BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

THERAPEUTIC GUIDELINES FOR OPPORTUNISTIC INFECTIONS CRYPTOCOCCOSIS

INITIAL RELEASE: MAY 2009

LAST UPDATED: OCTOBER 2023

Providence Health Care
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VERSION 27.10.2023

CRYPTOCOCCOSIS

Table of Contents

Abbreviations: ART, antiretroviral therapy; CFU, colony-forming units; CM, cryptococcal meningitis; CNS, central nervous system; CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; ECV, epidemiologic cut-off values; EDTA, ethylenediaminetetraacetic acid; EIA; enzyme immunoassay; FDA, Food and Drug Administration; ICP, intracranial pressure; IRIS, immune reconstitution inflammatory syndrome; LFA, lateral flow assay; LP, lumbar puncture; OP; opening pressure; PLWH, persons living with HIV; RCT, randomized controlled trial; TDM, therapeutic drug monitoring; VP, ventriculoperitoneal; WBC, white blood cell; WHO, World Health Organization

I) SCREENING

Recommendation: All patients living with HIV with a CD4 <100/μL should have a serum cryptococcal antigen (CrAg) test performed, regardless of symptoms. Those who test positive require spinal fluid analysis to exclude asymptomatic cryptococcal meningitis prior to initiating pre-emptive antifungal therapy (see *Treatment section c*) (AI).

Discussion. Isolated asymptomatic cryptococcal antigenemia has been shown to be a harbinger of clinical disease[1]. Among persons living with HIV (PLWH) with cryptococcal antigenemia, cryptococcal meningitis (CM) has been confirmed in up to 34% of those who are asymptomatic and 90% of those with headache only[2]. At 1 year follow-up, the incidence of CM was 21% among serum cryptococcal antigen (CrAg)-positive PLWH who did not receive pre-emptive fluconazole compared to 0.4% for those who were serum CrAg-negative at baseline[3]. Among PLWH with a CD4 count of less than 100 cell/μL, the average global prevalence of cryptococcal antigenemia is 6%[4]. A recent study in the USA demonstrated positive results for CrAg in 2.9% and 4.3% for those with CD4 counts <100 cells/μL and <50 cells/μL, respectively[5]. The prevalence of cryptococcal antigenemia among such persons in Canada has yet to be reported[4].

II) DIAGNOSIS

Cryptococcosis in PLWH is usually due to *Cryptococcus neoformans* rather than *Cryptococcus gattii*. The clinical spectrum of HIV-related cryptococcosis includes predominantly meningitis, less often pulmonary infection or other sites of disease, and asymptomatic cryptococcal antigenemia[6]. Diagnosis relies upon serology (antigen detection in serum or cerebrospinal fluid [CSF]), and for various clinical specimens the use of smears, cultures and histopathology. The recently introduced CrAg lateral flow assay (LFA) has outperformed other serologic methods, being a low cost, rapid, point-of-care dipstick test which doesn't require refrigeration, and has improved sensitivity (99.3%) and specificity (99.1%) compared to latex agglutination (LA) and enzyme immunoassay (EIA)[7] for CM. The CrAg LFA has been adopted by clinical laboratories in British Columbia in recent years. It should be noted that LFA titres are not equivalent to the previously available LA titres, given that the former are typically several fold higher[8]. In AIDS-related CM, cultures of blood and CSF are positive for *Cryptococcus neoformans* in 57% and 95% of patients, respectively. Any positive result for *Cryptococcus* (culture, antigen titre, smear, or histopathology) from extrameningeal sites should prompt evaluation including lumbar puncture to exclude meningitis, which may be asymptomatic. **Cryptococcal meningitis** is confirmed by a positive CSF test using either antigen detection or culture. Note that the diagnosis of relapsed CM is established by the presence of a positive CSF culture (after having previously converted from culture positive to negative), but not solely on the basis of other results such as CSF India ink smear, CrAg, or cell count[9].

