Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM

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Cryptococcosis is a major worldwide disseminated invasive fungal infection. Cryptococcosis, particularly in its most lethal manifestation of cryptococcal meningitis, accounts for substantial mortality and morbidity. The breadth of the clinical cryptococcosis syndromes, the different patient types at-risk and affected, and the vastly disparate resource settings where clinicians practice pose a complex array of challenges. Expert contributors from diverse regions of the world have collated data, reviewed the evidence, and provided insightful guideline recommendations for health practitioners across the globe. This guideline offers updated practical guidance and implementable recommendations on the clinical approaches, screening, diagnosis, management, and follow-up care of a patient with cryptococcosis and serves as a comprehensive synthesis of current evidence on cryptococcosis. This Review seeks to facilitate optimal clinical decision making on cryptococcosis and addresses the myriad of clinical complications by incorporating data from historical and contemporary clinical trials. This guideline is grounded on a set of core management principles, while acknowledging the practical challenges of antifungal access and resource limitations faced by many clinicians and patients. More than 70 societies internationally have endorsed the content, structure, evidence, recommendation, and pragmatic wisdom of this global cryptococcosis guideline to inform clinicians about the past, present, and future of care for a patient with cryptococcosis.

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Introduction

Cryptococcosis accounts for substantial morbidity and mortality globally. In 2022, WHO listed *Cryptococcus neoformans* as a top fungal priority pathogen.[1] Cryptococcosis often involves the CNS or the lungs, but disseminated disease can affect any organ, yet appear localised. Despite the knowledge gained and improvements in clinical outcomes generated by multiple interventional trials[2–7] done primarily in low-income settings with insufficient resources, mortality from cryptococcal meningoencephalitis is high, ranging from 24 to 47% at 10 weeks.[2,4,7,8] The highest burden of disease is in low-income and middle-income countries, especially in sub-Saharan Africa,[9] where HIV and AIDS are the dominant risk factor, although new non-HIV immunocompromised risk groups and putatively immunocompetent individuals are increasingly reported in high-income settings with sufficient resources.

Complementary diagnostic and management guidelines for cryptococcosis exist.[10–21] This comprehensive management guideline serves primarily to facilitate clinical decision making while also providing an overview of the uncertainties in cryptococcosis management. With contributors across the globe, this guideline gives voice to expertise and challenges from diverse settings in a globally relevant Review. General principles and treatment recommendations are provided, and clinicians are urged to use careful clinical judgement when formulating

Key points

- Accurate delineation of the cryptococcosis clinical syndrome is important as it guides antifungal treatment choice and duration; cryptococcosis syndromes are divided into CNS, disseminated disease, isolated pulmonary disease, or direct skin inoculation (figure 1)
- Liposomal amphotericin B 3–4 mg/kg daily and flucytosine 25 mg/kg four times a day is the most optimal induction therapy option for cryptococcal meningitis, disseminated cryptococcosis, and severe isolated pulmonary cryptococcosis in high-income settings
- In low-income settings, patients with HIV-associated cryptococcal meningitis are best treated with liposomal amphotericin B 10 mg/kg as a single-dose, with 14 days of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily as induction therapy; this induction therapy has not been trialled in non-HIV-associated cryptococcal meningitis or other non-CNS cryptococcosis syndromes
- Optimise outcomes by providing the most effective antifungal therapy while preventing, monitoring, and managing potential toxicity; do not stop or switch to an inferior regimen too early or unnecessarily
- Expect and monitor for clinical relapse and investigate thoroughly for causality; review adherence to antifungal therapy and consider drug–drug interactions; during treatment follow-up, do not escalate antifungal therapy for persistent blood antigenemia (blood cryptococcal antigen), persistently positive CSF cryptococcal antigen, visible cryptococci in CSF (without culture positivity), or abnormal CSF microscopy or biochemistry, as they are not necessarily indicators of microbiological failure
- Adapt and adopt these ECMM global guidelines to suit local practices, while constantly advocating for better antifungal access, scrutinising new trial data, and reviewing local data to improve patient outcomes

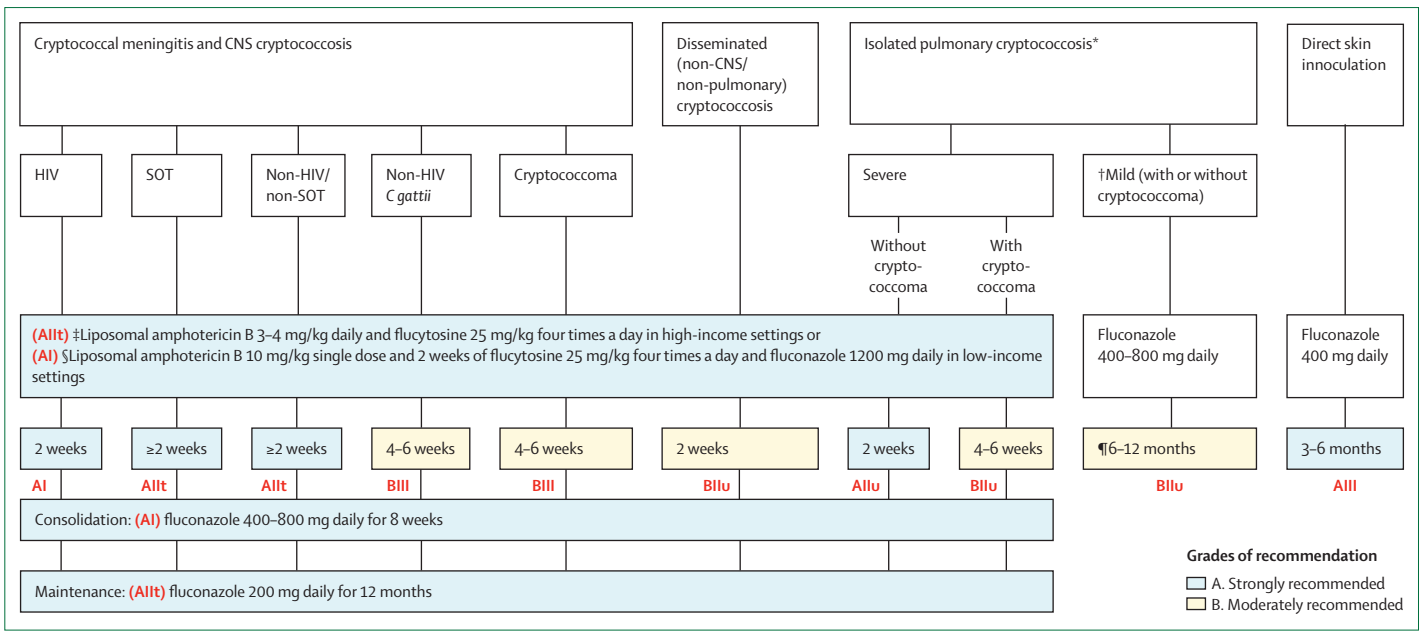

Figure 1: **Recommended first-line antifungal therapy by cryptococcosis syndrome**
Grading of recommendation and level of evidence in bolded red letters. Recommendation grading by shading: blue (strongly recommended; A) and yellow (moderately recommend; B). SOT=solid organ transplantation. *C gattii*=*Cryptococcal gattii*. w=weeks. *Isolated *Cryptococcal neoformans* or *Cryptococcal gattii* pulmonary cryptococcosis, mild is defined as asymptomatic or mildly symptomatic patients or with a solitary small nodule (<2 cm); whereas severe is defined as multiple lesions, large lesions (≥2 cm), lobar consolidation, cavitation, multi-lobar involvement, or hypoxaemic. †If the presence of *Cryptococcus* spp in respiratory specimens is deemed to be airway colonisation after careful evaluation and no treatment is elected, regular follow-up is recommended, especially in the setting of future immunosuppression. ‡Strongly preferred in cryptococcal meningitis and CNS cryptococcosis in SOT and non-HIV non-SOT patient populations, disseminated cryptococcosis, and severe pulmonary cryptococcosis. ‡Has not been directly compared against §. §Has only been trialled in people with cryptococcal meningitis and there are no supporting data of its use in SOT or non-HIV non-SOT patients or in other cryptococcosis syndromes. ¶Can consider a shorter duration (eg, 3 months) in immunocompetent individuals with mild isolated pulmonary cryptococcosis.

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treatment plans for the individual patient. See the appendix for more detailed text, tables, and panels relevant to each section. A summary of the first-line treatment for the different cryptococcosis syndromes is in figure 1.[3] An explanation of the evidence grading system used for the recommendations throughout is in panel 1.

Populations at high risk, clinical presentations, and outcomes

Primarily acquired via inhalation but occurring mainly upon reactivation after a period of latency, cryptococcosis has protean manifestations, with cryptococcal meningitis being the most common severe presentation. Pulmonary cryptococcosis is underdiagnosed and often subclinical. Disseminated cryptococcosis can involve any organ of the body, thus a thorough clinical assessment is required, even in individuals who appear asymptomatic.[24,25] Although classic patient populations at high risk include people living with HIV and solid organ transplant (SOT) recipients, individuals with other immunosuppressive conditions or receiving immunosuppressant drugs and people putatively immunocompetent are also affected by cryptococcosis (appendix pp 6, 79). Those who survive cryptococcosis report substantial morbidity, ranging from 10–70% depending on the disease syndrome and severity, underlying predisposing conditions of the host, and the health-care system in which the patient is managed[26–29] (panel 2; appendix pp 8, 39).

Yeasts causing cryptococcosis and diagnostic methods

C neoformans species complex is the predominant causative agent of cryptococcosis in people living with HIV, and *Cryptococcus gattii* species complex more commonly causes disease in people who appear immunocompetent. Although both can cause a similarly broad range of cryptococcosis syndromes, *C neoformans* has a predilection for CNS disease and *C gattii* is more often associated with pulmonary disease and large cryptococcomas.[30–32]

Diagnostic methods used to establish the diagnosis, extent, severity, and prognosis of cryptococcosis are constantly evolving (appendix pp 10, 41). Microscopy and culture of cerebrospinal fluid (CSF) pellet after centrifugation and blood culture, accompanied by CSF and blood (ie, serum, plasma, or whole blood) cryptococcal antigen testing (most commonly by lateral flow assay) and radiological studies, are central to the diagnosis of cryptococcosis (panel 3; appendix pp 10, 35, 41).[33,34]

Screening, primary prophylaxis, and pre-emptive therapy

Supportive evidence for cryptococcal screening is limited to people living with HIV and depends on blood cryptococcal antigen by lateral flow assay (panel 4; appendix p 49).

Panel 1: Grade of recommendation and level of evidence

This guideline follows the structure and definitions of previous European Confederation of Medical Mycology guidelines on invasive fungal infections,[22,23] which are in accordance with the Grading of Recommendations Assessment, Development and Evaluation and Appraisal of Guidelines for Research & Evaluation systems, as previously described. Strength of recommendation and quality of evidence are provided.

Grade of recommendation

- A: the guideline group strongly supports a recommendation for use
- B: the guideline group moderately supports a recommendation for use
- C: the guideline group marginally supports a recommendation for use
- D: the guideline group supports a recommendation against use

Level of evidence

- I: evidence from at least one well-designed randomised controlled trial (RCT)
- II: evidence from at least one well-designed clinical trial, without randomisation; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from results of uncontrolled experiments
- III: evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

Added index for source of level II evidence

- r: meta-analysis or systematic review of RCT
- t: transferred evidence (ie, results from different patient cohorts or similar immune-status situations)
- h: historical control as control group
- u: uncontrolled trials
- a: for published abstract presented at an international symposium or meeting

Panel 2: Recommendations for populations at high risk, clinical presentations, and outcomes

- (AIII) Cryptococcosis should be considered in any patient presenting with compatible symptoms or microbiology, regardless of their immune status.
- (AIII) Among patients without known predisposition to cryptococcosis, exclusion of an underlying immunodeficiency (eg, performing HIV serology and CD4 T-cell count) is recommended

Panel 3: Recommendations for yeast causing cryptococcosis and diagnostic methods

(AIIt) All patients with suspected or confirmed cryptococcosis (including cryptococcal antigenemia) require clinical assessment for CNS, pulmonary, and other body site involvement.

