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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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Summary

Cryptococcosis, particularly in its most lethal manifestation of cryptococcal meningitis (CM), accounts for significant mortality and morbidity. It is a major worldwide disseminated invasive fungal infection. The breadth of the clinical cryptococcosis syndromes, the different host types at-risk and affected, and the vastly disparate resource settings in which clinicians practice, pose a complex array of challenges. Expert contributors from diverse regions of the world: collated data, reviewed the evidence, and provided insightful guideline recommendations for health practitioners across the globe.

This guideline offers practical guidance and implementable recommendations on clinical approaches, screening, diagnosis, management, and follow-up care, and serves as a comprehensive synthesis and update on cryptococcosis. It seeks to facilitate optimal clinical decision-making on this complex condition and addresses its myriad of clinical complications, by incorporating data from historical and contemporary clinical trials, grounded on a set of core management principles, while simultaneously acknowledging the practical challenges of antifungal access and resource limitations faced by many. Over 70 societies internationally have endorsed this global cryptococcosis guideline for its content, structure, evidence, recommendation, and pragmatic wisdom to inform clinicians about the past, present, and future and in the care of a patient with cryptococcosis.

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Introduction

Cryptococcosis accounts for significant morbidity and mortality globally. The World Health Organization (WHO) in 2022 listed *Cryptococcus neoformans* as one of its top priority pathogens.¹ Cryptococcosis most often involves the central nervous system (CNS) and/or the lungs, but disseminated disease may affect any organ, yet appear seemingly localised. Despite the knowledge gained and improvement in clinical outcomes generated by multiple interventional trials^{2–7} conducted primarily in resource-limited health care settings (RLS), mortality from cryptococcal meningoencephalitis (CM) remains unacceptably high, ranging from 24%–47% at 10 weeks.^{2,4,7,8} The highest burden of disease is encountered in low- and middle-income countries, especially in sub-Saharan Africa⁹, where HIV/AIDS remains the dominant risk factor, although new non-HIV immunocompromised risk groups, and putatively immunocompetent individuals, are increasingly reported in resource-rich (RRS) settings.

Complementary diagnostic and management guidelines for cryptococcosis exist.^{10–21} This comprehensive synthesis and update of cryptococcosis management guidelines, serves primarily to facilitate clinical decision making, but also provides an overview of the current uncertainties in cryptococcosis. With contributors across the globe, this guideline gives voice to expertise and challenges from diverse settings in a globally relevant document. General principles and treatment recommendations are provided and clinicians are urged to utilise careful clinical judgement when formulating treatment plans for the individual patient. (See Appendix for processes on guideline development (s19–s20, s28), common abbreviations (s21), definitions (s23) and detailed text (s32)).

At-risk populations, clinical presentations, and outcomes

Evidence:

Primarily acquired via inhalation but occurring mainly upon reactivation after a period of latency, cryptococcosis has protean manifestations with CM 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 seemingly asymptomatic individuals.^{24,25} While classical at-risk patient populations include persons living with HIV (PLHIV) and solid organ transplant (SOT) recipients, individuals with other immunosuppressive conditions or receiving immunosuppressant drugs and putatively immunocompetent hosts are affected by cryptococcosis (s5).

Those who survive cryptococcosis still report significant morbidity, ranging from 10%–70% depending on the disease syndrome and severity; underlying predisposing conditions of the host; and the healthcare system in which the patient is managed^{26–29} (s7).

Recommendations:

- **(AIII)** Cryptococcosis should be considered in any patient presenting with compatible symptomatology and/or microbiology, regardless of their immune status.

- **(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 presenting with cryptococcosis.

Yeasts causing cryptococcosis and their diagnostic methods.

Evidence:

C. neoformans species complex is the predominant causative agent of cryptococcosis in PLHIV, while *C. gattii* species complex more commonly causes disease in apparently immunocompetent hosts. While both can cause a similarly broad repertoire of cryptococcosis syndromes, *C. neoformans* has a predilection for CNS disease while *C. gattii* is more often associated with pulmonary disease and large cryptococcomas.^{30–32}

Diagnostic modalities used to establish the diagnosis, extent, severity, and prognosis of cryptococcosis are constantly evolving (**s9** and **s31**). Microscopy and culture of CSF pellet after centrifugation, and blood culture, accompanied by CSF and blood (serum, plasma, or whole blood) cryptococcal antigen testing (most commonly by lateral flow assay (CrAg LFA)) and radiological studies are central to the diagnosis of cryptococcosis.^{33,34}

Recommendations:

(AIIt) All patients with suspected or confirmed cryptococcosis (including cryptococcal antigenemia) require careful clinical assessment for CNS, pulmonary and other body site involvement. Investigations for disseminated disease should include: (1) lumbar puncture (LP) with measurement of CSF opening pressure (OP), glucose, protein, cell counts, microscopy, culture, and quantification of CSF CrAg; (2) quantification of blood CrAg, and cultures of blood, sputum (or other respiratory specimens) and/or of other affected sites; (3) ideally, brain imaging (preferably MRI) and chest imaging (preferably CT).

Screening/Primary Prophylaxis/Pre-emptive Therapy

Evidence:

Supportive evidence for cryptococcal screening is limited to PLHIV and currently hinges on the blood CrAg LFA (see **s32** for detailed discussion, including prophylaxis and pre-emptive therapy).

Recommendation:

- For adult PLHIV with CD4 <200 cells/mm³ (ART-naïve or after a period of ART discontinuation):
 - **(AI)** Performing a blood CrAg by LFA for the screening of cryptococcosis, and determine the CrAg titre if positive.
 - **(AIIt)** All patients with cryptococcal antigenaemia should be carefully assessed and investigated for cryptococcosis (see section above) and treated as appropriate.

- **(AIIu)** In asymptomatic cryptococcal antigenaemic PLHIV without clinical cryptococcosis after thorough investigation (including at least a LP), fluconazole 1200 mg daily for 2 weeks (when ART may be initiated), followed by 800 mg daily for 8 weeks, and 200 mg thereafter for about 6 months is recommended. (Guidance may be updated contingent on results of prospective trials.)
- **(BI)** In clinical settings where CrAg LFA screening is not available (despite WHO's strong recommendations), universal primary prophylaxis with fluconazole 100 mg daily in PLHIV in high endemic areas with CD4 count <200 cells/mm³ is recommended (see Pregnancy section for suitable alternative)
- Other (non-HIV) populations:
 1. **(DIIu)** Routine blood CrAg screening, primary prophylaxis and pre-emptive therapy are not currently recommended in non-HIV populations.

Principles of treatment and navigating the guidelines

See s25 for how to navigate the treatment sections of these guidelines, s26 for a general discussion on antifungal drugs used in cryptococcosis, and common adverse events (s15).