III) PROPHYLAXIS

a) Primary prophylaxis. Both fluconazole and itraconazole have been shown to reduce the frequency of cryptococcal disease in PLWH. However, primary antifungal prophylaxis is not recommended because of the low frequency of disease in North America, lack of survival benefit in randomized controlled trials (RCTs), the efficacy of screening and pre-emptive treatment, the potential for development of drug resistance, and cost[10,11,12] (BII).

b) Secondary prophylaxis (maintenance therapy) is indicated for any patient who has completed initial treatment (both Induction and Consolidation Therapy, see below) in order to prevent relapse.

Recommended regimen for secondary prophylaxis:

Preferred regimen:

- Fluconazole 200 mg PO once daily (AI) for at least 12 months and until there has been adequate immune reconstitution to allow discontinuation of prophylaxis (see below, *Discontinuing secondary prophylaxis*).

Alternative regimen:

- Itraconazole 200 mg PO once daily (CI).

Discussion. In the absence of secondary prophylaxis, the relapse rate at 1 year for HIV-related CM was approximately 50% in the pre-ART (antiretroviral) era[13]. Fluconazole provides optimal efficacy and tolerance,[14,15] has predictable absorption, and does not require therapeutic drug monitoring (TDM)[16]. Prophylactic regimens other than fluconazole are generally discouraged because of reduced efficacy and/or tolerance[14,15]. Once weekly intravenous amphotericin B compared to daily oral fluconazole was associated with a higher rate of drug-related toxicity and lower likelihood of being relapse-free after 1 year (78% vs 97%, $p<0.001$)[14]. In a double-blind RCT, the rates of culture-positive relapse of cryptococcal meningitis during maintenance therapy with fluconazole and itraconazole were 4% and 23%, respectively ($p=0.006$)[15]. Subtherapeutic itraconazole levels may be related to various drug interactions, gastric achlorhydria, and malabsorption syndromes, making TDM a necessity with this agent. Itraconazole TDM[16] is available at St. Paul's Hospital (Vancouver) chemistry laboratory (St. Paul's Hospital, main switchboard: 604-682-2344). A trough itraconazole level (EDTA plasma sample) should be obtained after 4-7 days of treatment and periodically thereafter.

c) Discontinuing and restarting secondary prophylaxis for cryptococcosis:

Recommendation: Patients who have successfully completed initial therapy for cryptococcosis plus 1 year of secondary prophylaxis with an azole, have no signs or symptoms of cryptococcosis, and have sustained immunologic response to ART with CD4 counts >100 cells/μL and suppressed viral loads for >3 months should be considered for stopping fluconazole (or itraconazole) suppressive therapy (BII). Secondary prophylaxis should be restarted if the CD4 count subsequently falls again below 100 cells/μL (AIII).

Discussion. Few patients have been shown to subsequently develop relapse of cryptococcosis after discontinuing fluconazole within the above-mentioned parameters[17,18,19,20,21]. Based upon the published experience, neither the results of a repeat serum CrAg nor a repeat spinal fluid examination have been considered to be prerequisites for decision-making at the time of discontinuing fluconazole secondary prophylaxis[17]. Patients who stop fluconazole suppressive therapy should be advised of the possibility of relapse and the need to report symptoms promptly. Some cryptococcal clinical events which are culture-negative that have been reported after stopping secondary fluconazole prophylaxis appear likely to have been due to cryptococcal immune reconstitution inflammatory syndrome (IRIS),[18] which has not been shown to be prevented by ongoing antifungal maintenance therapy.

IV) TREATMENT

a) Cryptococcal Meningitis

Recommended treatment:

i) **Induction therapy** is continued for at least 2 weeks, until there is a clinical response and follow-up CSF culture is negative (BIII).

Preferred induction regimens in high resource settings (all 14-day regimens):

- Liposomal amphotericin B 3-4 mg/kg IV once daily plus 5-flucytosine 25 mg/kg PO 4 times a day (AI),

  OR

- Amphotericin B deoxycholate 0.7-1.0 mg/kg IV once daily plus 5-flucytosine 25 mg/kg PO 4 times a day (AI)

Alternative Regimens (all 14-day regimens)**:**

- Amphotericin B lipid complex 5 mg/kg IV once daily plus 5-flucytosine 25 mg/kg PO 4 times a day (BII),

  OR

- Liposomal amphotericin B 3-4 mg/kg IV once daily plus fluconazole 800-1,200 mg PO or IV once daily (12 mg/kg/day for children or adolescents, up to a maximum dose of 800 mg/day) (BIII),