Investigations for disseminated disease should include:

- Lumbar puncture with measurement of CSF opening pressure, glucose, protein, cell counts, microscopy, and culture and quantification of CSF cryptococcal antigen
- Quantification of blood cryptococcal antigen and cultures of blood, sputum (or other respiratory specimens), or other affected sites
- Brain imaging (preferably MRI) and chest imaging (preferably CT)

HIV-associated cryptococcal meningitis

Induction therapy

Multiple studies support the successful combination of amphotericin B plus flucytosine as the induction treatment of choice in HIV-associated cryptococcal meningitis. First trialled by van der Horst and colleagues, the addition of flucytosine to amphotericin B showed a trend towards improved CSF sterility at 2 weeks and reduced frequency of relapse.[35] In a subsequent trial, this combination cleared cryptococci (measured as early fungicidal activity [EFA]) more rapidly than either amphotericin B alone or amphotericin B plus fluconazole.[5] Importantly, the combination of amphotericin B 1 mg/kg daily plus flucytosine 25 mg/kg four times a day showed a survival advantage at day 70, compared with amphotericin B alone in the treatment of cryptococcal meningitis.[2] The nephroprotection of liposomal amphotericin B compared with amphotericin B is long recognised and the accessibility of liposomal amphotericin B in high-income settings led to the establishment of liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day for 2 weeks as the standard.

In low-income settings, challenges with antifungal access, adverse effects, and difficulty of monitoring and safely managing 2 weeks of amphotericin B induction treatment led to phase 2 studies exploring alternative regimens. Fluconazole monotherapy, even at doses up to 1200 mg daily, was associated with approximately 50% mortality at 10 weeks and up to 75% mortality at 1 year.[36–38] An oral combination of fluconazole 1200 mg daily plus flucytosine 25 mg/kg four times a day was associated with a significant improvement in EFA compared with fluconazole alone.[39] The addition of a short, 5–7 day course of amphotericin B at 1 mg/kg daily to oral fluconazole or combined oral fluconazole and flucytosine showed improved rates of cryptococcal clearance,[40,41] similar to rates observed with 14 days of amphotericin B.

In the phase 3 ACTA trial conducted in centres in Africa the oral combination of fluconazole 1200 mg daily and flucytosine 25 mg/kg four times a day for 2 weeks was compared with 1 week of amphotericin B 1 mg/kg daily and 2 weeks of amphotericin B 1 mg/kg daily as induction therapy, with the amphotericin B groups

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***Panel 4*: Recommendations for screening, primary prophylaxis, and pre-emptive therapy**

Adults living with HIV who are antiretroviral therapy (ART)-naive or after a period of ART discontinuation with less than 200 CD4 cells per mm³ must have:

- (AI) A lateral flow assay of blood cryptococcal antigen for the screening of cryptococcosis and the cryptococcal antigen titre should be measured if positive
- (AIIt) All patients with cryptococcal antigenaemia should be carefully assessed and investigated for cryptococcosis and treated as appropriate
- (AIIu) In people living with HIV who have asymptomatic cryptococcal antigenaemia but without clinical cryptococcosis after thorough investigation (including at least a lumbar puncture), fluconazole 1200 mg daily for 2 weeks (when ART can be initiated), followed by fluconazole 800 mg daily for 8 weeks, and 200 mg daily thereafter for 6 months is recommended (guidance might be updated contingent on results of prospective trials)
- (BI) In clinical settings where cryptococcal antigen lateral flow antigen screening is not available (despite WHO's strong recommendations), universal primary prophylaxis with fluconazole 100 mg daily in people living with HIV in high endemic areas with a CD4 count of less than 200 cells per mm³ is recommended

In patients without HIV:

- (DIIu) Routine blood cryptococcal antigen screening, primary prophylaxis, and pre-emptive therapy are not recommended

being further randomly assigned to either fluconazole 1200 mg daily or flucytosine 25 mg/kg four times a day.[7] 1 week of amphotericin B 1 mg/kg daily plus flucytosine followed by fluconazole 1200 mg daily in the second week was the best-performing induction group, with a 24% 10-week mortality rate. This regimen was adopted as the preferred 10-week induction regimen by WHO and southern African guidelines until the AMBITION-cm study.[16,18]

In the AMBITION-cm phase 3 study, which had sites across Africa, a single initial 10 mg/kg dose of liposomal amphotericin B with oral fluconazole 1200 mg daily plus flucytosine 25 mg/kg four times a day for 2 weeks was compared with the WHO recommendation of 1 week of amphotericin B 1 mg/kg daily plus flucytosine followed by 1 week of fluconazole 1200 mg daily.[6] This new regimen met non-inferiority criteria (10-week mortality 24·8% *vs* 28·7%) with similar EFAs and was significantly better tolerated. The WHO guidelines now recommend the AMBITION-cm regimen as the preferred antifungal therapy in people living with HIV and cryptococcal meningitis.[10]

The applicability of the ACTA and AMBITION-cm trials to high-income settings and in non-HIV populations is contentious. The standard regimen is liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day for 2 weeks, which is different to the comparators used in the trials. Retrospective database reviews in the USA showed low rates of acute inpatient mortality from cryptococcal meningitis (10·5% in HIV-cryptococcal meningitis and 13·3% in non-HIV cryptococcal meningitis) and a remarkably low mortality rate at 1 year of 11·6% in the past two decades.[42,43] The reliance on high-dose fluconazole and flucytosine as the basis of induction therapy in the AMBITION-cm study might not be pragmatic in high-income settings, where more comorbidities occur, potential drug–drug interactions need to be carefully considered, and the risk of hepatotoxicity is less tolerated than in low-income settings. In the USA, only a third of patients completed the 14 days of flucytosine.[44] Although some experts support the inclusion of the AMBITION-cm triple regimen as a primary option in high-income settings, other experts call for further comparative trials in high-income settings to assess the regimen's effect in patients with HIV and patients without HIV (in whom no supporting data exist). Regardless of the induction antifungal regimen used, the complications of cryptococcal meningitis, such as increased intracranial pressure, require intense clinical monitoring, and most patients with cryptococcal meningitis require inpatient care for 1–2 weeks or more.

Mycological success, defined as cryptococcocal culture negativity (also termed CSF sterility) has been associated with improved outcomes and reduced clinical relapse.[45] In people living with HIV and cryptococcal meningitis, CSF sterility before ART commencement has been shown to be associated with reduced occurrence of neurological deterioration, microbiological relapse, and cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS).[45] Some treatment guidelines advocate performing a lumbar puncture after 2 weeks of induction therapy (before changing to consolidation therapy) to assess CSF culture sterility as a marker of successful induction.[11,15,18,20] Other guidelines—particularly those focused on low-income settings—do not.[10,16]

Consolidation and maintenance therapy

There have been no trials of consolidation and maintenance therapy in cryptococcal meningitis within the past two decades. Two early studies established 400 mg daily fluconazole for consolidation therapy.[35,46] With the accumulation of safety data of a 800 mg fluconazole daily dose and evidence of a fluconazole dose-response effect,[36,47] this regimen is the preferred consolidation dose in low-income settings, where suboptimal antifungal regimens are used.[16,18] A gradual rise in median fluconazole minimum inhibitory concentrations (MICs) in cryptococcal isolates collected

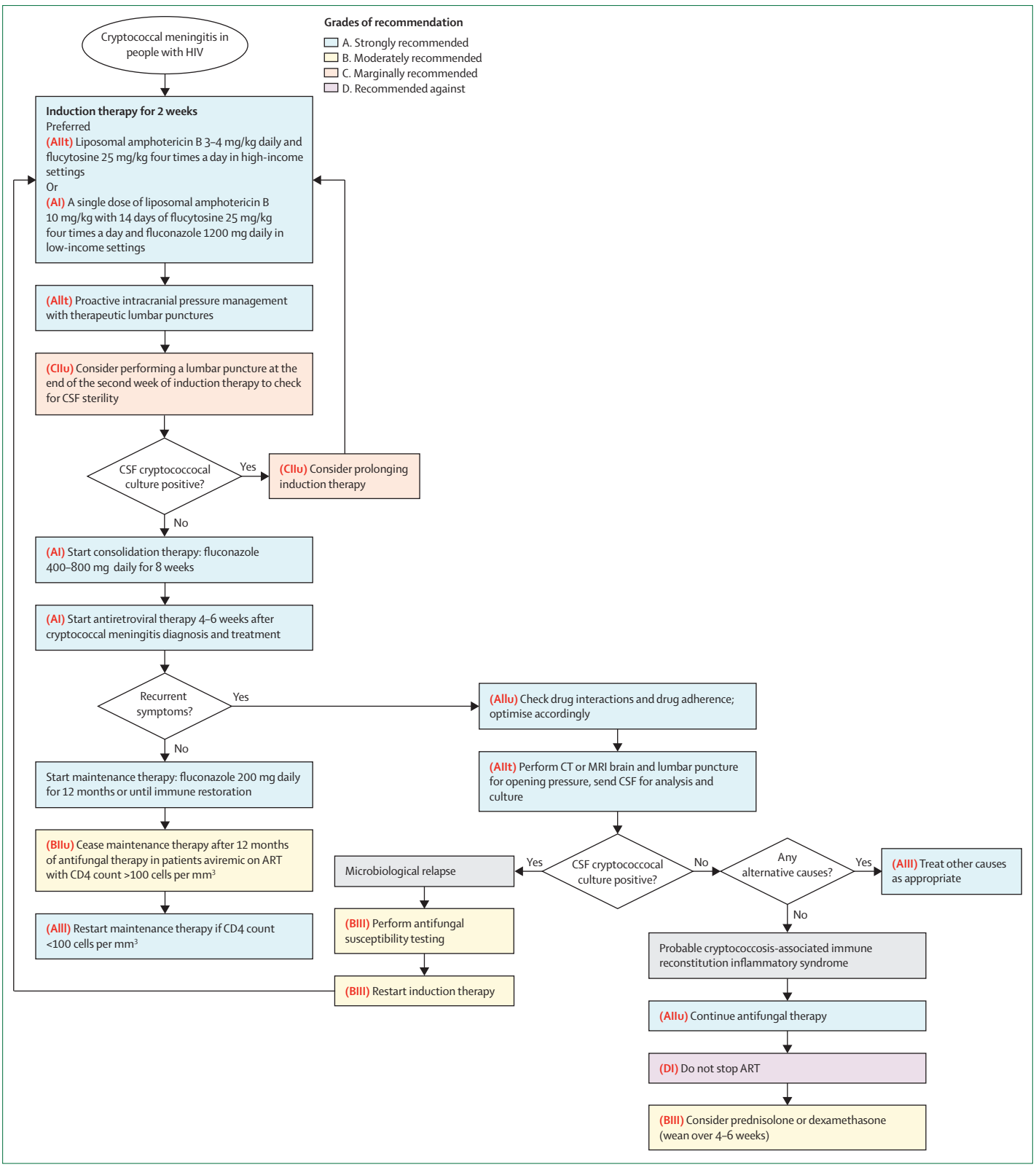

Figure 2: **Management algorithm for cryptococcal meningitis and cryptococcal meningoencephalitis in people with HIV**
ART=antiretroviral therapy. CSF=cerebrospinal fluid.

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Panel 5: Ten principles of cryptococcal meningitis management

The key principles in cryptococcal meningitis management are best read in context (see relevant sections in main text). Although most evidence and recommendations are derived from cryptococcal meningitis in people living with HIV, many of these principles are translatable to non-HIV settings.

1) Selectively screen, risk-stratify, and investigate for cryptococcosis

This principle is specific to people with HIV and cryptococcal meningitis (panel 4).

2) Provide best fungicidal induction regimen possible

- (AIIt) Liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day for 2 weeks (preferred in high-income settings and strongly recommended in SOT and non-HIV non-SOT settings); or (AI) a single dose of liposomal amphotericin B 10 mg/kg with 14 days of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily (note: only trialled in people living with HIV in low-income settings).
- (CIIu) Consider performing a lumbar puncture at the end of the first or second week of induction therapy to check for CSF sterility before ART commencement.
- (CIIu) Consider prolonging induction therapy if CSF is persistently culture positive at 2 weeks.
- (BIII) In *Cryptococcus gattii* CNS infection occurring in non-HIV patients or CNS cryptococcoma consider extending induction therapy to 4–6 weeks.