HIV-associated cryptococcal meningitis (CM) in RLS compared to RRS

Evidence:

Evolution of induction treatment: Multiple studies support the successful combination of amphotericin B deoxycholate (Amb-D) plus 5-flucytosine as the induction treatment of choice in HIV-associated CM. First trialled by van der Horst and colleagues, the addition of 5-flucytosine to Amb-D, 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 Amb-D alone or Amb-D plus fluconazole.⁵ Importantly, the combination of **Amb-D 1 mg/kg daily plus 5-flucytosine 25 mg/kg four times a day** showed a survival advantage at day 70, over Amb-D alone in the treatment of CM.² The nephroprotection of L-Amb compared with Amb-D is long recognised and accessibility of L-Amb in RRS led to the establishment of **L-Amb 3–4 mg/kg daily plus 5-flucytosine 25 mg/kg four times a day for 2 weeks**, as the current standard.

Resource-limited settings: In RLS, challenges with antifungal access, adverse effects and difficulty of monitoring and safely managing 2 weeks of Amb-D induction treatment led to phase 2 studies, exploring alternative regimens. Fluconazole monotherapy, even at doses up to 1200 mg daily, was associated >50% mortality at 10-weeks, and >75% mortality at one-year.^{36–38} An oral combination of fluconazole 1200 mg daily plus 5-flucytosine 25 mg/kg four times a day was associated with a significant improvement in EFA compared with fluconazole alone.³⁹ Unsurprisingly, the addition of a short, 5–7 day course of Amb-D

at 1 mg/kg daily to oral fluconazole or combined oral fluconazole and 5-flucytosine showed improved rates of cryptococcal clearance^{40,41}, similar to rates observed with 14 days of Amb-D.

In the phase 3 ACTA trial conducted in centres in Africa, the oral combination of fluconazole 1200 mg daily and 5-flucytosine 25 mg/kg four times a day for 2 weeks was compared with 1-week of Amb-D 1 mg/kg daily and 2 weeks of Amb-D 1 mg/kg daily as induction therapy, with the latter two arms being further randomised with either fluconazole 1200 mg daily or 5-flucytosine 25 mg/kg four times a day.⁷ **One-week Amb-D 1 mg/kg daily plus 5-flucytosine followed by fluconazole 1200 mg daily in the second week** was the best performing induction arm, with a 24% 10-week mortality. This regimen was adopted as the preferred induction regimen by the WHO and Southern African guidelines until the AMBITION-cm study.^{16,18}

In the AMBITION-cm phase III study across sites in Africa, a **single initial 10 mg/kg dose of liposomal amphotericin B (L-Amb), with an oral backbone of fluconazole 1200 mg daily plus 5-flucytosine 25 mg/kg four times a day for 2 weeks** was compared with the then WHO recommendation of 1-week Amb-D 1 mg/kg daily plus 5-flucytosine followed by 1 week of fluconazole 1200 mg daily.⁶ This 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 PLHIV with CM.¹⁰

Resource-rich settings: The applicability of the ACTA and AMBITION-cm trials to RRS and in non-HIV populations is contentious, where the current standard is **L-Amb 3–4 mg/kg daily plus 5-flucytosine 25 mg/kg four times a day for 2 weeks**, different to comparators used in these trials. Retrospective database reviews in the USA showed relatively low rates of acute inpatient mortality from CM (10.5% in HIV-CM and 13.3% in non-HIV) and remarkably low mortality rates at 1 year of 11.6% over the last two decades.^{42,43} The reliance on high-dose fluconazole and 5-flucytosine as the backbone to induction therapy in AMBITION-cm study may not be pragmatic in all RRS where more comorbidities occur, potential drug-drug interactions need to be carefully considered; and the risk of hepatotoxicity less tolerated. In the USA, only a third of patients completed the 14-days of 5-flucytosine.⁴⁴ While some experts cogently propose for the inclusion of the AMBITION-cm triple regimen as a primary option in RRS, others are calling for further comparative trials in RRS to assess the regimen's impact in HIV, and the inclusion of SOT and non-HIV, non-SOT populations where no supporting data exist. Regardless of the induction antifungal regimen used, the complications of CM such as increased intracranial pressure (ICP) require intense clinical monitoring, and most patients with CM require inpatient care for at least one, if not two or more weeks.

Significance of CSF sterility post-induction/pre-consolidation

therapy: Mycological success has been associated with improved outcomes and reduced clinical relapse.⁴⁵ In PLHIV with CM, CSF sterility prior to 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 2-week LP (prior to 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 RLS – do not.^{10,16}

Consolidation and maintenance treatment: There are no recent trials of consolidation and maintenance therapy in CM. Two early studies established fluconazole for consolidation therapy^{35,46}, with 400 mg daily. With the accumulation of safety data at an 800 mg daily dose and evidence of a fluconazole dose-response effect,^{36,47} this is the preferred consolidation dose in RLS, where suboptimal antifungal regimens are used.^{16,18} A gradual rise in median fluconazole MICs in cryptococcal isolates collected during initial CM presentation have been reported in South Africa and Uganda.^{48,49} While this may lend support for a higher consolidation dose of 800mg daily in these settings, whether this is required across all patient groups and settings is contentious. Widespread fluconazole use may also perpetuate further rises in MICs.

Maintenance therapy with fluconazole 200 mg daily has been shown to be highly effective at preventing relapse, and is superior to weekly Amb-D 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 RLS.

A very low incidence of CM relapse is observed after a minimum of 1 year of antifungal therapy in PLHIV established on ART, who are virologically suppressed, and/ or have a CD4 count > 100 cells/mm³.^{66–72}

Adjunctive therapy: Recent trials of adjunctive treatment in HIV-associated CM have all been shown to be ineffective, and in some cases harmful. These include high-dose dexamethasone,⁷³ sertraline,^{74,75} and tamoxifen.⁷⁶ The debate regarding adjunctive exogenous IFN-gamma remains unresolved. IFN-gamma has been studied in two randomised trials of HIV-associated CM, which suggest faster clearance of yeasts in the CSF^{77,78}, but further studies are needed. There is no trial evidence supporting its use in non-HIV associated CM.

Recommendations:

A management algorithm is described in Figure 1 and key principles discussed in Table 1.

Recommendations for CM treatment in PLHIV are based on availability of antifungal drugs; preferred and alternative strategies are offered (see Figure 2 and Table 2).