  OR

- Amphotericin B deoxycholate 0.7-1.0 mg/kg IV once daily plus fluconazole 800-1,200 mg PO or IV once daily (12 mg/kg/day for children or adolescents, up to a maximum dose of 800 mg/day) (BI),

  OR

- Liposomal amphotericin B 3-4 mg/kg IV once daily monotherapy (BI),

OR

- Amphotericin B deoxycholate 0.7-1.0 mg/kg IV once daily monotherapy (BI),

OR

- Fluconazole 800-1200 mg PO or IV once daily (12 mg/kg/day for children or adolescents, up to a maximum dose of 800 mg/day) plus 5-flucytosine 25 mg/kg PO 4 times a day (BI).

Preferred induction regimens in low resource settings (all 14-day regimens):

- Liposomal amphotericin B 10 mg/kg IV single dose (only on day 1 of treatment), plus 14 days of 5-flucytosine 25 mg/kg PO 4 times a day plus fluconazole 1200 mg PO once daily (AI),

OR

- Amphotericin B deoxycholate 1.0 mg/kg IV once daily plus 5-flucytosine 25 mg/kg PO 4 times a day, both for 7 days, followed by fluconazole 1,200 mg PO once daily for 7 days (AI).

Discussion. An amphotericin B formulation plus 5-flucytosine is associated with improved survival compared to alternate treatment regimens such as amphotericin B monotherapy, or amphotericin B plus fluconazole[22,23,24]. The inclusion of 5-flucytosine in the induction regimen has also been associated a reduction in the rate of subsequent relapse[15]. Although 5-flucytosine is not a licensed antifungal agent in Canada, it can be obtained under the special access program through the Health Protection Branch (HPB)*, although it may be immediately available from the closest tertiary care hospital which has drug supply. Intravenous saline (500-1000 mL) should be given prior to each dose of any amphotericin B formulation in order to reduce nephrotoxicity, although the studies demonstrating benefit were conducted with amphotericin B deoxycholate[25,26], rather than any of the lipid formulations. Monitoring blood work should include CBC, differential, liver enzymes, blood urea nitrogen (BUN), creatinine, electrolytes, and magnesium. The dosage of 5-flucytosine needs to be adjusted for renal dysfunction. Therapeutic drug monitoring (TDM) has been recommended for 5-flucytosine (2-hr post dose level with target of 25-100mg/L) both for efficacy and minimizing toxicity; however, 5-flucytosine drug levels are not currently available in British Columbia and there is evidence that 5-flucytosine TDM may not be necessary[27]. Instead, one can rely upon dosage adjustment in the presence of renal dysfunction and monitoring blood counts for cytopenias and hepatotoxicity.

Alternative induction regimens. There is less experience treating CM with amphotericin B lipid complex compared to liposomal amphotericin B[28]. Those regimens which include fluconazole have been associated with improved early fungicidal activity (as measured by quantitative culture of the CSF with the reduction in CFU/mL) using higher doses up to 800-1,200 mg/day rather than adult daily doses of <800mg[29,30,31]. Alternative induction regimens

*Health Protection Branch: https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs.html

such as monotherapy with amphotericin B or high dose fluconazole are associated with increased mortality[22,23].

Induction regimens in low resource settings. In 2018, management guidelines for cryptococcal disease in PLWH were published by the World Health Organization (WHO)[32]. This included a recommendation for CM induction therapy with an abbreviated 7-day course of amphotericin B 1.0 mg/kg IV once daily plus 5-flucytosine 25 mg/kg PO 4 times a day, followed by one week of monotherapy with high dose fluconazole (1,200 mg PO once daily for adults and 12 mg/kg PO once daily for children and adolescents, up to a maximum daily dose of 800 mg)[32], based upon the results of a meta-analysis[33], and in particular an RCT in a low-resource setting (the ACTA study)[23].