3) Monitor for and minimise drug toxic effects

- (AIIu) In-hospital care for the first 1–2 weeks is encouraged to manage the major early complications seen with cryptococcal meningitis management.
- (AIIu) The use of amphotericin B and liposomal amphotericin B should be accompanied by pre-hydration and aggressive potassium and magnesium replacement therapy.
- (AIIu) Frequent (at least every alternate day) complete blood counts, renal function tests, and electrolyte measurements are recommended to assess for therapy-related nephrotoxicity and bone marrow, fluid, and electrolyte changes. Liver function tests at baseline and at least weekly are recommended.
- See appendix pp 16, 30.

4) Manage raised intracranial pressure

- (AIIu) Opening pressure should be measured at every lumbar puncture in patients with cryptococcal meningitis.
- (AIIt) Acute symptomatic elevation of the intracranial pressure (≥20 cm of CSF) should be managed by daily therapeutic lumbar punctures (ie, removal of sufficient CSF, usually around 20–30 mL) to reduce the pressure to 50% of opening pressure or to a normal pressure of ≤20 cm of CSF (documented as a closing pressure).
- (BIIu) Perform a scheduled therapeutic lumbar puncture 48–72 h after initial lumbar puncture or 7 days, regardless of initial opening pressure.
- (AIIt) Persistent raised symptomatic intracranial pressure despite therapeutic lumbar punctures should be managed by surgical decompression via temporary lumbar drainage, shunting, or ventriculostomy, depending on local expertise and resources.

5) Look for an underlying immunosuppressive state

Exploring for an immunosuppressive state—particularly, but not limited to, HIV infection—is important in the management of cryptococcosis.

- (AIII) Among patients without known predisposition to cryptococcosis, exclusion of an underlying immunodeficiency (including performing HIV serology and CD4 T-cell count) is recommended in all patients with cryptococcosis.
- (BIII) Individuals without a known risk factor for disseminated cryptococcosis, particularly those with a history of other atypical fungal, mycobacterial, or bacterial infections, should be considered for evaluation of an undiagnosed immunodeficiency, preferably in consultation with a clinical immunologist (appendix pp 6, 79).

6) Provide and ensure adherence to consolidation and maintenance therapy

- Consolidation (8 weeks): (AI) Fluconazole 400–800 mg daily. 800 mg is preferred in low-income settings.
- Maintenance (12 months or until immune restoration): (AIIt) Fluconazole 200 mg daily.
- (AIIu) Check for drug–drug interactions and adjust the dose as necessary.
- (AIII) Close therapeutic drug monitoring of tacrolimus, cyclosporine, and sirolimus levels and dose reduction of these agents are recommended when azoles are co-administered.[73,74]

7) Optimal commencement of ART in people with HIV

This principle is specific to people with HIV and cryptococcal meningitis.

- (DI) Immediate or very early commencement of ART is not recommended.
- If there is inadequate access to antifungal induction therapy, (AI) delay ART for 4–6 weeks.
- If there is adequate access to antifungal induction therapy, (BIIu) consider further individualisation, taking into consideration resolution of symptoms and signs of cryptococcal meningitis and intracranial pressure (including normalisation of opening pressure), attainment of CSF cryptococcal sterility, successful identification and management of concurrent co-infections and other AIDS-defining illnesses, the patient's readiness for ART, and

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(Panel 5 continued from previous page)

local experience of cryptococcal meningitis and cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS) management (usual range is 4–6 weeks).

8) Monitor for clinical relapse and investigate causality

- (AIIt) Investigate thoroughly for causality (ie, CNS and non-CNS and infective and non-infective) in cases of apparent clinical relapse. Investigations should include CT or MRI of the brain, lumbar puncture for opening pressure, and CSF analyses including microscopy and culture.
- (AIIu) Review adherence to antifungal therapy, ART, immunosuppressants, and other medications and consider drug–drug interactions. Perform therapeutic drug monitoring if applicable. Optimise control of underlying diseases.
- (DIIu) The use of follow-up blood or CSF cryptococcal antigen (including monitoring of titres) for clinical decision making is discouraged.
- (DIIu) Do not escalate antifungal therapy for persistent blood antigenemia, persistently positive CSF cryptococcal antigen, visible cryptococci in CSF (without culture positivity), or abnormal CSF microscopy or biochemistry. These are not necessarily indicators of microbiological failure.

9) Evaluate for drug adherence, drug–drug interactions, and drug resistance

This principle is specific to people with culture-positive (microbiological) persistence or relapse.

- (BIII) Antifungal susceptibility testing should be done concurrently on all initial and relapse isolates (if stored and available). An increase in fluconazole minimum inhibitory concentration of >2 dilutions is concerning for the potential development of drug resistance.
- (BIII) Consider recommencing induction therapy with a more optimal regimen that is guided by antifungal susceptibility testing.

10) Carefully exclude alternative diagnoses before attributing clinical relapse to C-IRIS

- (AIIt) For patients with suspected paradoxical C-IRIS, carefully exclude recurrent cryptococcal disease or new infective or non-infective conditions before attributing symptoms and signs to C-IRIS. Perform a brain MRI and lumbar puncture to measure opening pressure and get CSF for microbiological, cellular, and biochemical analyses.
- (AIIu) Treatment of C-IRIS should include therapeutic lumbar puncture and symptomatic therapy, such as analgesia, antiemetics, and antiepileptics if appropriate.
- (AIII) Continue antifungal therapy.
- (BIII) High-dose prednisolone or prednisone (usually 0·5–1·0 mg/kg daily) or dexamethasone (usually 0·2–0·3 mg/kg daily), weaned over 4–6 weeks can be considered in those with persistent symptoms who are unresponsive to therapeutic lumbar punctures. Rarely, a second steroid course with taper is needed.
- (DIII) Do not stop ART.

during initial cryptococcal meningitis presentation have been reported in South Africa and Uganda.[48,49] Although this evidence could lend support for a higher consolidation dose of 800 mg daily of fluconazole in these settings, whether this regimen is required across all patient groups and settings is contentious. Widespread fluconazole use could also perpetuate further rises in MICs.

Maintenance therapy with fluconazole 200 mg daily has been shown to be highly effective at preventing relapse, superior to weekly amphotericin B and itraconazole capsules.[50–52] Rarely, triazoles, such as voriconazole,[53–60] posaconazole,[61–63] or isavuconazole,[64,65] are used as alternatives to fluconazole due to concerns of fluconazole resistance, drug toxicity, or drug–drug interactions. Notably, none of the newer triazoles have been formally trialled in cryptococcosis and none are readily available in low-income settings (appendix p 30).

A low incidence of cryptococcal meningitis relapse is observed after a minimum of 1 year of antifungal therapy in people living with HIV established on ART, who are virologically suppressed or have a CD4 count more than 100 cells/mm³.[66–72]

A management algorithm is described in figure 2 and key principles are discussed in panel 5. Recommendations for cryptococcal meningitis treatment in people living with HIV are based on the availability of antifungal drugs. Preferred and alternative strategies are offered in (figure 3 and figure 4A.

Adjunctive therapy

In the past decade, trials of adjunctive treatment in HIV-associated cryptococcal meningitis have all been shown to be ineffective, and in some cases harmful. These include high-dose dexamethasone,[75] sertraline,[76,77] and tamoxifen.[78] The debate regarding adjunctive exogenous interferon(IFN)-γ is unresolved. IFN-γ has been studied in two randomised trials of HIV-associated cryptococcal meningitis, which suggested faster clearance of yeasts in the CSF,[79,80] but further studies are needed. There is no trial evidence supporting its use in non-HIV-associated cryptococcal meningitis (appendix p 65).

Cryptococcal meningitis in SOT recipients

Cryptococcosis is the third most common invasive fungal infection in SOT recipients, with an incidence of 4·5–33·8%[26,28,29] and causing considerable mortality.[12] SOT recipients encompass a third of non-HIV-related cryptococcosis in the USA.[81] The majority of cryptococcosis

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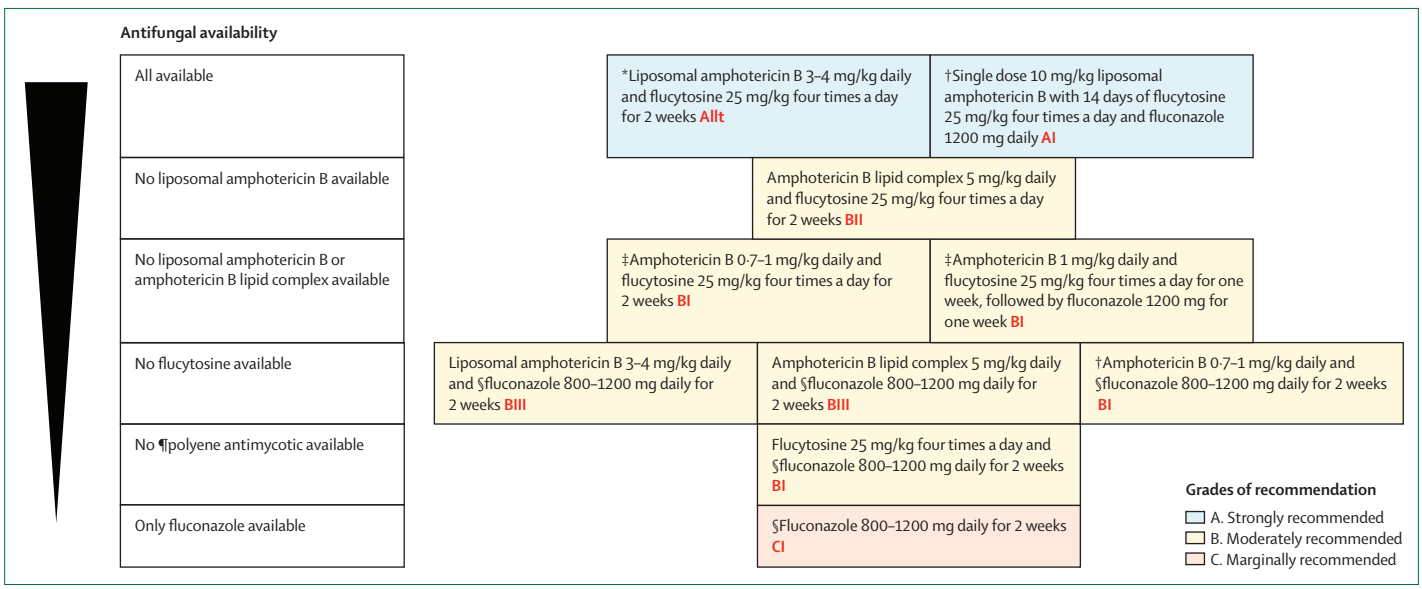

Figure 3: **HIV-cryptococcal meningitis antifungal induction treatment recommendations by antifungal drug availability**
Grading of recommendation and level of evidence in bolded red letters. *Has not been compared with †. †Has only been trialled in HIV-cryptococcal meningitis. ‡Amphotericin B: 1 mg/kg showed earlier fungicidal activity than 0·7 mg/kg, but some institutions use the low dose due to toxicity concerns. §Fluconazole induction doses of up to 1200 mg daily have been trialled but caution is advised; consider drug–drug interaction and liver toxicity. ¶Polyene antimycotic includes amphotericin B formulations such as conventional deoxycholate amphotericin B, liposomal amphotericin B, and amphotericin B lipid complex.

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in SOT occurs late (ie, months or years after transplantation) and is due to reactivated disease; however, acute donor-derived infections have been described.[14,82,83]

Anti-rejection drugs vary in their degree of immunosuppression and heart and small bowel transplant recipients are at the highest cryptococcal meningitis risk.[84] CNS and pulmonary cryptococcosis dominate but unusual manifestations, including cutaneous disease[85,86] and pericarditis,[87] have been reported. Notably, blood cryptococcal antigen can be negative in SOT recipients with cryptococcosis, particularly those with single pulmonary nodules or in lung transplant recipients.[88]

There are no randomised treatment trials targeted specifically at SOT recipients; hence, recommendations are extrapolated from evidence in people living with HIV. The use of lipid-formulations in SOT recipients with CNS cryptococcosis was independently associated with reduced mortality compared with amphotericin B.[89] The AMBITION-cm regimen has not been studied in non-HIV patients, and the evidence for high dose fluconazole (with the ensuant potential toxicity and drug–drug interactions) in this group is absent. A precipitous reduction in dosing of immunosuppressants, particularly calcineurin inhibitors, can lead to C-IRIS.[90] Figure 4B contains recommendations for treatment in SOT recipients (appendix p 62).

