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Abstract:	

Updating guidance for preventing and treating cryptococcal disease in low- and middle-income countries: how evidence and decisions interface

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ED000130

Cryptococcal meningitis causes an estimated 15% of all AIDS-related deaths globally.[1] The disease largely affects people with advanced HIV disease, mostly in low- and middle-income countries (LMICs). The high death rate in part relates to limited access to diagnostic tests for the disease and the high cost and limited availability of treatments.

In 2017 the World Health Organization (WHO) convened a guideline panel to update recommendations on preventing, diagnosing, and managing cryptococcal disease in HIV-infected people. These guidelines were published in March 2018.[2] This guideline update was supported by three Cochrane Reviews.[3,4,5] The recommendations put forward are presented in Table 1, and the research gaps identified through the guideline process are summarized in Table 2. The process helps ensure evidence-informed standards are set for a variety of healthcare contexts, and it illustrates how guidelines panels draw on reliable systematic reviews in intricate and precise ways.

Table 1: Summary of WHO recommendations on preventing, diagnosing, and managing of cryptococcal disease in HIV-infected people (March 2018) [2]

	WHO recommendation
Prevention of cryptococcal meningitis: screening with CrAg lateral flow assay (LFA)	Screening for cryptococcal antigen (CrAg) followed by pre-emptive antifungal therapy among CrAg-positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating antiretroviral therapy (ART) for adults and adolescents living with HIV who have a CD4 cell count < 100 cells/mm^3 *(strong recommendation; moderate-certainty evidence)* and may be considered at a higher CD4 cell count threshold of < 200 cells/mm^3 *(conditional recommendation; moderate-certainty evidence).*
Prevention of cryptococcal meningitis: primary fluconazole prophylaxis	When CrAg screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 cell count < 100 cells/mm^3 *(strong recommendation; moderate-certainty evidence) and* should be considered at a higher CD4 cell count threshold of < 200 cells/mm^3 *(conditional recommendation; moderate-certainty evidence).*
Treatment regimens	The following is recommended as the preferred induction regimen: • For adults, adolescents, and children, a short-course (one week) induction regimen with amphotericin B deoxycholate and flucytosine followed by one week of fluconazole is the preferred option for treating cryptococcal meningitis among people living with HIV *(strong recommendation, moderate-certainty evidence for adults, low-certainty evidence for children and adolescents)*. The following induction regimens are recommended as alternative options depending on drug availability:

	• Two weeks of fluconazole + flucytosine *(strong recommendation, moderate-certainty evidence)* • Two weeks of amphotericin B deoxycholate + fluconazole *(strong recommendation, moderate-certainty evidence)*.
Treatment with adjunctive corticosteroids	Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating HIV-associated cryptococcal meningitis among adults, adolescents, and children (*strong recommendation; high-certainty evidence for adults and adolescents, moderate-certainty evidence for children).*
ART initiation	Immediate ART initiation is not recommended for adults, adolescents, and children living with HIV who have cryptococcal meningitis, because of the risk of increased mortality, and it should be deferred by four to six weeks from the initiation of antifungal treatment *(strong recommendation; low-certainty evidence for adults and very-low-certainty evidence for children and adolescents).*

Table 2: Research needs for preventing, diagnosing, and managing cryptococcal disease in people with HIV, as identified through the WHO guideline process

Research area	Research gaps and ongoing research
Prevention of cryptococcal meningitis	• Cost-effectiveness of CrAg screening at CD4 cell count thresholds > 100 cells/mm^3 in ambulatory settings • The value of CrAg screening of ART-experienced patients with low CD4 cell counts • Evaluation of the value of screening with second-generation CrAg lateral-flow assays that can give a high or low cryptococcal antigen titre result
Discontinuation of maintenance therapy	• The optimal timing for discontinuing maintenance treatment among people with localized non-meningeal disease (such as pulmonary disease) or isolated serum cryptococcal antigen positivity • The optimal regimen and timing for discontinuing maintenance treatment for these populations
Treatment	• Phase III trial of high-dose, one-time injection in combination with high-dose fluconazole (1200 mg daily) and flucytosine for the induction phase of cryptococcal meningitis treatment • The optimal treatment of localized non-meningeal disease • The optimal treatment of cryptococcoma

Cryptococcal antigen (CrAg) can be detected in serum or plasma weeks to months before the symptoms of meningitis develop. One strategy for preventing cryptococcal meningitis in people with advanced HIV disease is to test for CrAg in serum or plasma and then treat people testing CrAg-positive with fluconazole. Earlier WHO guidelines (from 2013) recommended CrAg screening at a CD4 cell count threshold of < 100 cells/mm^3, an approach that research indicates is cost-effective.[6,7,8,9]

The 2017 guidelines panel considered the benefits of CrAg screening at higher CD4 cell count thresholds. A systematic review of 60 observational studies found that the pooled prevalence of

cryptococcal antigenaemia among people with a CD4 cell count ≤ 100 cells/mm^3 was 6.5% (95% confidence interval (CI) 5.7% to 7.3%) and 2.0% (95% CI 1.2% to 2.7%) among people with a CD4 cell count of 101 to 200 cells/mm^3.[10] Of the CrAg-positive cases identified at a CD4 cell count ≤ 200 cells/mm^3, 18.6% (95% CI 15.4% to 22.2%) were identified among individuals with a CD4 cell count of 101 to 200 cells/mm^3. This finding, in combination with results from the REMSTART trial that mortality was reduced as a result of CrAg screening of people with a CD4 cell count < 200 cells/mm^3,[11] led the guideline development group to recommend an expanded CD4 cell count threshold for CrAg screening at a CD4 cell count of < 200/mm^3 (Table 1).[2]