CM in Solid organ transplant (SOT) recipients

Evidence:

Cryptococcosis is the third most common invasive fungal infection in SOT recipients, with an incidence of 4.5%–33.8%^{26,28,29} and a significant mortality.¹² SOT recipients comprise a third of non-HIV related cryptococcosis in the USA.⁷⁹ The majority of cryptococcosis in

SOT occurs late and is due to reactivation disease; however, acute donor-derived infections have been described.^{14,80,81}

Anti-rejection drugs vary in their degree of immunosuppression and heart and small bowel transplant recipients are at the highest CM risk.⁸² CNS and pulmonary cryptococcosis predominate but unusual manifestations including cutaneous disease^{83,84} and pericarditis⁸⁵ have been reported. Notably, blood CrAg may be negative in SOT recipients with cryptococcosis, particularly those with single pulmonary nodules or in lung transplant recipients.⁸⁶

There are no randomised treatment trials targeted specifically at SOT recipients hence recommendations are extrapolated from experience in PLHIV. The use of lipid-formulations in SOTs with CNS cryptococcosis was independently associated with reduced mortality compared with Amb-D.⁸⁷ The AMBITION-cm regimen has not been studied in non-HIV patients, and experience with high dose fluconazole (with its ensuing potential toxicity and drug-drug interactions) in this group is lacking. A precipitous reduction in dosing of immunosuppressants, particularly calcineurin inhibitors, may lead to IRIS.⁸⁸

Recommendations:

See Table 2.

CM in Non-HIV, Non-Transplant Patients

Evidence

The non-HIV, non-SOT group is heterogeneous, ranging from apparently normal hosts to those with haematological malignancies or liver cirrhosis. There is no single therapeutic regimen or duration that meets all patients' needs but principally, this mirrors CM treatment in RRS with L-Amb and 5-flucytosine induction. Induction therapy may be extended in those with persistently positive CSF cultures and/or persistent symptoms at two weeks. Recently, the combination of L-Amb and 5-flucytosine was shown to have a low acute mortality of 6% in a nationwide observational study of non-HIV-associated CM in Japan.⁸⁹

Recommendations

See Table 2.

Pulmonary cryptococcosis

Evidence

Case series and clinical experience suggest that patients with cryptococcaemia, evidence of CNS involvement, blood CrAg titres $\geq 1:512$ by latex agglutination (or 10-fold higher by LFA⁹⁰), or severe pulmonary disease, should be treated as CM.^{33,35,91,92} Patients with mild isolated pulmonary disease without cryptococcoma have been previously successfully treated with fluconazole monotherapy of 400 mg daily.^{91,93,94} Some clinicians consider watchful-waiting and elect not to treat asymptomatic immunocompetent persons who incidentally culture any *Cryptococcus spp.*, in their sputum, and exhibit no radiological

features of pulmonary cryptococcosis, as they consider this as airway colonisation.⁹⁵ Criteria for distinguishing colonisation from infection is uncertain. There are no randomised treatment studies in pulmonary cryptococcosis.

Recommendations

Stratify treatment by disease severity and presence of pulmonary cryptococcoma (s17)s).

Non-pulmonary-Non-CNS Disease

Evidence:

Cryptococcosis can affect any organ following haematogenous dissemination. Clinical presentation of non-CNS/non-pulmonary disease without fungemia is rare, but possible. The absence of documented fungemia 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 CM are frequently related to raised ICP and do not necessarily indicate direct eye involvement. Ocular cryptococcosis can occur^{96,97} but is unusual and requires formal ophthalmological documentation and management. Isolated skeletal osteomyelitis is rare and often requires a combined surgical and medical approach.^{98–100} Skin lesions may be polymorphic.

Recommendations:

- Cryptococcaemia:
 - **(AIIu)** Treat as for CNS disease.
- Primary cutaneous (skin) cryptococcosis attributed to direct inoculation without evidence of dissemination:
 - **(AIII)** Fluconazole 400 mg daily for 3–6 months or until cicatrisation.
- All other non-CNS/ non-pulmonary disseminated disease:
 - **(BIIu)** Treat as for CNS disease.
- **(BIIu)** Cryptococcal eye disease should be managed in collaboration with an ophthalmologist.

Specific Management Issues

Raised intracranial pressure (ICP)

Evidence: Increased ICP has been associated with high burden of cryptococci leading to both acute and chronic symptoms and signs (e.g., 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 LPs result in significant improvement in survival, regardless of OP.^{101,102} For prolonged control of acute increased ICP, use of lumbar drains in cases without hydrocephaly or

ventriculostomies in cases with hydrocephaly may be required.^{103–105} Medical therapies including acetazolamide, mannitol, and corticosteroids may be detrimental.^{106,107}

Recommendations:

- **(AIIu)** Opening pressure should be measured at every LP in patients with CM.
- **(AIII)** Perform a CT brain (if CNS imaging not previously done) to exclude CNS outflow obstruction.
- **(Allt)** Acute symptomatic elevation of the ICP (≥ 20 cm of CSF) should be managed by daily therapeutic LPs (i.e., removal of sufficient CSF (usually around 20–30 ml) to reduce the pressure to 50% of OP and/or to a normal pressure of ≤ 20 cm of CSF (documented as a closing pressure).
- **(BIIu)** Perform a scheduled therapeutic LP around 48–72 hours of initial LP and/or 7 days, regardless of initial OP.
- **(Allt)** Persistent raised symptomatic ICP despite therapeutic LPs 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.

Timing of antiretroviral therapy (ART) commencement

Evidence: The optimal time to commence ART for HIV infection during cryptococcosis remains controversial. Four randomised trials^{3,108–110} to determine optimal timing of ART initiation in HIV-CM co-infection have been conducted in RLS settings, using induction regimens which are not currently preferred, including fluconazole (800 mg daily) monotherapy¹⁰⁸, Amb-D 0.7 mg/kg daily¹⁰⁹, and Amb-D 0.7–1mg/kg daily and fluconazole 800 mg daily for 2 weeks. These data seem to suggest that initiating ART within 2 weeks of CM 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 prior to ART commencement may be another factor.⁴⁵ A retrospective analysis of combined cohorts in RRS did not appreciate higher mortality in those receiving early ART in the first two weeks of antifungal therapy compared to those with delayed therapy.¹¹¹ In all, early ART in RRS, will need careful justification and close monitoring; further randomised studies may be helpful.¹¹²

There are no studies for timing of 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.¹¹³ Whether those presenting with CM within 2 weeks of starting ART require withholding of ART remains uncertain.^{114–116}

Recommendation:

- **(DI)** Immediate or very early commencement of ART is not recommended.
- Depending on antifungal induction therapy availability:
 - Sub-optimal/limited access: **(AI)** Delay ART for 4–6 weeks.
 - Optimal and in RRS: **(BIIu)** Consider further individualisation taking into consideration resolution of symptoms and signs of CM and ICP (including normalisation of OP), 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 local experience of CM and C-IRIS management. (Usual range is 4–6 weeks).
- **(CIIi)** Where possible, ensure CSF is cryptococcal culture negative prior to ART commencement.
- **(BIII)** For ART-experienced persons who develop CM and may 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 CM within 2 weeks of starting ART.
- **(BIII)** Patients with isolated pulmonary cryptococcosis or those with asymptomatic cryptococcal antigenemia may commence ART earlier (e.g., 2 weeks).