Cryptococcal meningitis in people without HIV or SOT

The group of people without HIV or SOT is heterogeneous, ranging from apparently healthy people to those with haematological malignancies or liver cirrhosis. There is no single therapeutic regimen or duration that meets all patients' needs, but the therapeutic principles mirror cryptococcal meningitis treatment in high-income settings, with liposomal amphotericin B 3–4 mg/kg daily and flucytosine 25 mg/kg four times a day as induction therapy. Induction therapy can be extended in those with persistently positive CSF cultures or persistent symptoms at 2 weeks. In 2022, the combination of liposomal amphotericin B and flucytosine was shown to have a low acute mortality of 6% in a nationwide observational study of non-HIV-associated cryptococcal meningitis in Japan.[91] Figure 4B contains recommendations for treatment in people without HIV or SOT (appendix pp 18, 62).

Pulmonary cryptococcosis

There are no randomised treatment studies in pulmonary cryptococcosis. Case series and clinical knowledge suggest that for patients with cryptococcaemia and evidence of CNS involvement, those with blood cryptococcal antigen titres more than 1:512 by latex agglutination (or ten-fold higher by lateral flow assay),[92] or severe pulmonary disease should be treated as cryptococcal meningitis.[33,35,93,94] Patients with mild isolated pulmonary disease without cryptococcoma have been successfully treated with fluconazole monotherapy of

Figure 4: **Antifungal treatment recommendations for cryptococcal meningitis**
(A) Recommendations for people with HIV. (B) Recommendations for SOT recipients and patients without HIV or SOT. SOT=solid organ transplant. CSF=cerebrospinal fluid. TDM=therapeutic drug monitoring.

A People with HIV

First-line therapies

Induction (2 weeks)
(AIIt) Liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day (preferred in high-income settings); or
(AI) Single dose liposomal amphotericin B 10 mg/kg and 14 days of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily (recommended in low-income settings)

→

Consolidation (8 weeks)
(AI) Fluconazole 400–800 mg daily (800 mg preferred in low-income settings)

→

Maintenance (12 months or until immune restoration)
(AIIt) Fluconazole 200 mg daily

Alternative therapies

If liposomal amphotericin B is not available:
(BIIt) Amphotericin B lipid complex 5 mg/kg daily plus flucytosine 25 mg/kg four times a day

If liposomal amphotericin B and amphotericin B lipid complex are not available:
(BI) Amphotericin B 0·7–1·0 mg/kg daily plus flucytosine 25 mg/kg four times a day; or
(BI) Amphotericin B 1 mg/kg daily and 5-flucytosine 25 mg/kg four times a day for 1 week, followed by fluconazole 1200 mg daily for 1 week

If flucytosine is not available:
(BIII) Liposomal amphotericin B 3–4 mg/kg daily plus fluconazole 800–1200 mg daily;
(BIII) Amphotericin B lipid complex 5 mg/kg daily plus fluconazole 800–1200 mg daily; or
(BI) Amphotericin B 0·7–1 mg/kg daily plus fluconazole 800–1200 mg daily

If amphotericin B-based therapies are not available:
(BI) Flucytosine 25 mg/kg four times a day and fluconazole 800–1200 mg daily

If only fluconazole is available:
(CI) Fluconazole 800–1200 mg daily

(BIII) Voriconazole 200 mg twice a day (with TDM)

(BIII) Posaconazole 300 mg daily (with TDM)

(BIII) Isavuconazole 200 mg daily

(CIIt) Itraconazole 200 mg twice a day (with TDM)

Comments:
- **(AIIu)** Opening pressure should be measured at every lumbar puncture in patients with cryptococcal meningitis
- **(AIIu)** The use of amphotericin B and liposomal amphotericin B should be accompanied by pre-hydration and aggressive potassium and magnesium replacement therapy
- **(AIIu)** In-hospital care for the first 1–2 weeks is encouraged to manage the early complications of cryptococcal meningitis therapy
- **(BIII)** Monitoring of flucytosine drug concentration is recommended, where available and if timely; particularly with renal dysfunction
- **(AIIu)** Check for drug–drug interactions and adjust doses as necessary
- **(CIIu)** Consider performing a lumbar puncture at the end of the first or second week of induction therapy to check for CSF sterility before antiretroviral therapy (ART) commencement
- **(CIIu)** Consider prolonging induction therapy if CSF is persistently culture positive at 2 weeks
- **(CIIt)** Adjunctive recombinant interferon-γ might be considered for persistently positive CSF yeast cultures in people with HIV-associated cryptococcal meningitis who have evidence of poor inflammatory responses or persistently positive cryptococcal CSF culture after prolonged antifungal therapy
- **(DI)** The routine use of high-dose dexamethasone in cryptococcal meningitis is not recommended
- **(CIII)** A short course of dexamethasone can be considered for specific indications such as symptomatic space-occupying lesions in the CNS with surrounding oedema or mass effect and cerebral vasculitis
- **(BIIu)** Cease maintenance therapy after 12 months of antifungal therapy in patients aviraemic on ART with a CD4 count more than 100 cells per mm^3
- **(AIII)** Restart maintenance therapy if CD4 count drops to less than 100 cells per mm^3

B SOT recipients and people without HIV or SOT

First-line therapies

Induction (minimum 2 weeks)
(AIIt) Liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day

→

Consolidation (8 weeks)
(AIIt) Fluconazole 400–800 mg daily

→

Maintenance (12 months)
(AIIt) Fluconazole 200 mg daily

Alternative therapies

If liposomal amphotericin B is not available:
(BIIt) Amphotericin B lipid complex 5 mg/kg daily plus flucytosine 25 mg/kg four times a day

If liposomal amphotericin B and amphotericin B lipid complex are not available:
(BIIt) Amphotericin B 0·7–1·0 mg/kg daily plus flucytosine 25 mg/kg four times a day

If amphotericin B-based therapies are not able to be used:
(CIIt) flucytosine 25 mg/kg four times a day plus fluconazole 800–1200 mg daily

(BIII) Voriconazole 200 mg twice a day (with TDM)

(BIII) Posaconazole 300 mg daily (with TDM)

(BIII) Isavuconazole 200 mg daily

(CIIt) Itraconazole 200 mg twice a day (with TDM)

Comments:
- Recommendations in HIV patient population are also applicable
- **(AIII)** Induction therapy with liposomal amphotericin B and flucytosine should be considered for any disseminated disease or isolation from a sterile site (even in the absence of CNS manifestations)
- **(AIII)** Close monitoring of tacrolimus, cyclosporine, and sirolimus concentrations (TDM) and dose reduction of these agents are recommended when azoles are co-administered[73,74]
- **(BIII)** Immunosuppressant doses need to be carefully adjusted to allow effective killing of yeasts but should be reduced slowly to avoid precipitating cryptococcosis-associated immune reconstitution inflammatory syndrome; consider a sequential or stepwise reduction of immunosuppressants with careful lowering of corticosteroids early and eliminating mycophenolate before considering reduction of the calcineurin inhibitors because of their direct anticryptococcal activity
- **(CIII)** In a patient treated for cryptococcosis, retransplantation or a new organ transplant can be considered, provided viable yeasts have been cleared from CSF and the patient is asymptomatic after receiving 12 months of anticryptococcal treatment

Grades of recommendation
- A. Strongly recommended
- B. Moderately recommended
- C. Marginally recommended

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See Online for appendix

***Panel 6:* Recommendations for pulmonary cryptococcosis**

- Stratify treatment by disease severity and presence of pulmonary cryptococcoma (appendix pp 22, 67, 84)
- Isolated pulmonary cryptococcosis in immunocompetent or immunocompromised host:
  - (AIIu) Severe disease: as for CNS disease
  - (BIIu) Mild disease: fluconazole 400 mg daily for 6–12 months (range guided by symptom resolution)
- Pulmonary cryptococcosis with CNS manifestations or other evidence of dissemination (eg, cryptococcaemia or skin lesions)
  - (AIIt) as for CNS disease
- (AIII) If the presence of *Cryptococcus* spp in respiratory specimen is deemed as airway colonisation after careful evaluation and no treatment is elected, regular follow-up is recommended, especially in the setting of future immunosuppression
- Pulmonary cryptococcoma (see cryptococcoma section)

***Panel 7:* Recommendations for non-pulmonary non-CNS disease**

- (AIIu) The recommendation for cryptococcaemia is to treat the same as for CNS disease
- (AIII) The recommendation for primary cutaneous (skin) cryptococcosis, attributed to direct inoculation without evidence of dissemination, is fluconazole 400 mg daily for 3–6 months or until healed
- (BIIu) For all other non-CNS non-pulmonary disseminated disease treat the same as CNS disease
- (BIIu) Cryptococcal eye disease should be managed in collaboration with an ophthalmologist

400 mg daily.[93,95,96] Some clinicians consider watchful-waiting and elect not to treat asymptomatic immunocompetent people who incidentally culture any *Cryptococcus* spp in their sputum and have no radiological features of pulmonary cryptococcosis, as they consider this presentation to be airway colonisation.[97] Criteria for distinguishing colonisation from infection is uncertain (panel 6; appendix pp 22, 67).

Non-pulmonary non-CNS disease

Cryptococcosis can affect any organ following haematogenous dissemination. Clinical presentation of non-CNS non-pulmonary disease without fungaemia is rare, but possible. The absence of documented fungaemia does not exclude dissemination. Barring direct inoculation into the skin following trauma, extrapulmonary disease is by definition disseminated disease and generally requires consideration for aggressive induction therapy. There are no clinical treatment trials for non-pulmonary non-CNS cryptococcosis.

Importantly, visual changes noted in cryptococcal meningitis are frequently related to raised intracranial pressure and do not necessarily indicate direct eye involvement. Ocular cryptococcosis can occur[98,99] but is unusual and requires formal ophthalmological documentation and management. Isolated skeletal osteomyelitis is rare and often requires a combined surgical and medical approach.[100–102] Skin lesions might be polymorphic (panel 7; appendix p 67).

Specific management issues

Raised intracranial pressure

Increased intracranial pressure has been associated with a high burden of cryptococci, leading to both acute and chronic symptoms and signs (eg, visual and hearing loss) and decreased short-term survival. Clinical experience has shown that CSF outflow obstruction can be improved by removal of CSF; observational studies suggested that scheduled therapeutic lumbar punctures result in substantial improvement in survival, regardless of opening pressure.[103,104] For prolonged control of acute increased intracranial pressure, use of lumbar drains in cases without hydrocephaly or ventriculostomies in cases with hydrocephaly might be required.[105–107] Medical therapies including acetazolamide, mannitol, and corticosteroids can be detrimental (panel 8; appendix p 79).[108,109]

Timing of ART commencement

The optimal time to commence ART for HIV infection during cryptococcosis is controversial. Four randomised trials[3,110–112] to find out the optimal timing of ART initiation in HIV-cryptococcal meningitis co-infection have been done in low-income settings, using induction regimens that are not currently preferred, including fluconazole (800 mg daily) monotherapy,[110] amphotericin B 0·7 mg/kg daily,[111] and amphotericin B 0·7–1 mg/kg daily and fluconazole 800 mg daily for 2 weeks. These data seem to suggest that initiating ART within 2 weeks of cryptococcal meningitis presentation is too early in the setting of suboptimal antifungal therapy, and that delaying ART initiation for 4–6 weeks reduces the incidence of C-IRIS and death. CSF sterility before ART commencement might be another factor.[45] A retrospective analysis of combined cohorts in high-income settings did not show higher mortality in those receiving early ART in the first two weeks of antifungal therapy compared with those with delayed therapy.[113] Early ART in high-income settings will need careful justification and close monitoring; further randomised studies might be helpful.[114]

There are no studies for timing ART initiation in other forms of cryptococcosis, those with cryptococcal antigenemia, or those recommencing ART after a period of interruption. Early concerns that potent integrase inhibitors pose an increased risk of C-IRIS have been disproven.[115] Whether those presenting with cryptococcal meningitis within 2 weeks of starting ART require withholding of ART is uncertain (panel 9; appendix p 70).[116–118]