Given that CrAg testing is not available in many LMICs, an alternative strategy is to provide fluconazole prophylaxis to people with advanced HIV, without testing for CrAg status. The panel also debated this strategy. A Cochrane systematic review of antifungal prophylaxis in people living with HIV regardless of CrAg status found a 70% reduction in mortality from cryptococcal disease in those with low CD4 cell counts (relative risk of mortality due to cryptococcal disease 0.29, 95% CI 0.11 to 0.72), but overall mortality was not reduced.[3] On top of this, there may be increased risk of fluconazole-resistant *Candida* strains emerging with this strategy (relative risk 1.25, 95% CI 1.00 to 1.55), but no impact was demonstrated on resistant *Candida* disease occurrence. This blanket strategy did not increase the risk of other serious adverse events.[3]

In the light of this evidence, the WHO guideline panel made a second recommendation that primary prophylaxis with fluconazole should be given to adults and adolescents presenting with advanced HIV disease in situations where CrAg testing is not available or if results are delayed.[2] The importance of avoiding long delays in CrAg testing is supported by data from the REALITY trial reporting that cryptococcal disease and mortality peak in the first four weeks in people presenting with a CD4 cell count < 100 cells/mm^3.[12]

The guideline panel also considered the treatment of HIV-associated cryptococcal meningitis, a formidable problem in LMICs. The conventional two-week induction treatment regimen with amphotericin B deoxycholate (AmBd) and flucytosine (5FC) often causes side effects from drug toxicity, and these effects are difficult to manage in low-resource settings. On top of this, these antifungal agents are expensive and often not available.[13,14] As a result, healthcare providers often use inferior treatment regimens. In order to decrease cost and toxicity of antifungal drugs, studies have investigated shorter induction regimens.[15] The Cochrane Review of randomized trials comparing antifungal induction therapies for treating HIV-associated cryptococcal meningitis identified 13 eligible studies that compared 21 drug regimens, and found that AmBd and 5FC for one week, followed by fluconazole on days 8 to 14, was the best induction therapy compared with other regimens.[4] This was supported by pair-wise comparisons and a 10-week mortality network meta-analysis that ranked treatments. AmBd and 5FC for one week followed by fluconazole on days 8 to 14 reduced mortality at 10 weeks by 38% compared with the standard two weeks of AmBd and 5FC (95% CI 7% to 58%) and by 51% compared with one week of AmBd and fluconazole (95% CI 28% to 66%). The shortened one-week AmBd and 5FC regimen also had greater efficacy and a lower risk of severe anaemia compared with a two-week regimen. Based on these findings the guideline panel recommended one week of AmBd and 5FC therapy (followed by one week of fluconazole 200 mg) as the preferred antifungal regimen for the induction phase of treatment. The guideline panel also made a recommendation on alternative drug regimens in situations where specific antifungal drugs are not available (Table 1).

The panel noted that it is better to use liposomal amphotericin B than AmBd, mainly because the liposomal form seems to have similar efficacy but is less toxic.[16,17] Access to liposomal amphotericin B remains extremely limited in LMICs because it is expensive, and it was therefore not included in the WHO recommendation.

The Cochrane Review also provided evidence showing that use of the adjuvant corticosteroid dexamethasone increased the risk of serious adverse events, although the higher rate of mortality was not statistically significant (relative risk of death 1.15, 95% CI 0.93 to 1.42).[4] The WHO guidelines recommend against the routine use of adjunctive corticosteroid therapy (Table 1).[2]

There has been uncertainty about how soon antiretroviral therapy (ART) should be started in people with HIV-associated cryptococcal meningitis, because of the risks of immune reconstitution inflammatory syndrome (IRIS) and death when ART is initiated within four weeks of starting antifungal therapy. A Cochrane systematic review compared the outcomes of ART initiation within four weeks of starting antifungal treatment compared with delayed initiation of ART (four weeks or more after starting antifungal treatment) in this population.[5] Four trials with a total 294 adult participants were included in the review. The findings of the review suggested a 42% increased risk of mortality among people who initiate ART within four weeks of cryptococcal meningitis diagnosis (risk ratio 1.42, 95% CI 1.02 to 1.97) However, it is unclear if this higher mortality risk is related to cryptococcal meningitis-IRIS. Based on these findings the WHO guideline panel recommended that clinicians should defer ART by four to six weeks from starting antifungal treatment. Although clear data are lacking, the consensus was that for ART-experienced people, ART switches should be similarly deferred by four to six weeks.

To reduce HIV-associated mortality there needs to be better access to ART, and new diagnostics, preventative therapies, and therapeutics. The updated WHO guidelines offer a range of approaches for preventing and managing cryptococcal meningitis, and these can be adapted according to the resources and logistical capabilities of LMICs. Poor access to first-line antifungal drugs in many LMICs is likely to remain a major barrier; 5FC is currently not registered in any country in Africa despite being included in the WHO list of essential medicines.[14,18] Thus it is important that people in the field advocate for country registration of recommended first-line antifungal drugs and their inclusion on national lists of essential medicines, as well as lobbying for drug price reductions. The high cost of liposomal amphotericin B has been another major barrier, although a preferential price was recently announced for LMICs, which is a positive step towards improving access.[19] Education of healthcare providers regarding the development of national guidance on managing cryptococcal disease as well as supportive supervision and prescribing decision-making aids will also help ensure appropriate options are used and adapted to current healthcare needs and resources available.

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