Subsequently, the largest RCT of induction therapy in HIV-related CM was conducted in Africa (Ambition study) and included 814 patients who received either the WHO 2018 preferred regimen (as above) or a single high dose of liposomal amphotericin B (10 mg/kg) only on day 1 plus 14 days of 5-flucytosine (25 mg/kg PO 4 times a day) plus fluconazole (1,200 mg PO once daily)[34]. This study demonstrated that the induction regimen which included a single high-dose of liposomal amphotericin B was non-inferior to the WHO 2018 guideline recommended treatment and was associated with fewer adverse events[34]. At least in those low resource settings where liposomal amphotericin B and 5-flucytosine are available, this regimen is particularly attractive and logistically less demanding compared to a longer duration of amphotericin B. The findings of the Ambition study prompted a further update of the WHO guidelines in June, 2022[35].

However, there remains uncertainty regarding whether or not these shorter amphotericin B/flucytosine induction regimens favoured by WHO are fully applicable to high-income countries[33,36]. The Ambition study regimen with just a single dose of liposomal amphotericin B IV may facilitate early hospital discharge; however, close monitoring for complications during the first 2 weeks of treatment (e.g., raised intracranial pressure, serial lumbar punctures, seizure management etc.) may be more easily accomplished in hospital. The Ambition study regimen would be an option for the occasional patient in a high resource setting who strongly refuses hospitalization despite being informed of the risks associated with induction therapy management in the community.

ii) Intracranial pressure management

Opening pressure (OP) should be measured provided there are no contraindications to lumbar puncture (LP) (e.g., coagulopathy, intracranial mass lesions or midline shift on imaging). The LPs should be performed in the lateral position to facilitate OP measurements. If the patient has symptoms or signs consistent with raised intracranial pressure (ICP) (e.g. headache, vomiting, hearing or visual loss, cranial neuropathies, reduced level of consciousness) or the OP is >250 mm H_2O, then LP should be performed with removal of up to 20-30 ml of CSF in order to reduce the pressure by approximately 50%[9,37,38,39]. The CSF pressure should be rechecked after removing every 10 ml of CSF[40]. A common misconception is that if the patient's symptoms have improved (e.g., headache has resolved)

then the LP doesn't need to be repeated[37]. The assessment of symptoms and signs is unreliable for excluding the presence of raised ICP, which is often clinically silent[40,41]. Repeat LPs should continue every 1-2 days depending upon the clinical urgency and how extreme the pressure elevation until the OP is consistently <250 mm H_2O[36,37]. An association between the use of therapeutic LPs and improved survival has been demonstrated in HIV-related CM with raised ICP[39]. If the patient doesn't tolerate repeated LPs or if markedly elevated ICP persists with or without symptoms or signs beyond the first 1-2 weeks of antifungal therapy and multiple LPs, then neurosurgical consultation should be obtained regarding surgical management (e.g., ventriculoperitoneal [VP] shunt, or lumbar drain)[9,37,42,43,44,45]. A VP shunt can be safely inserted during active infection provided that antifungal therapy is started prior to shunt placement[9,37]. VP shunt placement would usually be performed after induction therapy had been completed.

Recommendation: All patients with HIV-related CM should be considered for serial therapeutic lumbar punctures during induction therapy (on days 1,3,7, and 14), regardless of the initial opening pressure measurement (BII).

Discussion. Multiple studies have demonstrated that baseline ICP<200 mm H_2O or >350 mm H_2O are associated with increased mortality in HIV-related CM[46,47]. Most existing guidelines don't recommend therapeutic LPs in patients with OP <250 mm H_2O in the absence of clinical evidence of raised ICP[9,35]. However, in a prospective study of CM in Uganda (2013-2017), the 30-day mortality was assessed in relation to the number of follow-up therapeutic LPs that were performed within the first 7 days[46]. The 30-day mortality was 50% higher among those who did not receive any additional therapeutic LPs compared to those with >1 (33% vs 22%; P=0.04), regardless of the baseline ICP. Similar results were observed in another African CM study with a relative risk of mortality of 0.31 (95% confidence interval [CI] 0.12-0.82) associated with the use of at least one therapeutic LP following the initial diagnostic LP[39].

In two other observational African studies, reduced mortality in CM was associated with the scheduling of 4 LPs during either the first 7 or 14 days of treatment (e.g. days 1,3,7, and 14) irrespective of baseline ICP, compared to those who had fewer therapeutic LPs[48,49]. Why survival is improved in association with therapeutic LPs in those with a baseline OP <200 mm H_2O is unclear, but may be explained by falsely low baseline measurements, subsequent development of raised ICP, or a reduction in fungal burden by way of manual drainage[46].