Panel 8: Recommendations for raised intracranial pressure

- (AIIu) Opening pressure should be measured at every lumbar puncture in patients with cryptococcal meningitis
- (AIII) A brain CT should be done (if CNS imaging not already done) to exclude CNS outflow obstruction
- (AIIt) Acute symptomatic elevation of the intracranial pressure (≥20 cm of CSF) should be managed by daily therapeutic lumbar punctures (ie, removal of sufficient CSF, usually around 20–30 mL), to reduce the pressure to 50% of opening pressure or to a normal pressure of ≤20 cm of CSF (documented as a closing pressure)
- (BIIu) Perform a scheduled therapeutic lumbar puncture 48–72 h after initial lumbar puncture or 7 days, regardless of initial opening pressure
- (AIIt) Persistent raised symptomatic intracranial pressure, despite therapeutic lumbar punctures, should be managed by surgical decompression via temporary lumbar drainage, shunting, or ventriculostomy, depending on local expertise and resources
- (BIII) Consider ventriculoperitoneal (preferential) and lumboperitoneal shunts (alternative) to control both acute and chronic hydrocephalus if temporary measures are not successful. Ideally, insert shunts after institution of effective antifungal therapy

Panel 9: Recommendations for the timing of ART commencement

- (DI) Immediate or very early commencement of ART is not recommended.
- (AI) If suboptimal antifungal induction therapy is used, delay ART for 4–6 weeks.
- (BIIu) If optimal antifungal induction therapy was used, consider further individualisation, taking into consideration resolution of symptoms and signs of cryptococcal meningitis, intracranial pressure (including normalisation of opening pressure), attainment of CSF cryptococcal sterility, successful identification, management of concurrent co-infections and other AIDS-defining illnesses, the patient's readiness for ART, and local experience of cryptococcal meningitis and C-IRIS management (usual range is 4–6 weeks).
- (CIIt) If possible, ensure CSF is cryptococcal culture negative before ART commencement.
- (BIII) For people who have had ART who develop cryptococcal meningitis and might need to switch to second-line ART or recommence ART, a delay of 4–6 weeks is recommended.
- (CIII) Pending further studies, consider withholding ART and restarting at 4–6 weeks in those presenting with cryptococcal meningitis within 2 weeks of starting ART.
- (BIII) Patients with isolated pulmonary cryptococcosis or those with asymptomatic cryptococcal antigenemia can commence ART earlier (eg, at 2 weeks).

Panel 10: Recommendations for antifungal resistance

For those with fluconazole resistance or emerging fluconazole resistance:

- (BIII) Consider a long (eg, 4 weeks) course of induction treatment with amphotericin B (1 mg/kg daily) or high dose of liposomal amphotericin B (3–6 mg/kg daily) together with flucytosine
- (BIII) Consider amphotericin B 1 mg/kg weekly or liposomal amphotericin B 3–6 mg/kg weekly as consolidation or maintenance therapy. Consider daily voriconazole, posaconazole, isavuconazole, or itraconazole for isolates without evidence of pan-azole resistance, as guided by antifungal susceptibility testing
- (CIII) If amphotericin B or liposomal amphotericin B are not available, adding flucytosine to high-dose fluconazole (1200 mg daily) could be considered

Resistance to antifungals

Developing secondary resistance to flucytosine is common when given as monotherapy, necessitating its use with a partner drug in cryptococcosis. Acquired resistance to polyenes, such as amphotericin B, is rare, but the emergence of fluconazole resistance is concerning.[48,49,119] Fluconazole monotherapy as induction therapy has been associated with secondary resistance.[120–123]

There are no clinical MIC breakpoints for fluconazole against *Cryptococcus* spp and insufficient data to suggest that high MICs imply worse outcomes. Interpretation of epidemiological cutoff values with the Clinical and Laboratory Standards Institute (CLSI) method for fluconazole requires accurate species identification. The epidemiological cutoff values is 8 ug/mL for *C neoformans* VNI, 16 ug/mL for *C gattii* VGI, and 32 ug/mL for *Cryptococcus deuterogattii* VGII.[124] In principle, a higher than two-fold increase in MIC during treatment could suggest development of resistance and the need for closer clinical monitoring. There are no European Committee on Antimicrobial Susceptibility Testing (EUCAST) epidemiological cutoff values available for fluconazole (panel 10; appendix p 72).

Cryptococcal persistence, clinical relapse, and culture-positive (microbiological) relapse

Distinguishing clinical relapse from persistent cryptococcal infection is challenging. Clinical relapse can be due to a microbiological relapse, C-IRIS, raised intracranial pressure (whether related to C-IRIS or not), or other infective and non-infective (CNS and non-CNS) causes (figure 2). Cryptococcal antigen persists in the CSF and blood, thus it has little clinical utility in distinguishing clinical responders from non-responders.[125] Most cases of culture-positive (microbiological) relapse occur early and result from inadequate or suboptimal induction therapy or early discontinuation of consolidation or maintenance therapy (figure 2; panel 11; appendix p 74).

Panel 11: **Recommendations for cryptococcal persistence, clinical relapse, and culture-positive (microbiological) relapse**

- (AIIt) Think broadly and investigate thoroughly for causality (CNS or non-CNS and infective or non-infective) in cases of apparent clinical relapse; investigations should include brain CT or MRI, lumbar puncture for opening pressure, and CSF analyses, including microscopy and culture
- (AIIu) Review adherence to antifungal therapy, ART, immunosuppressants, and other medications and consider drug–drug interactions; perform therapeutic drug monitoring if applicable. Optimise control of underlying diseases
- (CIII) Consider escalating antifungal therapy while awaiting CSF results (and de-escalate if culture-negative)
- (DIIu) The use of follow-up blood or CSF cryptococcal antigen (including monitoring of titres) for clinical decision making is discouraged
- (DIIu) Do not escalate antifungal therapy for persistent blood antigenemia, persistently positive CSF cryptococcal antigen, visible cryptococci in CSF (without culture positivity), or abnormal CSF microscopy or biochemistry; these are not necessarily indicators of microbiological failure

For culture-positive (microbiological) persistent or relapsed infection (figure 1):

- (BIII) Antifungal susceptibility testing should be done concurrently on all initial and relapse isolates (if stored and available); an increase in fluconazole MIC of more than two dilutions is considered concerning for the potential development of drug resistance
- (BIII) Consider reinduction with a more optimal regimen (guided by antifungal susceptibility testing)

Panel 12: **Recommendations for C-IRIS**

- (AIIt) For patients with suspected paradoxical C-IRIS, carefully exclude recurrent cryptococcal disease or new infective or non-infective conditions before attributing symptoms and signs to C-IRIS; perform a brain MRI and lumbar puncture to measure opening pressure and get CSF for microbiological and biochemical analyses
- (AIIu) Treatment of C-IRIS should include therapeutic lumbar puncture and symptomatic therapy, such as analgesia, antiemetics, and antiepileptics, if appropriate
- (AIII) Continue antifungal therapy
- (BIII) High-dose prednisolone or prednisone (usually 0·5–1·0 mg/kg daily) or dexamethasone (usually 0·2–0·3 mg/kg daily), weaned over 4–6 weeks, can be considered in those with persistent symptoms who are unresponsive to therapeutic lumbar punctures; rarely a second steroid course with taper is needed
- (DIII) Do not stop ART
- (BIII) Cases of steroid-refractory or recurrent C-IRIS should be discussed with experts in the field
- (BIIu) Steroids could be considered for PIIRS

Panel 13: **Recommendations for *C gatti***

In *C gattii* CNS disease:

- (AIII) Treat the same as *C neoformans* CNS infection
- (BIII) In non-HIV patients, consider extending induction therapy to 4–6 weeks
- (AIII) Early CSF shunting is indicated for obstructive chronic hydrocephalus

Treatment of *C gattii* lung disease is summarised in the appendix (p 17).

C-IRIS

C-IRIS has been described in people with HIV usually between 2 weeks and 3 months after commencement of ART. Patients develop exaggerated symptoms and signs or atypical inflammation, reminiscent of a paradoxical recurrence,[126,127] but C-IRIS can also occur in the setting of immune recovery or withdrawal of immunosuppressants. It has also been observed in seemingly immunocompetent individuals, including in *C gattii* infections, as a post-infectious inflammatory immune response syndrome (PIIRS).[90,128] There is no diagnostic biomarker for C-IRIS. It is diagnosed by diagnosis of exclusion (figure 2).

There have been no therapeutic trials in C-IRIS. Management strategies include therapeutic lumbar puncture and symptomatic therapies. In severe C-IRIS, corticosteroids are commonly used to dampen inflammation, although their efficacy has not been rigorously examined in clinical trials. In steroid-refractory C-IRIS, there are case reports on the use of tumour necrosis factor-α blockers, such as adalimumab[129–132] or thalidomide,[133–135] with mixed success. Corticosteroids can also be beneficial in PIIRS (panel 12; appendix p 76).[136]

C gattii

About 50–70% of *C gattii* infections occur in putatively immunocompetent hosts,[137–139] compared with 2–30% in people with HIV.[140–144] Autoantibodies to granulocyte-macrophage colony-stimulating factor and idiopathic CD4 lymphopenia are reported risk factors.[137,145–147] Notably, not all commercial lateral flow assays are able to detect *C gattii* disease.[148] Antifungal agents used for treatment are the same as for *C neoformans*.[30,32,141] However, 4–6 weeks of induction therapy might be required in some cases of non-HIV-associated meningitis with *C gattii* (panel 13; appendix p 81).[149]

Cryptococcomas

Cryptococcomas occur predominantly in the lungs and brain and are more frequent in *C gattii* infection.[140,150] CNS cryptococcomas can manifest as neurological deficits or raised intracranial pressure,[140] which requires urgent management. Corticosteroids and surgical resection can be of value.[149,151,152] Radiological lesions can persist indefinitely despite clinical and microbiological cure (panel 14; appendix p 84).[32,153] Recommendations for cryptococcomas are in.

Non-*C neoformans* and non-*C gattii* strains of cryptococcus

There are individual case reports and small case series of non-*C neoformans* and non-*C gattii* cryptococcus infections, predominantly in immunosuppressed patients. *Papiliotrema laurentii* (previously *Cryptococcus laurentii*)[154] and *Naganishia albida* (previously *Cryptococcus albidus*)[155] account for about 80% of the invasive infections in this group and usually involve the skin, lungs, bloodstream, or CNS.[156] Colonisation, especially of the skin, respiratory, and

***Panel 14:* Recommendations for cryptococcomas**

- (AIII) Perform a biopsy or aspirate to exclude a secondary pathogen or an underlying tumour in non-responding cryptococcomas (particularly in immunosuppressed patients)
- (BIII) Consider surgical resection for accessible brain lesions more than 3 cm, lesions at risk of compressing critical structures, or large lesions not responding to therapy
- (DIII) During follow-up, do not prolong or escalate therapy for persistent radiological findings in the absence of new or worsening symptoms or signs

For CNS cryptococcoma:

- (BIII) Consider prolonging CNS antifungal induction therapy to 4–6 weeks
- (BIII) Consider corticosteroids for large cryptococcomas with surrounding mass effect or if neurological symptoms and cerebral imaging signs worsen despite a good microbiological response

The appendix (pp 22, 84) summarises treatment of lung cryptococcoma.

gastrointestinal tracts must be distinguished from true disease. In some cases, the laboratory might misidentify another yeast as *P laurentii* or *N albida* on the basis of non-definitive commercial identification methods.[157] Elevated MICs against flucytosine, fluconazole, and other azoles for some isolates have been documented but are of uncertain clinical significance (panel 15; appendix p 85).[158,159]

Pregnancy

The majority of cases of cryptococcosis in pregnancy occur in the third trimester or postpartum.[160,161] Maternal mortality from disseminated cryptococcosis is approximately 25%, and less than 50% of women carry their pregnancy to term.[161] Extensive clinical experience suggests that amphotericin B and liposomal amphotericin B are safe during pregnancy (Category B drug), and thus are the cornerstone of treatment.[161,162] Flucytosine is rated by the USA Food and Drug Administration as a Category C drug because of its direct effects on RNA and DNA metabolism. Fluconazole is a Category D drug due to its increased risk of musculoskeletal malformations, tetralogy of Fallot, and spontaneous abortions (panel 16; appendix p 86).[163–167]

Paediatrics

There is a clear need for paediatric-specific studies in cryptococcosis. CNS disease seems to predominate in paediatrics, but non-CNS disease is probably under-reported.[168–174] Clinical efficacy trials and studies to validate diagnostic tests and therapies for cryptococcosis in children are scarce. Recommendations are extrapolated from studies in adult populations. Dosing of antifungal agents needs particular attention for the paediatric patient (panel 17; appendix p 87).