Resistance to antifungals

Evidence: Developing secondary resistance to 5-flucytosine is common when given as monotherapy, necessitating its use with a partner drug in cryptococcosis. Acquired resistance to polyenes such as Amb-D is rare, but the emergence of fluconazole resistance is concerning.^{48,49,117} Fluconazole monotherapy as induction therapy has been associated with secondary resistance.^{118–121}

There are presently no clinical MIC breakpoints for fluconazole against *Cryptococcus* species and a lack of convincing data to suggest that high MICs imply worse outcomes. Interpretation of epidemiological cut-off values (ECVs), using the CLSI method for fluconazole requires accurate species identification. Based on CLSI, the ECV for *C. neoformans* VNI is 8 ug/mL, and 16 and 32 ug/mL, for *C. gattii* VGI and *C. deuterogattii* VGII, respectively.¹²² In principle, a higher than 2-fold increase in MIC during treatment may suggest development of resistance, and the need for closer clinical monitoring. There are no EUCAST ECOFFs available for fluconazole.

Recommendation:

- For those with concerns of fluconazole-resistance or emerging fluconazole-resistance:

- **(BIII)** Consider a longer course of treatment with Amb-D (1 mg/kg daily) or higher dose of L-Amb (3–6 mg/kg daily) together with 5-flucytosine (about 4 weeks) as induction therapy.
- **(BIII)** Consider Amb-D 1 mg/kg weekly or L-Amb 3–6 mg/kg weekly as consolidation/maintenance therapy. Consider daily voriconazole, posaconazole, isavuconazole or itraconazole for isolates without evidence of pan-azole resistance, as guided by AFST.
- **(CIII)** Where Amb-D or L-Amb are not available, adding 5-flucytosine to high-dose fluconazole (1200 mg daily) may be considered.

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

Evidence: Distinguishing clinical relapse from persistent cryptococcal infection is challenging. **Clinical relapse** may be due to a microbiological relapse, C-IRIS, raised ICP (whether or not related to C-IRIS) or other infective and non-infective (CNS and non-CNS) causes (Figure 1). Cryptococcal antigen persists in the CSF and blood thus has little clinical utility in distinguishing clinical responders from non-responders.¹²³ 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.

Recommendations: See Table 1 and Figure 1.

- **(AIIIt)** Think broadly and investigate thoroughly for causality (CNS and non-CNS; infective and non-infective) in cases of apparent clinical relapse. Investigations should include CT/MRI brain, LP for OP and CSF analyses including microscopy and culture.
- **(AIIlu)** Review adherence to antifungal therapy, ART/ immunosuppressants and other medications and consider drug-drug interactions. Perform therapeutic drug monitoring (TDM) if applicable. Optimise control of underlying disease(s).
- **(CIII)** Consider escalating antifungal therapy while awaiting CSF results (and de-escalate if culture-negative)
- **(DIIlu)** The use of follow-up blood or CSF CrAg (including monitoring of titres) for clinical decision-making is discouraged.
- **(DIIlu)** Do not escalate antifungal therapy for persistent blood antigenemia, persistently positive CSF CrAg, visible cryptococci in CSF (without culture positivity), nor abnormal CSF microscopy or biochemistry. These are not necessarily indicators of microbiological failure.
- For **culture-positive (microbiological) persistent or relapsed infection** (Figure 1):
 - **(BIII)** AFST should be performed concurrently on all initial and relapse isolates (if stored and available). An increase in fluconazole MIC of >2

dilutions is considered as concerning for the potential development of drug resistance.

- **(BIII)** Consider re-induction with a more optimal regimen (guided by AFST).

Cryptococcosis-associated Immune Reconstitution Inflammatory Syndrome (C-IRIS)

Evidence: IRIS has been classically described in PLHIV between 2 weeks and 3 months after commencement of ART, where patients develop exaggerated symptoms and signs and/or atypical inflammation, reminiscent of a paradoxical recurrence^{124,125}, but 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).^{88,126} There is no diagnostic biomarker for C-IRIS, thus this is a clinical diagnosis of exclusion (Figure 1).

There have been no therapeutic trials in C-IRIS. Management strategies include therapeutic LP, 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 TNF-alpha blockers such as adalimumab^{127–130} or thalidomide^{131–133} with mixed success. Corticosteroids may also be beneficial in PIIRS.¹³⁴

Recommendation:

- **(Allt)** For patients with suspected paradoxical C-IRIS, carefully exclude recurrent cryptococcal disease or new infective or non-infective conditions, prior to attributing symptoms and signs to C-IRIS. Perform an MRI brain and LP to measure OP and obtain CSF for microbiological and biochemical analyses.
- **(AIIu)** Treatment of C-IRIS should include therapeutic LP, symptomatic therapy such as analgesia, antiemetics and antiepileptics where appropriate.
- **(AIII)** Continue current antifungal therapy.
- **(BIII)** High-dose prednisone/prednisolone (usually 0.5–1.0 mg/kg daily) or dexamethasone (usually 0.2–0.3 mg/kg daily), weaned over 4–6 weeks may be considered in those with persistent symptoms, unresponsive to therapeutic LPs. Rarely a second steroid course with taper is needed.
- **(DIII)** Do not stop ART.
- **(BIII)** Cases of steroid-refractory or recurrent C-IRIS be discussed with experts in the field.
- **(CIIu)** Steroids may be considered for PIIRS.

Cryptococcus gattii

Evidence: About 50–70% of *C. gattii* infection occur in putatively immunocompetent hosts^{135–137} compared with 2–30% in PLHIV.^{138–142} Autoantibodies to GM-CSF and

idiopathic CD4 lymphopenia are reported risk factors.^{135,143–145} Notably, not all commercial LFAs are able to detect *C. gattii* disease.¹⁴⁶ Antifungal agents used for treatment are the same as for *C. neoformans*.^{30,32,139} However, 4–6 weeks of induction therapy may be required in some cases of non-HIV-associated meningitis with *C. gattii*.¹⁴⁷

Recommendations:

- *C. gattii* CNS disease
 - **(AIII)** Treat as for *C. neoformans* CNS infection.
 - In non-HIV patients: **(BIII)** Consider extending induction therapy to 4–6 weeks.
 - **(AIII)** Early CSF shunting is indicated for obstructive chronic hydrocephalus.
- *C. gattii* lung disease (see *pulmonary cryptococcosis, pulmonary cryptococcoma and s17*).