Further evidence supporting the role of therapeutic LPs in HIV-related CM comes from analysis of 12 clinical trials conducted in Africa and Thailand in which all participants underwent serial LPs on days 1,3,7, and 14 regardless of their baseline OP[40,47]. In contrast to other studies, with the use of serial LPs there was no observed increase in mortality associated with high baseline OP[40,47]. These observations have prompted the recommendation that follow-up therapeutic LPs should be performed in all patients with CM on day 3 and day 7[46], in addition to the previously recommended LP at day 14[9].

Treatments not recommended: Acetazolamide[50] (AI), corticosteroids[51] (AI) and mannitol are not recommended for managing raised ICP in AIDS-related CM. However, there is limited evidence supporting the role of corticosteroids in the management of CM-IRIS which may be associated with raised ICP (*see Cryptococcal IRIS*, below).

iii) Monitoring response to treatment.

Resolution of neurologic signs and symptoms and normalization of intracranial pressure are expected during the course of induction therapy. The primary laboratory indicator of successful induction therapy is the conversion of CSF to culture-negative by the 2 week time point, not the results of follow-up serum or CSF CrAg titres, neither of which are recommended. Although at the time of diagnosis there is a strong correlation between the CSF cryptococcal burden of disease as measured by CSF colony-forming units (CFU)/mL in culture and the CSF CrAg titre, during the first few weeks of treatment there is no correlation between the rate of decline in CSF CFU/mL (which reflects treatment efficacy) and subsequent CSF CrAg titres[52]. In regard to adverse drug reactions, monitoring blood work should include CBC, differential, liver enzymes, BUN, creatinine, electrolytes, and magnesium as outlined above for induction therapy.

iv) Consolidation therapy is continued for at least 8 weeks.

Recommended treatment:

Preferred Regimen:

Fluconazole 800 mg/day orally or IV (AI).

Alternative Regimen:

Itraconazole 200 mg twice daily (CI).

Discussion. Although earlier clinical trials of consolidation therapy in PLWH were performed with fluconazole 400 mg/day[24], the higher dose of 800 mg/day is well-tolerated, and associated with more rapid reduction in CFU/mL of CSF[29,30,31,35]. In contrast to itraconazole, fluconazole is better tolerated, more effective[24], predictably achieves therapeutic levels, and does not require TDM[16]. Consequently, itraconazole is seldom used for either consolidation or maintenance therapy in cryptococcosis. Subtherapeutic itraconazole levels may be related to various drug interactions, achlorhydria, or malabsorption syndromes, making TDM a necessity with this agent[16]. A trough itraconazole level (EDTA plasma sample) should be obtained after 4-7 days of treatment and periodically thereafter and sent to the chemistry laboratory at St. Paul's Hospital (main switchboard: 604-682-2344), Vancouver, BC.

v) Maintenance therapy (Secondary prophylaxis)

See Secondary Prophylaxis (above).

vi) Susceptibility testing.

Previous guidelines have not recommended the routine performance of *Cryptococcus neoformans* susceptibility testing[9] due to very infrequent de novo resistance to first line antifungals[53], the lack of established clinical breakpoints for defining resistance (although epidemiologic cut-off values [ECVs] may be helpful in clarifying whether a particular strain is wild-type in cases of suspected resistance)[54,55], the limited number of clinical laboratories that perform fungal susceptibility testing, interlaboratory variability of results, and the significant possibility that the results may be sometimes be misleading to clinicians.

However, there have been recent reports of increasing fluconazole resistance in *C. neoformans* in Africa[56,57] and Asia[58], prompting a call for fluconazole resistance screening at sentinel surveillance sites in sub-Saharan Africa[56]. Although there are some conflicting results, the larger and better designed studies have failed to demonstrate an association between in vitro susceptibility and mortality outcome using a definition of fluconazole susceptibility as a minimum inhibitory concentration (MIC) ≤8 μg/mL[59].