***Panel 15:* Recommendations for non-*C neoformans* and non-*C gattii* strains of cryptococcus**

- (AIII) As non-*C neoformans* and non-*C gattii Cryptococcus* spp are rarely pathogenic, careful assessment of the laboratory identification and clinical context is required to ascertain clinical significance
- (CIII) For CNS or disseminated disease, treat the same as *C neoformans* CNS infection

***Panel 16:* Recommendations for cryptococcosis in pregnancy**

- (AIII) Use liposomal amphotericin B or amphotericin B in induction, consolidation, and maintenance therapy and for the treatment of isolated cryptococcal antigenemia
- (DII) Avoid the use of flucytosine and fluconazole in pregnancy, particularly in the first trimester; their use in the second and third trimester requires careful individualised risk–benefit assessment
- (BIII) Fluconazole can be used after delivery despite its excretion into breastmilk
- (AIII) Apply clinical judgement when considering initiation of antifungal therapy and duration of therapy, factoring in trimester of pregnancy and severity of illness
- (CIII) For asymptomatic cryptococcal antigen in pregnancy, consider intermittent polyene therapy, especially in the first trimester

***Panel 17:* Recommendations for paediatric cryptococcosis**

For the treatment of CNS or disseminated disease:

- (AIIt) Induction: amphotericin B 1 mg/kg daily or liposomal amphotericin B 3–4 mg/kg daily plus flucytosine (100–150 mg/kg daily in 4 divided doses) for 2 weeks
- (AIIt) Consolidation: fluconazole 12 mg/kg (maximum 800 mg) daily for 8 weeks
- Maintenance: fluconazole 6 mg/kg daily (maximum 800 mg) for 6–12 months
  - (AIIt) Should be provided for people who live with HIV and are immunocompromised
  - (BIIt) Can be provided for people who are immunocompetent
- (AIII) For the treatment of severe isolated pulmonary diseases: treat the same as CNS disease
- (AIII) Treatment of mild isolated pulmonary disease: fluconazole 12 mg/kg daily (maximum 800 mg) for 6–12 months
- (AIII) Screening is recommended for children older than 10 years living with HIV in high disease prevalence areas

Conclusions

Cryptococcosis and its management is complex and challenging. Adherence to clinical practice guidelines can improve outcomes.[44,175] Although there has been substantial development of evidence from randomised controlled trials over the past 20 years, there are considerable unmet needs (appendix pp 23, 91). Addressing these challenges is particularly crucial in low-income settings, where the burden of disease is high and access to antifungal therapy is inadequate. Equally, more clinical research needs to be done in high-income settings, where host risk profiles are changing and an increasing array of presentations of cryptococcosis are being recognised, necessitating more nuanced and individualised treatment plans.

Contributors

JRP guided the structure, content, and development of the guideline. OAC contributed to the conceptual planning, management, and supervision of the project. CCC and JRP coordinated the work of the

authors. TAB, CCC, MC, FH, TSH, OL, RO, JRP, TCS, AS, and AW contributed to the coordination of data collection, data visualisation, and participants' contributions and communication and wrote the first manuscript draft. All authors contributed towards the literature review, collection and preparation of data, creation of tabled recommendations, and critical review of the manuscript.

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References

1 WHO. WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization, 2022.
2 Day JN, Chau TTH, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med* 2013; **368:** 1291–302.
3 Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med* 2014; **370:** 2487–98.
4 Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med* 2016; **374:** 542–54.
5 Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet* 2004; **363:** 1764–67.
6 Jarvis JN, Lawrence DS, Meya DB, et al. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. *N Engl J Med* 2022; **386:** 1109–20.
7 Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *N Engl J Med* 2018; **378:** 1004–17.
8 Bicanic T, Wood R, Meintjes G, et al. High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: a randomized trial. *Clin Infect Dis* 2008; **47:** 123–30.

9 Rajasingham R, Govender NP, Jordan A, et al. The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis. *Lancet Infect Dis* 2022; **22:** 1748–55.

10 WHO. Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV. Geneva: World Health Organization, 2022.

11 Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. *Clin Infect Dis* 2010; **50:** 291–322.

12 Baddley JW, Forrest GN. Cryptococcosis in solid organ transplantation—guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; **33:** e13543.

13 Schmidt-Hieber M, Silling G, Schalk E, et al. CNS infections in patients with hematological disorders (including allogeneic stem-cell transplantation)—guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Oncol* 2016; **27:** 1207–25.

14 Singh N, Huprikar S, Burdette SD, Morris MI, Blair JE, Wheat LJ. Donor-derived fungal infections in organ transplant recipients: guidelines of the American Society of Transplantation, infectious diseases community of practice. *Am J Transplant* 2012; **12:** 2414–28.

15 Chang CC, Hall V, Cooper C, et al. Consensus guidelines for the diagnosis and management of cryptococcosis and rare yeast infections in the haematology/oncology setting, 2021. *Intern Med J* 2021; **51** (suppl 7)**:** 118–42.

16 Govender NP, Meintjes G, Mangena P, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. *South Afr J HIV Med* 2019; **20:** 1030.

17 No authors listed. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. July 1, 2021. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/cryptococcosis?view=full (accessed May 30, 2022).

18 WHO. Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization, 2018.

19 Kung HC, Huang PY, Chen WT, et al. 2016 guidelines for the use of antifungal agents in patients with invasive fungal diseases in Taiwan. *J Microbiol Immunol Infect* 2018; **51:** 1–17.

20 European AIDS Clinical Society. Cryptococcosis. October 2021. https://eacs.sanfordguide.com/ois/cryptococcosis (accessed Aug 18, 2022).

21 Izumikawa K, Kakeya H, Sakai F, et al. Executive summary of JSMM clinical practice guidelines for diagnosis and treatment of cryptococcosis 2019. *Med Mycol J* 2020; **61:** 61–89.

22 Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis* 2019; **19:** e405–21.

23 Chen SC, Perfect J, Colombo AL, et al. Global guideline for the diagnosis and management of rare yeast infections: an initiative of the ECMM in cooperation with ISHAM and ASM. *Lancet Infect Dis* 2021; **21:** e375–86.

24 Huang SH, Chuang YC, Lee YC, et al. Lumbar puncture for non-HIV-infected non-transplant patients with cryptococcosis: should it be mandatory for all? *PLoS One* 2019; **14:** e0221657.

25 Baddley JW, Perfect JR, Oster RA, et al. Pulmonary cryptococcosis in patients without HIV infection: factors associated with disseminated disease. *Eur J Clin Microbiol Infect Dis* 2008; **27:** 937–43.

26 Brizendine KD, Baddley JW, Pappas PG. Predictors of mortality and differences in clinical features among patients with cryptococcosis according to immune status. *PLoS One* 2013; **8:** e60431.

27 Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis* 2017; **17:** 873–81.

28 George IA, Spec A, Powderly WG, Santos CAQ. Comparative epidemiology and outcomes of human immunodeficiency virus (HIV), non-HIV non-transplant, and solid organ transplant associated cryptococcosis: a population-based study. *Clin Infect Dis* 2018; **66:** 608–11.

29 Hevey MA, George IA, Raval K, Powderly WG, Spec A. Presentation and mortality of cryptococcal infection varies by predisposing illness: a retrospective cohort study. *Am J Med* 2019; **132:** 977–83.

30 Baddley JW, Chen SC, Huisingh C, et al. MSG07: an international cohort study comparing epidemiology and outcomes of patients with *Cryptococcus neoformans* or *Cryptococcus gattii* infections. *Clin Infect Dis* 2021; **73:** 1133–41.

31 Ngamskulrungroj P, Chang Y, Sionov E, Kwon-Chung KJ. The primary target organ of *Cryptococcus gattii* is different from that of *Cryptococcus neoformans* in a murine model. *MBio* 2012; **3:** e00103–12.

32 Mitchell DH, Sorrell TC, Allworth AM, et al. Cryptococcal disease of the CNS in immunocompetent hosts: influence of cryptococcal variety on clinical manifestations and outcome. *Clin Infect Dis* 1995; **20:** 611–16.

33 Charlier C, Dromer F, Lévêque C, et al. Cryptococcal neuroradiological lesions correlate with severity during cryptococcal meningoencephalitis in HIV-positive patients in the HAART era. *PLoS One* 2008; **3:** e1950.

34 Tien RD, Chu PK, Hesselink JR, Duberg A, Wiley C. Intracranial cryptococcosis in immunocompromised patients: CT and MR findings in 29 cases. *AJNR Am J Neuroradiol* 1991; **12:** 283–89.

35 van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *N Engl J Med* 1997; **337:** 15–21.

36 Longley N, Muzoora C, Taseera K, et al. Dose response effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in southwestern Uganda. *Clin Infect Dis* 2008; **47:** 1556–61.

37 Gaskell KM, Rothe C, Gnanadurai R, et al. A prospective study of mortality from cryptococcal meningitis following treatment induction with 1200 mg oral fluconazole in Blantyre, Malawi. *PLoS One* 2014; **9:** e110285.

38 Rothe C, Sloan DJ, Goodson P, et al. A prospective longitudinal study of the clinical outcomes from cryptococcal meningitis following treatment induction with 800 mg oral fluconazole in Blantyre, Malawi. *PLoS One* 2013; **8:** e67311.

39 Nussbaum JC, Jackson A, Namarika D, et al. Combination flucytosine and high-dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomized trial in Malawi. *Clin Infect Dis* 2010; **50:** 338–44.

40 Muzoora CK, Kabanda T, Ortu G, et al. Short course amphotericin B with high dose fluconazole for HIV-associated cryptococcal meningitis. *J Infect* 2012; **64:** 76–81.

41 Jackson AT, Nussbaum JC, Phulusa J, et al. A phase 2 randomized controlled trial adding oral flucytosine to high-dose fluconazole, with short-course amphotericin B, for cryptococcal meningitis. *AIDS* 2012; **26:** 1363–70.

42 Charalambous LT, Premji A, Tybout C, et al. Prevalence, healthcare resource utilization and overall burden of fungal meningitis in the United States. *J Med Microbiol* 2018; **67:** 215–27.

43 Pyrgos V, Seitz AE, Steiner CA, Prevots DR, Williamson PR. Epidemiology of cryptococcal meningitis in the US: 1997–2009. *PLoS One* 2013; **8:** e56269.

44 Bratton EW, El Husseini N, Chastain CA, et al. Approaches to antifungal therapies and their effectiveness among patients with cryptococcosis. *Antimicrob Agents Chemother* 2013; **57:** 2485–95.

45 Chang CC, Dorasamy AA, Gosnell BI, et al. Clinical and mycological predictors of cryptococcosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2013; **27:** 2089–99.

46 Mootsikapun P, Chetchotisakd P, Anunnatsiri S, Choksawadphinyo K. The efficacy of fluconazole 600 mg/day versus itraconazole 600 mg/day as consolidation therapy of cryptococcal meningitis in AIDS patients. *J Med Assoc Thai* 2003; **86:** 293–98.

47 Hope W, Stone NRH, Johnson A, et al. Fluconazole monotherapy is a suboptimal option for initial treatment of cryptococcal meningitis because of emergence of resistance. *MBio* 2019; **10:** e02575–19.

48 Naicker SD, Mpembe RS, Maphanga TG, et al. Decreasing fluconazole susceptibility of clinical South African *Cryptococcus neoformans* isolates over a decade. *PLoS Negl Trop Dis* 2020; **14:** e0008137.

49 Smith KD, Achan B, Hullsiek KH, et al. Increased antifungal drug resistance in clinical isolates of *Cryptococcus neoformans* in Uganda. *Antimicrob Agents Chemother* 2015; **59:** 7197–204.

50 Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. *Clin Infect Dis* 1999; **28:** 291–96.

51 Bozzette SA, Larsen RA, Chiu J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. *N Engl J Med* 1991; **324:** 580–84.

52 Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1992; **326:** 793–98.

