-dose liposomal amphotericin B–containing regimen. There was a general preference for the single-dose liposomal amphotericin B regimen because it was associated with fewer intravenous doses. The single intravenous dose took longer to prepare on the first day of treatment, but the entire regimen was less time-consuming to administer over the course of the induction therapy.	Acceptable to all stakeholders.
Feasibility	The short-course high-dose liposomal amphotericin regimen requires just a single intravenous infusion versus seven with the current WHO-recommended regimen and has significantly fewer side-effects. As a result, it may be feasible to reduce the duration of hospital admission in some cases, and the need for toxicity monitoring is reduced. Unlike amphotericin B deoxycholate, liposomal amphotericin B does not require refrigeration. The short-course treatment would be feasible to implement in all settings in which amphotericin B deoxycholate treatment is currently being used and could be implemented in some settings that are currently unable to implement seven-day courses of amphotericin B deoxycholate. Further, the intervention does not require refrigeration. The Guideline Development Group noted limited access to flucytosine, which is part of the induction therapy for cryptococcal disease and expects feasibility to improve with this recommendation.	Probably feasible
Cost-effectiveness	A detailed costing and a cost–effectiveness analysis was performed alongside the AMBITION trial and estimated that the mean total costs per person (using Malawi as a reference case) were US$ 1369 in the liposomal amphotericin B group and US$ 1237 in the control group. The difference between groups was US$ 132 (95% CI US$ 53–211) and the incremental cost–effectiveness ratio was US$ 128 (95% CI US$ 59–257) per life-year saved. Excluding protocol-driven cost, using a real-world toxicity monitoring schedule, the cost per life-year saved declined to US$ 80 (95% CI US$ 15–275). Cost–effectiveness was robust in sensitivity analysis, including those assuming higher drug costs.	Probably favors intervention

Factor	Explanation and evidence	Judgement
Resource use	The Guideline Development Group indicated that costs could change based on settings and may not be available in some countries, such as those from the WHO Region of the Americas. Also important to consider is that the intervention is part of a three-drug regimen – with flucytosine and fluconazole (both comparison and intervention), there is some variability in access prices at the time of the guidelines meeting (liposomal amphotericin varied between US$ 17 and US$ 83 in the surveyed countries per vial, flucytosine varying between US$ 0.50 and US$ 2.32 per 500 mg, Fluconazole varied between US$ 0.04 and US$ 0.25 per 200 mg), and MSF and the Global Fund reported more consistent pricing. The expected price of the entire WHO-recommended regimen with conventional amphotericin is about US$ 145, and with liposomal amphotericin about US$ 502. The costs reported from the AMBITION trial were US$ 340 for the regimen per person.	Resource requirements may vary based on setting.
Equity	Implementing the short-course high-dose liposomal amphotericin regimen could increase access to effective treatment for HIV-associated cryptococcal meningitis for people at health-care facilities unable to safely administer seven or more days of amphotericin B deoxycholate treatment. The PADO group noted that use may be extrapolated to children, and therefore improving therapeutic options for children living with HIV, who would not have to receive conventional amphotericin therapy.	The impact of the intervention will probably increase equity across population subgroups.

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

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