Despite the above-mentioned limitations, susceptibility testing is warranted in patients failing primary therapy with CSF cultures positive beyond 2 weeks of standard induction treatment, or if there is culture-positive relapse, or a history of recent antifungal drug exposure before the diagnosis of cryptococcal infection (see section vii, *Assessment of suspected treatment failure*). Simultaneous antifungal susceptibility testing of 5-flucytosine and fluconazole for both the baseline and most recent positive culture isolates is recommended, with a three-fold increase in MIC compared to the baseline (pretreatment) isolate being suggestive of the development of drug resistance.

vii) Assessment for suspected treatment failure.

Either continued (beyond 2 weeks) or recurrent CSF culture positivity, or symptoms which are persistent, recurrent, or new towards the time of completion of induction therapy or beyond should prompt consideration of possible complications (e.g., raised ICP, IRIS, adverse drug effects) or microbiologic failure. The latter, which may occur with persistent or recurrent culture-positive CSF is usually due to inadequate induction therapy, treatment non-adherence, drug interactions, or antifungal drug resistance. However, the recurrence or persistence of symptoms in CM due to microbiologic relapse must be differentiated from IRIS, uncontrolled raised intracranial pressure (with or without IRIS), and sometimes other causes. For microbiologic relapse, adherence to therapy should be confirmed in addition to requesting antifungal susceptibility testing (see section IV a-vi above).

Diagnosis. Diagnostic confirmation of microbiologic failure depends upon CSF culture, which usually becomes positive within 2 weeks in microbiologic failure. Pending this result, strong consideration should be given to restarting combination reinduction antifungal therapy in the setting of clinical relapse. In a recent Ugandan study, at the time of recurrent symptoms in CM, PLWH whose laboratory markers indicated poor immune reconstitution (CSF WBC <5 cells/μL or CD4 count <50 cells/μL) usually turned out to have microbiologic failure (86% and 91%, respectively), providing an important prompt for the reinitiating of induction therapy[60]. However, higher levels of these markers did not definitively exclude

microbiologic relapse. CSF cryptococcal antigen testing is not useful in differentiating CM microbiologic failure (relapse) from IRIS. However, a multiplex PCR for CSF (FilmArray Meningitis/Encephalitis panel, Biofire Diagnostics, LLC, Salt Lake City, Utah) appears promising with negative or positive results for *Cryptococcus* being predictive of IRIS or microbiologic failure, respectively[61].

Management. PLWH with culture-positive persistent or recurrent disease should receive another cycle of reinduction therapy with a preferred regimen and repeat follow-up CSF culture at 2 week intervals before transitioning to maintenance therapy. If there is evidence of fluconazole resistance, then the use of other triazoles (e.g. voriconazole[62], posaconazole[63], or isavuconazole[64]) should be considered for consolidation and maintenance therapy. Adjunctive therapy with interferon gamma is a consideration for those who have refractory CSF culture-positive disease despite optimal antifungal therapy, no drug resistance, and have received 4 weeks of effective ART[65]. In an RCT, interferon gamma combined with a preferred induction antifungal regimen was associated with a significant increase in the rate of clearance of cryptococcal infection from the CSF (early fungicidal activity, EFA)[66]. Although the study was not powered to evaluate a mortality difference, increased EFA has been independently associated with reduced mortality and serves as a surrogate marker[67].

b) Cryptococcosis without central nervous system (CNS) involvement (confirmed to be absent by spinal fluid analysis)

Recommended Treatment:

Pulmonary

1. Mild-moderate disease (mild-moderate symptoms, no diffuse pulmonary infiltrates)

- Fluconazole 400 mg (6 mg/kg) daily for 6-12 months (BIII) indefinitely, unless meeting criteria for discontinuing secondary prophylaxis (see above, *Discontinuing secondary prophylaxis*).

2. Severe disease (severe symptoms, or diffuse pulmonary infiltrates)

- The same as for cryptococcal meningitis (BIII)

Disseminated (applies to both isolated cryptococcemia and most cases of disease which are both non-meningeal and non-pulmonary, even if appearing to be localized to one anatomic site)

- The same as for cryptococcal meningitis (BIII)

Discussion. Randomized, controlled clinical trials for the management of cryptococcal infection for sites other than the CNS are not available. The above recommendations are based upon observational studies and expert opinion[9,68,69].

c) Cryptococcal antigenemia (without other evidence of cryptococcosis)

Recommended Treatment (after asymptomatic meningitis has been excluded):

- Fluconazole 800 mg for adults (or 6-12 mg/kg for adolescents) daily for 10 weeks followed by maintenance therapy (fluconazole 400 mg for adults or 6 mg/kg daily for adolescents) for at least 12 months (AII); indefinitely unless meeting criteria for discontinuing secondary prophylaxis.