53 Bandettini R, Castagnola E, Calvillo M, et al. Voriconazole for cryptococcal meningitis in children with leukemia or receiving allogeneic hemopoietic stem cell transplant. *J Chemother* 2009; **21:** 108–09.

54 Carbonara S, Regazzi M, Ciracì E, et al. Long-term efficacy and safety of TDM-assisted combination of voriconazole plus efavirenz in an AIDS patient with cryptococcosis and liver cirrhosis. *Ann Pharmacother* 2009; **43:** 978–84.

55 Gamaletsou MN, Sipsas NV, Kontoyiannis DP, et al. Successful salvage therapy of refractory HIV-related cryptococcal meningitis with the combination of liposomal amphotericin B, voriconazole, and recombinant interferon-γ. *Diagn Microbiol Infect Dis* 2012; **74:** 409–11.

56 Nierenberg NE, Thompson GR 3rd, Lewis JS 2nd, Hogan BK, Patterson TF. Voriconazole use and pharmacokinetics in combination with interferon-gamma for refractory cryptococcal meningitis in a patient receiving low-dose ritonavir. *Med Mycol* 2010; **48:** 532–36.

57 Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis* 2003; **36:** 1122–31.

58 Loyse A, Wilson D, Meintjes G, et al. Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis* 2012; **54:** 121–28.

59 Sabbatani S, Manfredi R, Pavoni M, Consales A, Chiodo F. Voriconazole proves effective in long-term treatment of a cerebral cryptococcoma in a chronic nephropathic HIV-negative patient, after fluconazole failure. *Mycopathologia* 2004; **158:** 165–71.

60 Yao Y, Zhang JT, Yan B, et al. Voriconazole: a novel treatment option for cryptococcal meningitis. *Infect Dis (Lond)* 2015; **47:** 694–700.

61 Espinel-Ingroff A, Aller AI, Canton E, et al. *Cryptococcus neoformans–Cryptococcus gattii* species complex: an international study of wild-type susceptibility endpoint distributions and epidemiological cutoff values for fluconazole, itraconazole, posaconazole, and voriconazole. *Antimicrob Agents Chemother* 2012; **56:** 5898–906.

62 Esposito V, Viglietti R, Gargiulo M, et al. Successful treatment of cryptococcal meningitis with a combination of liposomal amphotericin B, flucytosine and posaconazole: two case reports. *In Vivo* 2009; **23:** 465–68.

63 Pitisuttithum P, Negroni R, Graybill JR, et al. Activity of posaconazole in the treatment of central nervous system fungal infections. *J Antimicrob Chemother* 2005; **56:** 745–55.

64 Schwartz S, Cornely OA, Hamed K, et al. Isavuconazole for the treatment of patients with invasive fungal diseases involving the central nervous system. *Med Mycol* 2020; **58:** 417–24.

65 Thompson GR 3rd, Rendon A, Ribeiro Dos Santos R, et al. Isavuconazole treatment of cryptococcosis and dimorphic mycoses. *Clin Infect Dis* 2016; **63:** 356–62.

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

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

68 Martínez E, García-Viejo MA, Marcos MA, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in HIV-infected patients responding to highly active antiretroviral therapy. *AIDS* 2000; **14:** 2615–17.

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

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

71 Sheng WH, Hung CC, Chen MY, Hsieh SM, Chang SC. Successful discontinuation of fluconazole as secondary prophylaxis for cryptococcosis in AIDS patients responding to highly active antiretroviral therapy. *Int J STD AIDS* 2002; **13:** 702–05.

72 Lortholary O, Poizat G, Zeller V, et al. Long-term outcome of AIDS-associated cryptococcosis in the era of combination antiretroviral therapy. *AIDS* 2006; **20:** 2183–91.

73 Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. *Pharmacotherapy* 2010; **30:** 842–54.

74 Glotzbecker B, Duncan C, Alyea E 3rd, Campbell B, Soiffer R. Important drug interactions in hematopoietic stem cell transplantation: what every physician should know. *Biol Blood Marrow Transplant* 2012; **18:** 989–1006.

75 Beardsley J, Wolbers M, Day JN. Dexamethasone in cryptococcal meningitis. *N Engl J Med* 2016; **375:** 189–90.

76 Rhein J, Huppler Hullsiek K, Tugume L, et al. Adjunctive sertraline for HIV-associated cryptococcal meningitis: a randomised, placebo-controlled, double-blind phase 3 trial. *Lancet Infect Dis* 2019; **19:** 843–51.

77 Villanueva-Lozano H, Treviño-Rangel RJ, González GM, et al. Clinical evaluation of the antifungal effect of sertraline in the treatment of cryptococcal meningitis in HIV patients: a single Mexican center experience. *Infection* 2018; **46:** 25–30.

78 Ngan NTT, Thanh Hoang Le N, Vi Vi NN, et al. An open label randomized controlled trial of tamoxifen combined with amphotericin B and fluconazole for cryptococcal meningitis. *eLife* 2021; **10:** 10.

79 Pappas PG, Bustamante B, Ticona E, et al. Recombinant interferon-gamma 1b as adjunctive therapy for AIDS-related acute cryptococcal meningitis. *J Infect Dis* 2004; **189:** 2185–91.

80 Jarvis JN, Meintjes G, Rebe K, et al. Adjunctive interferon-γ immunotherapy for the treatment of HIV-associated cryptococcal meningitis: a randomized controlled trial. *AIDS* 2012; **26:** 1105–13.

81 Marr KA, Sun Y, Spec A, et al. A multicenter, longitudinal cohort study of cryptococcosis in human immunodeficiency virus-negative people in the United States. *Clin Infect Dis* 2020; **70:** 252–61.

82 Sun HY, Alexander BD, Lortholary O, et al. Unrecognized pretransplant and donor-derived cryptococcal disease in organ transplant recipients. *Clin Infect Dis* 2010; **51:** 1062–69.

83 Santos DWCL, Hagen F, Meis JF, et al. Donor-Derived Transmission of Cryptococcus gattii sensu lato in Kidney Transplant Recipients. *Emerg Infect Dis* 2020; **26:** 1329–31.

84 Wu G, Vilchez RA, Eidelman B, Fung J, Kormos R, Kusne S. Cryptococcal meningitis: an analysis among 5521 consecutive organ transplant recipients. *Transpl Infect Dis* 2002; **4:** 183–88.

85 Sun HY, Alexander BD, Lortholary O, et al. Cutaneous cryptococcosis in solid organ transplant recipients. *Med Mycol* 2010; **48:** 785–91.

86 Osawa R, Alexander BD, Lortholary O, et al. Identifying predictors of central nervous system disease in solid organ transplant recipients with cryptococcosis. *Transplantation* 2010; **89:** 69–74.

87 El Helou G, Hellinger W. Cryptococcus neoformans pericarditis in a lung transplant recipient: case report, literature review and pearls. *Transpl Infect Dis* 2019; **21:** e13137.

88 Singh N, Alexander BD, Lortholary O, et al. Pulmonary cryptococcosis in solid organ transplant recipients: clinical relevance of serum cryptococcal antigen. *Clin Infect Dis* 2008; **46:** e12–18.

89 Sun HY, Alexander BD, Lortholary O, et al. Lipid formulations of amphotericin B significantly improve outcome in solid organ transplant recipients with central nervous system cryptococcosis. *Clin Infect Dis* 2009; **49:** 1721–28.

90 Sun HY, Alexander BD, Huprikar S, et al. Predictors of immune reconstitution syndrome in organ transplant recipients with cryptococcosis: implications for the management of immunosuppression. *Clin Infect Dis* 2015; **60:** 36–44.

91 Takazono T, Hidaka Y, Morimoto S, et al. Comparison of liposomal amphotericin B alone and in combination with flucytosine in the treatment of non-HIV cryptococcal meningitis: a nationwide observational study. *Mycoses* 2022; **65:** 897–902.

92 Aissaoui N, Benhadid-Brahmi Y, Sturny-Leclère A, et al. Investigation of CryptoPS LFA-positive sera in patients at risk of cryptococcosis. *Med Mycol* 2022; **60:** myac078.

93 Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis* 2001; **33:** 690–99.

94 Vilchez RA, Linden P, Lacomis J, Costello P, Fung J, Kusne S. Acute respiratory failure associated with pulmonary cryptococcosis in non-aids patients. *Chest* 2001; **119:** 1865–69.

95 Nadrous HF, Antonios VS, Terrell CL, Ryu JH. Pulmonary cryptococcosis in nonimmunocompromised patients. *Chest* 2003; **124:** 2143–47.

96 Skolnik K, Huston S, Mody CH. Cryptococcal lung infections. *Clin Chest Med* 2017; **38:** 451–64.

97 Shirley RM, Baddley JW. Cryptococcal lung disease. *Curr Opin Pulm Med* 2009; **15:** 254–60.

98 Avendaño J, Tanishima T, Kuwabara T. Ocular cryptococcosis. *Am J Ophthalmol* 1978; **86:** 110–13.

99 Wong BJ, Rao NA, Ameri H. Optical coherence tomography imaging of presumed *Cryptococcus neoformans* infection localized to the retina. *J Curr Ophthalmol* 2019; **31:** 353–56.

100 Wood L, Miedzinski L. Skeletal cryptococcosis: case report and review of the literature. *Can J Infect Dis* 1996; **7:** 125–32.

101 Medaris LA, Ponce B, Hyde Z, et al. Cryptococcal osteomyelitis: a report of five cases and a review of the recent literature. *Mycoses* 2016; **59:** 334–42.

102 Zhou HX, Lu L, Chu T, et al. Skeletal cryptococcosis from 1977 to 2013. *Front Microbiol* 2015; **5:** 740.

103 Rolfes MA, Hullsiek KH, Rhein J, et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. *Clin Infect Dis* 2014; **59:** 1607–14.

104 Kagimu E, Engen N, Ssebambulidde K, et al. Therapeutic lumbar punctures in human immunodeficiency virus-associated cryptococcal meningitis: should opening pressure direct management? *Open Forum Infect Dis* 2022; **9:** ofac416.

105 Cherian J, Atmar RL, Gopinath SP. Shunting in cryptococcal meningitis. *J Neurosurg* 2016; **125:** 177–86.

106 Manosuthi W, Sungkanuparph S, Chottanapund S, et al. Temporary external lumbar drainage for reducing elevated intracranial pressure in HIV-infected patients with cryptococcal meningitis. *Int J STD AIDS* 2008; **19:** 268–71.

107 Zhang Q, Li H, Zhang K, et al. Lumbar drainage for the treatment of refractory intracranial hypertension in HIV-negative cryptococcal meningitis. *Future Microbiol* 2019; **14:** 859–66.

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

109 Hu Z, Yang Y, Cheng J, Cheng C, Chi Y, Wei H. The use of mannitol in HIV-infected patients with symptomatic cryptococcal meningitis. *Drug Discov Ther* 2017; **10:** 329–33.

110 Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. *Clin Infect Dis* 2010; **50:** 1532–38.

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

112 Zhao T, Xu XL, Lu YQ, et al. The effect of early vs deferred antiretroviral therapy initiation in HIV-infected patients with cryptococcal meningitis: a multicenter prospective randomized controlled analysis in China. *Front Med (Lausanne)* 2021; **8:** 779181.

113 Ingle SM, Miro JM, May MT, et al. Early antiretroviral therapy not associated with higher cryptococcal meningitis mortality in people with human immunodeficiency virus in high-income countries: an international collaborative cohort study. *Clin Infect Dis* 2023; **77:** 64–73.

114 Boulware DR, Jarvis JN. Timing of antiretroviral therapy in cryptococcal meningitis: what we can (and cannot) learn from observational data. *Clin Infect Dis* 2023; **77:** 74–76.

115 Kityo C, Szubert AJ, Siika A, et al. Raltegravir-intensified initial antiretroviral therapy in advanced HIV disease in Africa: a randomised controlled trial. *PLoS Med* 2018; **15:** e1002706.

116 Rhein J, Hullsiek KH, Evans EE, et al. Detrimental outcomes of unmasking cryptococcal meningitis with recent ART initiation. *Open Forum Infect Dis* 2018; **5:** ofy122.

117 Kalata N, Ellis J, Kanyama C, et al. Short-term mortality outcomes of HIV-associated cryptococcal meningitis in antiretroviral therapy-naïve and therapy-experienced patients in sub-Saharan Africa. *Open Forum Infect Dis* 2021; **8:** ofab397.