Cryptococcomas

Evidence: Cryptococcomas occur predominantly in the lungs and brain and are more frequent in *C. gattii* infection.^{138,148} CNS cryptococcomas can manifest as neurological deficits and/or raised ICP,¹³⁸ which requires urgent management. Corticosteroids and surgical resection may be of value.^{147,149,150} Radiological lesions can persist indefinitely despite clinical and microbiological cure.^{32,151}

Recommendations:

All 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 >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.

CNS cryptococcoma

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

Lung cryptococcoma

- see s17

Non-neoformans and non-gattii strains of *Cryptococcus*

Evidence: There are individual case reports and small case series of non-*neoformans*/non-*gattii* *Cryptococcus* infections, predominantly in immunosuppressed patients. *Papiliotrema* (previously *Cryptococcus*) *laurentii*¹⁵² and *Naganishia albida* (previously *Cryptococcus albidus*)¹⁵³ account for about 80% of the invasive infections in this group and usually involve skin, lungs, bloodstream, or CNS.¹⁵⁴ Colonisation, especially of the skin, respiratory and gastrointestinal tracts must be distinguished from true disease. In some cases, the laboratory may misidentify another yeast as *P. laurentii* or *N. albida* based on non-definitive commercial identification methods.¹⁵⁵ Elevated MICs against 5-flucytosine, fluconazole and other azoles for some isolates have been documented but are of uncertain clinical significance.^{156,157}

Recommendations:

- **(AIII)** As non-*neoformans*/non-*gattii* *Cryptococcus* species 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 as for *C. neoformans* CNS infection.

Pregnancy

Evidence: The majority of cases of cryptococcosis in pregnancy occur in the third trimester or postpartum.^{158,159} Maternal mortality from disseminated cryptococcosis is approximately 25%; and <50% carry their pregnancy to term.¹⁵⁹ Extensive clinical experience suggests that Amb-D and L-Amb are relatively safe during pregnancy (Category B drug), and thus are the cornerstone of treatment.^{159,160} 5-Flucytosine is rated by the USA FDA as a Category C drug because of its direct effects on RNA/DNA metabolism. Fluconazole is a Category D drug due to its increased risk of musculoskeletal malformations, tetralogy of Fallot and spontaneous abortions.^{161–165}

Recommendations:

- **(AIII)** Use L-Amb or Amb-D in induction, consolidation, and maintenance therapy, and for treatment of isolated cryptococcal antigenemia.
- **(DII)** Avoid use of 5-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 may be used after delivery despite its excretion into breast milk.
- **(CIII)** 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 CrAg in pregnancy, consider intermittent polyene therapy especially in the first trimester.

Paediatrics

Evidence: There is a clear need for paediatric-specific studies in cryptococcosis. CNS disease seems to predominate in paediatrics but non-CNS disease is likely under-reported.^{166–172} Clinical efficacy trials and studies to validate diagnostics tests and therapies for cryptococcosis in children are lacking. Recommendations are extrapolated from studies in adult populations. Dosing of antifungal agents needs particular attention for the paediatric patient.

Recommendations:

- Treatment of CNS or disseminated disease:
 - Induction: **(AIIIt)** Amb-D 1 mg/kg daily or L-Amb 3–4 mg/kg daily plus 5-flucytosine (100–150 mg/kg daily in 4 divided doses) for 2 weeks.
 - Consolidation: **(AIIIt)** Fluconazole 12 mg/kg (maximum 800 mg) daily for 8 weeks.
 - Maintenance: **(AIIIt)** for PLHIV and immunocompromised; **(BIIt)** for immunocompetent. Fluconazole 6 mg/kg daily (maximum 800 mg) for 6–12 months.
- Treatment of severe isolated pulmonary diseases: **(AIII)** Treat as for CNS disease.
- Treatment of mild isolated pulmonary disease: **(AIII)** Fluconazole 12 mg/kg daily (maximum 800 mg) for 6–12 months.
- **(AIII)** Screening is recommended for children living with HIV in high disease prevalence areas at ages ≥ 10 years.

Conclusions

Cryptococcosis and its management remain complex and challenging. Adherence to clinical practice guidelines can improve outcomes^{44,173} While there has been significant development of evidence from randomised controlled trials over the past 20 years, there remain significant unmet needs (see **s19**). This is particularly critical in RLS where the burden of disease is high and access to antifungal therapy remains inadequate. Equally, more needs to be learnt in RRS where host risk profiles are changing and an increasing array of presentations of cryptococcosis are being recognised, necessitating more nuanced and individualised treatment plans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Delineating the cryptococcosis clinical syndrome involved (central nervous system CNS vs. non-CNS, non-pulmonary disseminated disease vs. isolated pulmonary vs. direct skin inoculation) guides choice of antifungal treatment and duration (see Figure 3).
- L-Amb 3–4mg/kg daily and 5-flucytosine 25 mg/kg four times a day, remains the most optimal induction therapy option for cryptococcal meningitis (CM), disseminated cryptococcosis and severe isolated pulmonary cryptococcosis in all hosts in resource-rich settings.
- In resource-limited settings, patients with HIV-associated CM are best treated with L-Amb 10 mg/kg as a single-dose, with 14 days of 5-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 CM 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, think broadly, 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 (serum CrAg), persistently positive CSF CrAg, visible cryptococci in CSF (without culture positivity), nor abnormal CSF microscopy or biochemistry. These 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.

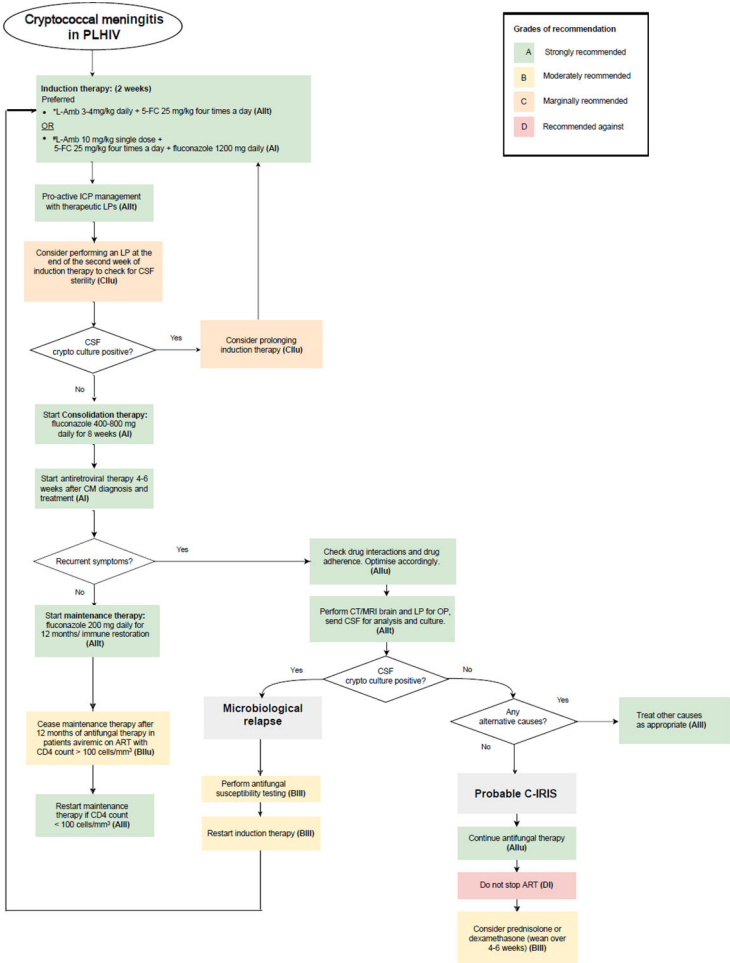


Figure 1:
Management algorithm for cryptococcal meningitis/ cryptococcal meningoencephalitis (CM) in PLHIV