Discussion. Among PLWH with a CD4 less than 100 cells/μL, the average global prevalence of cryptococcal antigenemia is 6%[4]. All such individuals should be investigated to exclude the possibility of asymptomatic meningitis prior to initiating pre-emptive fluconazole treatment. A recent meta-analysis of targeted pre-emptive fluconazole for cryptococcal antigenemia in ART-naïve PLWH with CD4 counts of <100 cells/μL demonstrated that after a median follow-up of 1 year, those who had meningitis excluded by LP at baseline and then received treatment with fluconazole 800 mg/day, compared to those who were just treated with fluconazole 800 mg/day and those who were neither investigated further nor treated, subsequently developed cryptococcal disease in 0%, 5.7%, and 21.4% of cases, respectively[3]. The proportion of patients who subsequently developed CM was lower (5.7%) with a fluconazole induction dose of 800 mg/day compared to doses of <800 mg/day (9.1%)[3].

V) CRYPTOCOCCAL IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Cryptococcal IRIS is characterized by a paradoxical clinical deterioration following the initiation of ART in approximately one third of patients with a previous (usually recent) diagnosis of cryptococcosis[70], or may occur as an "unmasking" event in a patient with subclinical disease. It is more likely to occur in patients who: i) have low CSF white blood cell counts of <25 cell/μL[71], ii) have higher initial CSF CrAg titres, iii) are ART naïve, iv) begin ART within 30 days after the diagnosis of cryptococcosis[72], and v) begin ART when the CSF is still culture-positive[73]. Clinical manifestations may include recurrent culture-negative meningitis (often with a higher CSF pleocytosis), cryptococcomas, lymphadenitis, and pulmonary nodules or infiltrates. The diagnosis of paradoxical IRIS is usually established in a patient with a relapse of symptoms, but with culture-negative CSF in association with a virologic (>1 $\log_{10}$ reduction in HIV RNA) and/or CD4 response to ART[72]. A positive CSF culture favours treatment failure due to relapse rather than IRIS, but may take weeks to become positive. In the setting of recurrent symptoms in HIV-related CM, a preliminary study suggests that a multiplex PCR panel (FilmArray Meningitis/Encephalitis panel, Biofire Diagnostics, LLC, Salt Lake City, Utah) for CSF showing a negative or positive result for *Cryptococcus* is predictive of IRIS or microbiologic relapse, respectively (see IV a-vii, Assessment for suspected treatment failure)[61]. Clinical case definitions have been proposed for HIV-related CM IRIS[74]. In a prospective study in Uganda, the overall mortality at 1 year in CM with and without the complication of CM-IRIS was 36% and 21%, respectively (HR= 2.3, 95% CI 1.1-5.1, p=0.04)[75]. In high resource settings, CM-IRIS may have a lower mortality risk[72], but fatal cases are reported[76].

Management includes continuation of antifungal therapy plus ART, and management of

raised ICP if present (as above). Anecdotal evidence suggests a role for anti-inflammatory treatment (e.g. high dose corticosteroids) for severe CNS manifestations[76] (BIII). The use of more aggressive antifungal therapy (e.g., restarting liposomal amphotericin B plus 5-flucytosine) is appropriate pending repeat CSF culture results and for patients whose CSF remains culture-positive, which is usually observed in association with a suboptimal or alternative antifungal treatment regimen; however, there is no evidence this is beneficial in the management of either raised ICP or IRIS in patients with culture-negative CSF[77].

VI) TIMING OF ANTIRETROVIRAL THERAPY IN CRYPTOCOCCAL MENINGITIS

Recommendation: ART initiation or revision should be delayed for 4-6 weeks after the initiation of antifungal therapy for cryptococcal meningitis (AII).