118 Alufandika M, Lawrence DS, Boyer-Chammard T, et al. A pragmatic approach to managing antiretroviral therapy-experienced patients diagnosed with HIV-associated cryptococcal meningitis: impact of antiretroviral therapy adherence and duration. *AIDS* 2020; **34:** 1425–28.

119 Chen YC, Chang TY, Liu JW, et al. Increasing trend of fluconazole-non-susceptible Cryptococcus neoformans in patients with invasive cryptococcosis: a 12-year longitudinal study. *BMC Infect Dis* 2015; **15:** 277.

120 Bicanic T, Harrison T, Niepieklo A, Dyakopu N, Meintjes G. Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: the role of fluconazole resistance and immune reconstitution. *Clin Infect Dis* 2006; **43:** 1069–73.

121 Van Wyk M, Govender NP, Mitchell TG, Litvintseva AP, GERMS-SA. Multilocus sequence typing of serially collected isolates of *Cryptococcus* from HIV-infected patients in South Africa. *J Clin Microbiol* 2014; **52:** 1921–31.

122 Stone NR, Rhodes J, Fisher MC, et al. Dynamic ploidy changes drive fluconazole resistance in human cryptococcal meningitis. *J Clin Invest* 2019; **129:** 999–1014.

123 Bongomin F, Oladele RO, Gago S, Moore CB, Richardson MD. A systematic review of fluconazole resistance in clinical isolates of *Cryptococcus* species. *Mycoses* 2018; **61:** 290–97.

124 Procop GW, Dufresne PJ, Berkow E, et al. Epidemiological cutoff values for antifungal susceptibility testing. 4th ed. Berwyn, PA: Institute and Laboratory Standards, 2022.

125 Aberg JA, Watson J, Segal M, Chang LW. Clinical utility of monitoring serum cryptococcal antigen (sCRAG) titers in patients with AIDS-related cryptococcal disease. *HIV Clin Trials* 2000; **1:** 1–6.

126 French MA. HIV/AIDS: immune reconstitution inflammatory syndrome: a reappraisal. *Clin Infect Dis* 2009; **48:** 101–07.

127 Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis* 2010; **10:** 791–802.

128 Panackal AA, Wuest SC, Lin YC, et al. Paradoxical immune responses in non-HIV cryptococcal meningitis. *PLoS Pathog* 2015; **11:** e1004884.

129 Deshayes S, Bouvier N, Chatelet V, et al. Severe cryptococcal-associated neurological immune reconstitution inflammatory syndrome in a renal transplant recipient treated with adalimumab. *Transpl Infect Dis* 2016; **18:** 461–65.

130 Scemla A, Gerber S, Duquesne A, et al. Dramatic improvement of severe cryptococcosis-induced immune reconstitution syndrome with adalimumab in a renal transplant recipient. *Am J Transplant* 2015; **15:** 560–64.

131 Gaube G, De Castro N, Gueguen A, et al. Treatment with adalimumab for severe immune reconstitution inflammatory syndrome in an HIV-infected patient presenting with cryptococcal meningitis. *Med Mal Infect* 2016; **46:** 154–56.

132 Sitapati AM, Kao CL, Cachay ER, Masoumi H, Wallis RS, Mathews WC. Treatment of HIV-related inflammatory cerebral cryptococcoma with adalimumab. *Clin Infect Dis* 2010; **50:** e7–10.

133 Brunel AS, Reynes J, Tuaillon E, et al. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. *AIDS* 2012; **26:** 2110–12.

134 Lortholary O, Fontanet A, Mémain N, Martin A, Sitbon K, Dromer F. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. *AIDS* 2005; **19:** 1043–49.

135 Somerville LK, Henderson AP, Chen SC, Kok J. Successful treatment of *Cryptococcus neoformans* immune reconstitution inflammatory syndrome in an immunocompetent host using thalidomide. *Med Mycol Case Rep* 2014; **7:** 12–14.

136 Anjum S, Dean O, Kosa P, et al. Outcomes in previously healthy cryptococcal meningoencephalitis patients treated with pulse taper corticosteroids for post-infectious inflammatory syndrome. *Clin Infect Dis* 2021; **73:** e2789–98.

137 Chen SC, Slavin MA, Heath CH, et al. Clinical manifestations of *Cryptococcus gattii* infection: determinants of neurological sequelae and death. *Clin Infect Dis* 2012; **55:** 789–98.

138 Chen SC, Meyer W, Sorrell TC. *Cryptococcus gattii* infections. *Clin Microbiol Rev* 2014; **27:** 980–1024.

139 Harris JR, Galanis E, Lockhart SR. *Cryptococcus gattii* infections and virulence. *Curr Fungal Infect Rep* 2014; **8:** 81–89.

140 Chen S, Sorrell T, Nimmo G, et al. Epidemiology and host-dependent and variety-dependent characteristics of infection due to *Cryptococcus neoformans* in Australia and New Zealand. *Clin Infect Dis* 2000; **31:** 499–508.

141 Morgan J, McCarthy KM, Gould S, et al. *Cryptococcus gattii* infection: characteristics and epidemiology of cases identified in a South African province with high HIV seroprevalence, 2002–04. *Clin Infect Dis* 2006; **43:** 1077–80.

142 Litvintseva AP, Thakur R, Reller LB, Mitchell TG. Prevalence of clinical isolates of *Cryptococcus gattii* serotype C among patients with AIDS in sub-Saharan Africa. *J Infect Dis* 2005; **192:** 888–92.

143 Nyazika TK, Hagen F, Meis JF, Robertson VJ. *Cryptococcus tetragattii* as a major cause of cryptococcal meningitis among HIV-infected individuals in Harare, Zimbabwe. *J Infect* 2016; **72:** 745–52.

144 Steele KT, Thakur R, Nthobatsang R, Steenhoff AP, Bisson GP. In-hospital mortality of HIV-infected cryptococcal meningitis patients with *C gattii* and *C neoformans* infection in Gaborone, Botswana. *Med Mycol* 2010; **48:** 1112–15.

145 Saijo T, Chen J, Chen SC, et al. Anti-granulocyte-macrophage colony-stimulating factor autoantibodies are a risk factor for central nervous system infection by *Cryptococcus gattii* in otherwise immunocompetent patients. *MBio* 2014; **5:** e00912–14.

146 Yang DH, England MR, Salvator H, et al. *Cryptococcus gattii* species complex as an opportunistic pathogen: underlying medical conditions associated with the infection. *MBio* 2021; **12:** e0270821.

147 Viola GM, Malek AE, Rosen LB, et al. Disseminated cryptococcosis and anti-granulocyte-macrophage colony-stimulating factor autoantibodies: an underappreciated association. *Mycoses* 2021; **64:** 576–82.

148 Shi D, Haas PJ, Boekhout T, Hahn RC, Hagen F. Neglecting genetic diversity hinders timely diagnosis of *Cryptococcus* infections. *J Clin Microbiol* 2021; **59:** e02837–20.

149 Chen SC, Korman TM, Slavin MA, et al. Antifungal therapy and management of complications of cryptococcosis due to *Cryptococcus gattii*. *Clin Infect Dis* 2013; **57:** 543–51.

150 Phillips P, Galanis E, MacDougall L, et al. Longitudinal clinical findings and outcome among patients with *Cryptococcus gattii* infection in British Columbia. *Clin Infect Dis* 2015; **60:** 1368–76.

151 Phillips P, Chapman K, Sharp M, et al. Dexamethasone in *Cryptococcus gattii* central nervous system infection. *Clin Infect Dis* 2009; **49:** 591–95.

152 Fujita NK, Reynard M, Sapico FL, Guze LB, Edwards JE Jr. Cryptococcal intracerebral mass lesions: the role of computed tomography and nonsurgical management. *Ann Intern Med* 1981; **94:** 382–88.

153 Hospenthal DR, Bennett JE. Persistence of cryptococcomas on neuroimaging. *Clin Infect Dis* 2000; **31:** 1303–06.

154 Kordossis T, Avlami A, Velegraki A, et al. First report of *Cryptococcus laurentii* meningitis and a fatal case of *Cryptococcus albidus* cryptococcaemia in AIDS patients. *Med Mycol* 1998; **36:** 335–39.

155 Choe YJ, Blatt DB, Yalcindag A, Geffert SF, Bobenchik AM, Michelow IC. *Cryptococcus albidus* fungemia in an immunosuppressed child: case report and systematic literature review. *J Pediatric Infect Dis Soc* 2020; **9:** 100–05.

156 Khawcharoenporn T, Apisarnthanarak A, Mundy LM. Non-neoformans cryptococcal infections: a systematic review. *Infection* 2007; **35:** 51–58.

157 Xiao M, Fan X, Chen XX, et al. Misidentification of a rare species, *Cryptococcus laurentii*, by commonly used commercial biochemical methods and matrix-assisted laser desorption ionization-time of flight mass spectrometry systems: challenges for clinical mycology laboratories. *J Clin Microbiol* 2016; **54:** 226–29.

158 Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA, Lortholary O. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. *Clin Microbiol Infect* 2014; **20** (suppl 3)**:** 76–98.

159 Oliveira LSS, Pinto LM, de Medeiros MAP, et al. Comparison of *Cryptococcus gattii/neoformans* species complex to related genera (*Papiliotrema* and *Naganishia*) reveal variances in virulence associated factors and antifungal susceptibility. *Front Cell Infect Microbiol* 2021; **11:** 642658.

160 Ely EW, Peacock JE Jr, Haponik EF, Washburn RG. Cryptococcal pneumonia complicating pregnancy. *Medicine (Baltimore)* 1998; **77:** 153–67.

161 Pastick KA, Nalintya E, Tugume L, et al. Cryptococcosis in pregnancy and the postpartum period: case series and systematic review with recommendations for management. *Med Mycol* 2020; **58:** 282–92.

162 Bright PD, Lupiya D, van Oosterhout JJ, Chen A, Harrison TS, Chan AK. The treatment of a pregnant HIV positive patient with cryptococcal meningitis in Malawi—case report and review of treatment options. *Med Mycol Case Rep* 2017; **19:** 9–12.

163 Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis* 1996; **22:** 336–40.

164 Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol* 1996; **175:** 1645–50.

165 Zhu Y, Bateman BT, Gray KJ, et al. Oral fluconazole use in the first trimester and risk of congenital malformations: population based cohort study. *BMJ* 2020; **369:** m1494.

166 Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA* 2016; **315:** 58–67.

167 Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med* 2013; **369:** 830–39.

168 Lenz D, Held J, Goerke S, et al. Primary cutaneous cryptococcosis in an eight-year-old immunocompetent child: how to treat? *Klin Padiatr* 2015; **227:** 41–44.

169 Molina-Leyva A, Ruiz-Carrascosa JC, Leyva-Garcia A, Husein-Elahmed H. Cutaneous *Cryptococcus laurentii* infection in an immunocompetent child. *Int J Infect Dis* 2013; **17:** e1232–33.

170 Sweeney DA, Caserta MT, Korones DN, Casadevall A, Goldman DL. A ten-year-old boy with a pulmonary nodule secondary to *Cryptococcus neoformans*: case report and review of the literature. *Pediatr Infect Dis J* 2003; **22:** 1089–93.

171 Ramdial PK, Sing Y, Deonarain J, Bhimma R, Chotey N, Sewram V. Pediatric renal cryptococcosis: novel manifestations in the acquired immunodeficiency syndrome era. *Int J Surg Pathol* 2011; **19:** 386–92.

172 Lizarazo J, Escandón P, Agudelo CI, Castañeda E. Cryptococcosis in Colombian children and literature review. *Mem Inst Oswaldo Cruz* 2014; **109:** 797–804.

173 Gao LW, Jiao AX, Wu XR, et al. Clinical characteristics of disseminated cryptococcosis in previously healthy children in China. *BMC Infect Dis* 2017; **17:** 359.

174 Joshi NS, Fisher BT, Prasad PA, Zaoutis TE. Epidemiology of cryptococcal infection in hospitalized children. *Pediatr Infect Dis J* 2010; **29:** e91–95.

175 Gassiep I, Douglas J, Emeto TI, Crawley K, Playford EG. Cryptococcal infections over a 15 year period at a tertiary facility & impact of guideline management. *Mycoses* 2018; **61:** 633–38.