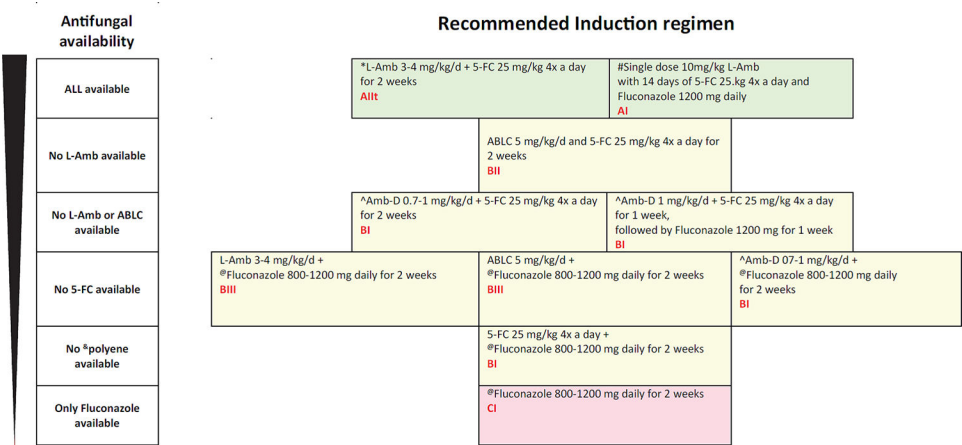


Figure 2:
HIV-CM Induction antifungal treatment recommendations by antifungal drug availability

- *(L-Amb 3–4 mg/kg/d + 5-FC 25 mg/kg 4x a day for 2 weeks) has not been compared to #(Single dose 10mg/kg L-Amb with 14d of 5-FC 25.kg 4x a day and Fluconazole 1200 mg daily). # has only been trialled in HIV-CM.
- &Polyene includes Amphotericin B formulations such as conventional deoxycholate Amphotericin B (Amb-D), Liposomal Amphotericin (L-Amb), Amphotericin B lipid complex (ABLC).
- ^Amb-D: 1 mg/kg showed earlier fungicidal activity than 0.7 mg/kg but some institutions use the lower 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.
- Grading of recommendation and level of evidence in bolded red letters.
- Recommendations by shading: green (Strong), yellow (Moderate), pink (marginal)

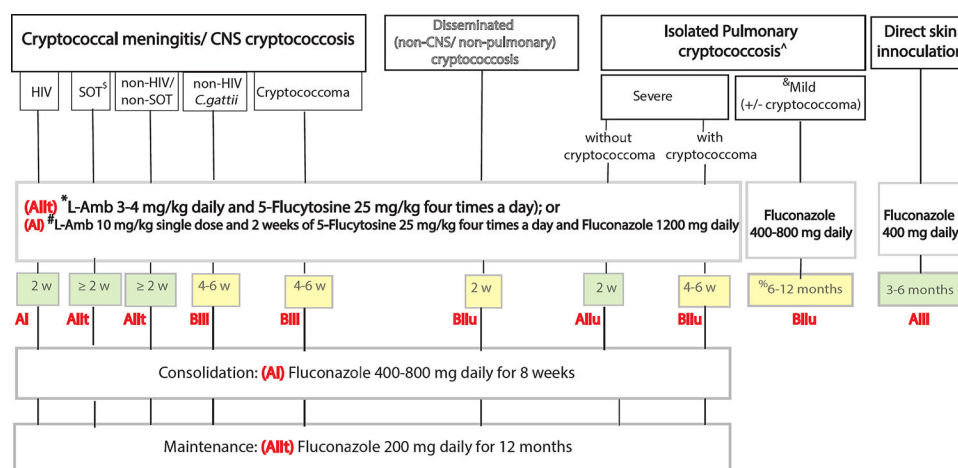


Figure 3: Recommended first-line antifungal therapy by cryptococcosis syndrome.

This simplified figure summarises the recommendations for first-line antifungal therapy where optimal antifungal options are available. The grading of recommendation and level of evidence is in red, with the duration of the therapy shaded by strength of recommendation. Isolated pulmonary cryptococcosis may be divided into severe or mild, and with or without pulmonary cryptococcoma. Mild pulmonary cryptococcosis is defined as asymptomatic or mildly symptomatic patients, or those with a solitary small nodule (< 2 cm) while severe pulmonary cryptococcosis includes those with multiple lesions, large lesions (≥ 2 cm), lobar consolidation, cavitation, multi-lobar involvement, and those with hypoxaemia.

In **HIV-associated CM/ CNS cryptococcosis** we recommend L-Amb 3–4 mg/kg daily and 5-Flucytosine 25 mg/kg four times a day OR single-dose L-Amb 10 mg/kg and 14 days of 5-Flucytosine 25 mg/kg four times a day and Fluconazole 1200 mg daily, for a minimum of 2 weeks. Importantly, the single-dose L-Amb 10 mg/kg and 14 days of 5-Flucytosine 25 mg/kg four times a day and Fluconazole 1200 mg daily has only been trialled in HIV-CM. There is currently no data of its application in non-HIV-CM settings. See Figure 2 for treatment cascade in HIV-CM by antifungal availability.

In **non-HIV associated CM/ CNS cryptococcosis, disseminated cryptococcosis** and **severe isolated pulmonary cryptococcosis**, we recommend L-Amb 3–4 mg/kg daily and 5-Flucytosine 25 mg/kg four times a day for 2 weeks or more. Extensions in the duration of induction therapy may be considered in SOT recipients, non-HIV-non-SOT patients, and in non-HIV patients with *C. gattii* infection (4–6 weeks), those with CNS cryptococcomas (4–6 weeks) or severe isolated pulmonary cryptococcosis with lung cryptococcomas (4–6 weeks). All CNS-based induction therapy should be followed by 8 weeks of fluconazole 400–800 mg daily as **consolidation** therapy, then fluconazole 200 mg daily as **maintenance** therapy for 12 months or until immune restoration. The consolidation dose for HIV-CM in resource limited settings (RLS) is currently commonly prescribed as fluconazole 800 mg daily, and the 400 mg daily dose is used in other non-RLS settings, and other non-CM cryptococcosis syndromes. In settings where antifungal therapy availability is limited, refer to Figure 2 for alternatives.