Discussion:

Conflicting results have been reported for different studies evaluating the outcome of early (within 1-2 weeks) vs late (2-10 weeks) initiation of ART in CM. Three prospective RCTs performed in resource-limited settings in Africa using non-preferred induction antifungal regimens reported an association between early ART initiation and increased mortality[78,79] or frequency of IRIS reactions[80]. Mortality was particularly high (hazard ratio 3.87, 95% CI 1.41-10.58, p=0.008) with early ART when the CSF WBC count was low (<5 WBC/μL)[78]. In contrast, an RCT of early (within 2 weeks) vs deferred (6-12 weeks) ART initiation following the start of treatment for various opportunistic infections (n=282) in the USA included predominantly PLWH with *Pneumocystis jiroveci* pneumonia (63%) and only 35 patients with CM, but demonstrated overall lower rates of AIDS progression or death in the early ART arm[81].

An observational study conducted with multiple cohorts from Europe and North America showed no difference in mortality between those starting ART early (within 2 weeks) vs those starting late (2-8 weeks), although mortality was increased among those who started more than 8 weeks after the start of antifungal therapy[82]. This prompted the International Antiviral Society (IAS)-USA panel to recommend in 2016 that patients with CM in high-resource settings with optimal antifungal therapy, monitoring, and aggressive management of increased ICP should start ART within 2 weeks of starting antifungal therapy[83]. However, the details of this study were only recently published and revealed significant limitations related to both study design and incomplete data[84,85]. The most recent 2022 IAS-USA guidelines indicate a change in the recommendation to a 2-4 week delay before initiating ART[86].

It remains unclear as to whether the apparently discordant outcomes for early ART in CM for high and low resource settings is explained by the differing circumstances (e.g., limited availability of preferred antifungal drugs in resource limited settings) or by the lack of an adequately powered randomized controlled trial in a high-resource setting. In summary,

considering the current lack of evidence to indicate a survival advantage of starting ART early during the induction phase (<2 weeks) of CM antifungal therapy, it appears that the safest approach may be to delay until 4-6 weeks after starting antifungals in both high and low-resource settings, as indicated in a recent meta-analysis[87]. This is also consistent with the recommendations of both the Department of Health and Human Services (DHHS) USA[36] and the WHO 2022 guidelines[35].

VII) PREGNANCY CONSIDERATIONS IN CRYPTOCOCCOSIS

The preferred treatment of CM in pregnancy is liposomal amphotericin B[36] which is not teratogenic and is listed as an FDA pregnancy drug category B (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well controlled studies in pregnant women). 5-flucytosine is teratogenic in animals; however, there is little human experience with this antifungal in pregnancy and it is an FDA drug category C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite risks). The severity of disease and risk-benefit considerations should be reviewed before using 5-flucytosine in combination with liposomal amphotericin B. Treatment of CM during the 1st trimester should be exclusively with liposomal amphotericin B (+/- 5-flucytosine), during which time fluconazole and other azoles should be avoided due to teratogenicity concerns. Fluconazole is an FDA category D drug (evidence of human fetal risk; however, the potential benefit may warrant its use despite the risk). After the 1st trimester, fluconazole can be considered. Neonates born of mothers who have received extended courses of amphotericin B formulations should be evaluated for renal dysfunction and hypokalemia.

VIII) PROGNOSIS

At the time of CM diagnosis, various host and infection characteristics have been associated with increased mortality. These include baseline altered mental status, increased fungal burden (CFU/mL in CSF), age over 50 years, peripheral blood leukocytosis, low body weight (<50 kg), anemia (hemoglobin <75 g/L)[47], and CSF OP <200 mm H_2O or >350 mm H_2O[46]. Other laboratory indicators associated with increased mortality included elevated baseline C-reactive protein (≥29 mg/L)[88], elevated CSF lactate (>5 mmol/L)[89], and hyponatremia (serum sodium <125 mmol/L)[90].

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RATING SYSTEM FOR RECOMMENDATIONS

Strength of Recommendation	Quality of Evidence for the Recommendation
A. Strong recommendation for the statement B. Moderate recommendation for the statement C. Optional recommendation for the statement	I. One or more randomized trials with clinical outcomes and/or validated endpoints II. One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes III. Expert opinion