Patients with **mild isolated pulmonary cryptococcosis** (regardless of immune state, presence of cryptococcoma or infecting strain) may be treated with fluconazole 400–800 mg daily for 6–12 months (note: a shorter duration of 3 months may be considered in those

who are immunocompetent). If the presence of *Cryptococcus spp.* in respiratory specimens 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 (see **Table 6**). In the rare case of **skin cryptococcosis from direct skin inoculation**, fluconazole 400 mg daily for 3–6 months is recommended. See Table 6 for details on pulmonary cryptococcosis and pulmonary cryptococcoma.

Footnote:

*L-Amb 3–4 mg/kg daily and 5-Flucytosine 25 mg/kg four times a day has not been directly compared against #L-Amb 10 mg/kg single dose and 2 weeks of 5-Flucytosine 25 mg/kg four times a day and Fluconazole 1200 mg daily.

*L-Amb 3–4 mg/kg daily and 5-Flucytosine 25 mg/kg four times a day is strongly preferred in CM/ CNS cryptococcosis in SOT and non-HIV non-SOT settings, disseminated cryptococcosis and severe pulmonary cryptococcosis.

#L-Amb 10 mg/kg single dose and 2 weeks of 5-Flucytosine 25 mg/kg four times a day and Fluconazole 1200 mg daily. This regimen has only been trialled in HIV-CM. There is no supporting data of its use in SOT, or non-HIV non-SOT patients, and in other cryptococcosis syndromes.

§: solid organ transplant (SOT) recipients. *L-Amb 3–4 mg/kg daily and 5-Flucytosine 25 mg/kg four times a day is strongly preferred in SOT patients.

^: Isolated *C. neoformans* or *C. gattii* pulmonary cryptococcosis.

Mild pulmonary cryptococcosis (with or without cryptococcoma): asymptomatic or mildly symptomatic patients or with a solitary small nodule (< 2 cm).

Severe pulmonary cryptococcosis: multiple lesions, large lesions (≥ 2 cm), lobar consolidation, cavitation, multi-lobar involvement, hypoxaemic.

%: May consider a shorter duration (e.g., 3 months) in immunocompetent individuals with mild isolated pulmonary cryptococcosis.

&: If the presence of *Cryptococcus spp.* in respiratory specimens 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.

W: weeks

Grading of recommendation and level of evidence in bolded red letters

Recommendations by shading: green (strongly recommended), yellow (moderately recommend)

Table 1:

Ten principles of CM management

Ten principles of CM management	
1.	Selectively screen, risk-stratify and investigate for cryptococcosis. • (AI) Perform a blood CrAg by LFA for the screening of cryptococcosis in newly diagnosed PLHIV with CD4 <200 cells/mm³, and in PLHIV recommencing ART after a period of discontinuation (with CD4 <200 cells/mm³), and determine the CrAg titre if positive. • (AII) All patients with suspected or confirmed cryptococcosis (including cryptococcal antigenemia) require careful clinical assessment for CNS, pulmonary and other body site involvement. Investigations for disseminated disease should include: (1) lumbar puncture (LP) with measurement of CSF opening pressure (OP), glucose, protein, cell counts, microscopy, culture, and quantification of CSF CrAg; (2) quantification of blood CrAg, and cultures of blood, sputum (or other respiratory specimens) and/or of other affected sites; (3) ideally, brain imaging (preferably MRI) and chest imaging (preferably CT). • (AIU) In asymptomatic cryptococcal antigenaemic PLHIV without clinical cryptococcosis after thorough investigation (including at least a LP), fluconazole 1200 mg daily for 2 weeks (when ART may be initiated), followed by 800 mg daily for 8 weeks, and 200 mg thereafter for about 6 months is recommended. (Guidance may be updated contingent on results of present prospective trials.) • (BI) In clinical settings where CrAg LFA screening is not available (despite WHO's strong recommendations), universal primary prophylaxis with fluconazole 100 mg daily in PLHIV with CD4 count <200 cells/mm³ is recommended
2.	Provide best fungicidal induction regimen possible. • (AII) L-Amb 3–4 mg/kg daily plus 5-flucytosine 25 mg/kg four times a day, for 2 weeks (<i>preferred in resource-rich settings; and strongly recommended in SOT, and non-HIV non-SOT settings</i>); OR • (AI) a single dose of L-Amb 10 mg/kg with 14 days of 5-flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily (<i>note: only trialled in PLHIV in RLS</i>) • (CIU) Consider performing an LP at the end of the first or second week of induction therapy to check for CSF sterility prior to ART commencement. • (CIU) Consider prolonging induction therapy if CSF is persistently culture positive at 2 weeks. • (BIII) In <i>C. gattii</i> CNS infection occurring in non-HIV patients or CNS cryptococcoma consider extending induction therapy to 4–6 weeks
3.	Monitor for and minimise drug toxicity. • (AIU) In-hospital care for the first 1–2 weeks is encouraged to manage the significant early complications seen with CM management. • (AIU) The use of Amb-D and L-Amb should be accompanied by pre-hydration and aggressive potassium and magnesium replacement therapy. • (AIU) Frequent (at least every alternate day) complete blood counts, renal function tests and electrolyte measurements, are recommended to assess for therapy-related bone marrow, nephrotoxicity, and fluid and electrolyte changes. Liver function tests at baseline and at least weekly are recommended.
4.	Manage raised intracranial pressure (ICP). • (AIU) Opening pressure (OP) should be measured at every LP in patients with CM. • (All) Acute symptomatic elevation of the ICP (≥ 20 cm of CSF) should be managed by daily therapeutic LPs (i.e., removal of sufficient CSF (usually around 20–30 ml) to reduce the pressure to 50% of OP and/or to a normal pressure of ≤ 20 cm of CSF (documented as a closing pressure). • (BIU) Perform a scheduled therapeutic LP around 48–72 hours of initial LP and/or 7 days, regardless of initial OP. • (All) Persistent raised symptomatic ICP despite therapeutic LPs 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.
5.	Look for an underlying immunosuppressive state.***

Ten principles of CM management	
	• (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 presenting 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, be considered for evaluation of an undiagnosed immunodeficiency, preferably in consultation with a clinical immunologist.
6.	Provide and ensure adherence to consolidation and maintenance therapy. • Consolidation (8 weeks): (AI) Fluconazole 400–800 mg daily. <i>Note: 800 mg preferred in RLS.</i> • Maintenance (12 months or until immune restoration): (AII) Fluconazole 200 mg daily. • (AIIu) Check for drug-drug interactions and dose-adjust as necessary. • (AIII) Close monitoring of tacrolimus, cyclosporine and sirolimus (TDM) levels and dose reduction of these agents are recommended when azoles are co-administered.^{174,175}
7.	Optimal commencement of ART in PLHIV. • (DI) Immediate or very early commencement of ART is not recommended • Depending on antifungal induction therapy availability: – Sub-optimal/limited access: (AI) Delay ART for 4–6 weeks. – Optimal and in RRS: (BIu) Consider further individualisation taking into consideration resolution of symptoms and signs of CM and ICP (including normalisation of OP), 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 local experience of CM and C-IRIS management. (Usual range is 4–6 weeks).
8.	Monitor for clinical relapse and investigate for causality. • (AIIu) Think broadly and investigate thoroughly for causality (CNS and non-CNS; infective and non-infective) in cases of apparent clinical relapse. Investigations should include CT/MRI brain, LP for OP 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 (TDM) if applicable. Optimise control of underlying disease(s). • (DIIu) The use of follow-up blood or CSF CrAg (including monitoring of titres) for clinical decision-making is discouraged. • (DIIu) Do not escalate antifungal therapy for persistent blood antigenemia, persistently positive CSF CrAg, visible cryptococci in CSF (without culture positivity), nor abnormal CSF microscopy or biochemistry. These are not necessarily indicators of microbiological failure.
9.	In culture-positive (microbiological) persistence or relapse, evaluate for drug adherence, drug-drug interactions, and drug resistance. • (BIII) AFST should be performed concurrently on all initial and relapse isolates (if stored and available). An increase in fluconazole MIC 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 AFST.
10.	Carefully exclude alternative diagnoses before attributing clinical relapse to C-IRIS. • (Allt) For patients with suspected paradoxical C-IRIS, carefully exclude recurrent cryptococcal disease or new infective or non-infective conditions, prior to attributing symptoms and signs to C-IRIS. Perform an MRI brain and LP to measure OP and obtain CSF for microbiological, cellular, and biochemical analyses. • (AIIu) Treatment of C-IRIS should include therapeutic LP, symptomatic therapy such as analgesia, antiemetics and antiepileptics where appropriate. • (AIII) Continue current antifungal therapy. • (BIII) High-dose prednisone/prednisolone (usually 0.5–1.0 mg/kg daily) or dexamethasone (usually 0.2–0.3 mg/kg daily), weaned over 4–6 weeks may be considered in those with persistent symptoms, unresponsive to therapeutic LPs. Rarely, a second steroid course with taper is needed. • (DIII) Do not stop ART.

Table 1 highlights the key principles in CM management, best read in context (see relevant sections in main text). While most evidence and recommendations are derived from CM in PLHIV populations, many of these principles are translatable to non-HIV settings.

Principles specific to CM in PLHIV are shaded in grey.

Unique considerations for non-HIV *C. gattii* CNS infection are underlined.

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

Antifungal treatment recommendations for CM in adult PLHIV, SOT, non-HIV-non-SOT populations.

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Patient population	First-line agent	SoR QoE	Alternative agents	SoR QoE	Other recommendations
			Where only fluconazole is available: Fluconazole 800–1200 mg daily	CI	- aviremic on ART with CD4 count >100 cells/mm³. (AIII) Restart maintenance therapy if CD4 drops <100 cells/mm³.
	CONSOLIDATION(8w): % Fluconazole 400–800 mg daily (Note: 800 mg preferred in RLS)	AI	Voriconazole 200 mg twice a day (with TDM)	BIII	
			Posaconazole 300 mg daily (with TDM)	BIII	
			Isavuconazole 200 mg daily	BIII	
			Itraconazole 200 mg twice a day (with TDM)	CIIt	
	MAINTENANCE(12m/immune restoration): Fluconazole 200 mg daily	AIIt	Voriconazole 200 mg twice a day (with TDM)	BIII	
			Posaconazole 300 mg daily (with TDM)	BIII	
			Isavuconazole 200 mg daily	BIII	
			Itraconazole 200 mg twice a day (with TDM)	CIIt	
Solid Organ Transplant recipients	INDUCTION(minimum 2w): L-Amb 3–4 mg/kg daily plus 5-FC 25 mg/kg four times a day	AIIt	Where <i>L-Amb</i> is not available: ABLC 5 mg/kg daily plus 5-FC 25 mg/kg four times a day	BlIt	(AIII) We recommend that CNS-based therapy 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 (TDM) levels and dose reduction of these agents are recommended when azoles are co-administered.^{174,175} (BIII) Immunosuppressant doses need to be carefully adjusted to allow effective killing of yeasts but should be reduced slowly to avoid precipitating C-IRIS. 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 anticytotoxic activity. (CIII) In a patient treated for cryptococcosis, re-transplantation or a new organ transplant may be considered provided viable yeasts have been cleared from CSF and the patient is asymptomatic after receiving 12 months of anticytotoxic treatment.
			Where <i>L-Amb</i> nor <i>ABLC</i> are available: Amb-D 0.7–1.0 mg/kg daily plus 5-FC 25 mg/kg four times a day	BlIt	
			Where <i>amphotericin B</i> -based therapies are not able to be used: 5-FC 25 mg/kg four times a day plus Fluconazole 800–1200 mg daily	CIIt	
	CONSOLIDATION(8w): Fluconazole 400–800 mg daily	AIIt	Voriconazole 200 mg twice a day (with TDM)	BIII	

Patient population	First-line agent	SoR QoE	Alternative agents	SoR QoE	Other recommendations
			Posaconazole 300 mg daily (with TDM)	BIII	
			Isavuconazole 200 mg daily	BIII	
			Itraconazole 4200 mg twice a day (with TDM)	CIIt	
	MAINTENANCE (12m): Fluconazole 200 mg daily	AIIIt	Voriconazole 200 mg twice a day (with TDM)	BIII	
			Posaconazole 300 mg daily (with TDM)	BIII	
			Isavuconazole 200 mg daily	BIII	
			Itraconazole 200 mg twice a day (with TDM)	CIIt	
Non-HIV non- transplant	Induction (minimum of 2w), Consolidation and Maintenance: Same options as for CNS/CM treatment in SOT	AIIIt	Same as for CNS/CM treatment in SOT	Bllt	• (BIII) Consider extending induction therapy for <i>C. gattii</i> CNS infection to 4–6 weeks in non-HIV patients.

Footnote:

* preferred in resource-rich settings (RRS)

recommended in resource-limited settings (RLS)

% consolidation dose of Fluconazole 800 mg daily is preferred in RLS

TDM: therapeutic drug monitoring