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

POLICY BRIEF

World Health Organization

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

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1. BACKGROUND

Cryptococcal disease is one of the most common opportunistic infections among people living with advanced HIV disease and is a major contributor to illness, disability and mortality *(1,2)*. From 2020 estimates, there are 179,000 cases of cryptococcal antigenemia (infection) globally in 2020, 152,000 cases of cryptococcal meningitis, resulting in 112,000 cryptococcal-related deaths. Despite a reduction in the estimated absolute global burden of HIV-associated cryptococcal meningitis compared to 2014, likely due to ART expansion, cryptococcal disease still accounts for 19% of AIDS-related deaths, similar to 2014 estimates *(3)*. Cryptococcal meningitis is uncommon among children living with HIV.

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

In June 2022, WHO released updated recommendations for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV. These guidelines recommend simpler and safer treatment for cryptococcal disease among people living with HIV *(4)*.

In addition to providing updated recommendations for treating cryptococcal meningitis with combination antifungal therapy regimens, these guidelines include recommendations and good practice guidance on the following:

- the optimal approach to diagnosing cryptococcal meningitis;
- strategies for preventing invasive cryptococcal disease through cryptococcal antigen screening and pre-emptive fluconazole therapy;
- preventing, monitoring and managing amphotericin B drug toxicity;
- recommendations against adjunctive therapy with systemic corticosteroids; and
- recommendations on the timing of antiretroviral therapy (ART) initiation.

Early diagnosis and treatment of cryptococcal meningitis is key to reducing mortality from cryptococcal disease. Health-care professionals should have a low threshold for suspecting cryptococcal meningitis among people with advanced HIV disease.

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2. RECOMMENDATIONS

Diagnosis, screening, and prevention of cryptococcal meningitis
Lumbar puncture with measurement of cerebrospinal fluid (CSF) opening pressure, rapid CSF antigen assay, or CSF India ink test are the preferred diagnostic approaches
Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people is recommended before ART (re)initiation for adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3 Screening for cryptococcal antigen can be considered at CD4 cell count <200 cells/mm^3[a]
Induction therapy (2022 recommendations)
A single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) should be used as the preferred induction regimen for treating people with cryptococcal meningitis. *Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children* **Alternative induction regimens** If liposomal amphotericin B is not available: A seven-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by seven days of fluconazole (1200 mg daily for adults and 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). *Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children and adolescents* If no amphotericin B formulations are available: 14 days of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) + flucytosine (100 mg/kg per day, divided into four doses per day). *Strong recommendation; moderate-certainty evidence* Note: fluconazole + flucytosine is the only recommended oral combination regimen and has been associated with lower mortality compared with amphotericin B deoxycholate + fluconazole *(3)*. If flucytosine is not available: 14 days of liposomal amphotericin (3–4 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). *Strong recommendation; moderate-certainty evidence for adults* If liposomal amphotericin B and flucytosine are not available: 14 days of amphotericin B deoxycholate (1 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). *Strong recommendation; moderate-certainty evidence* Note: flucytosine-containing regimens are superior, and steps should be taken to ensure access to this drug.

[a] This recommendation is conditional, based on resource availability.

These guidelines also provide guidance on preventing, monitoring and managing amphotericin B–related toxicity. Table 1 contrasts the monitoring schedules for single high-dose liposomal amphotericin B and amphotericin B deoxycholate.

3. ACCESS TO OPTIMAL ANTIFUNGAL TREATMENT

Access to essential antifungal drugs remains inadequate in many settings, and laboratory monitoring of treatment and drug toxicity continue to be important barriers. Lack of local generic manufacturers and national in-country registration, and the higher cost of therapeutics, are some of the main barriers. Challenges exist to acquiring each drug that is part of the preferred regimen.

Liposomal amphotericin B is included in the 2021 WHO List of Essential Medicines and WHO Prequalification Expression of Interest list *(5,6)*. Although liposomal amphotericin B has been off patent since 2016 and there are preferential pricing arrangements from the originator for some countries, the current price of liposomal amphotericin B remains substantially higher than that of amphotericin B deoxycholate in most countries. As of February 2022, liposomal amphotericin B was only registered in two countries in sub-Saharan Africa (Ethiopia and South Africa).

Fluconazole is widely registered and is available in low- and middle-income countries. However, several countries have not included fluconazole in their national list of essential medicines.

Flucytosine is not widely registered or available in most low- and middle-income countries and registering standard formulations of flucytosine is the current priority. A sustained-release formulation is currently being developed to simplify inpatient and outpatient treatment of cryptococcal infections.

Antifungal medications for treating cryptococcal meningitis can be made more accessible through a range of strategies (see Box 1).

Box 1. Strategies to increase access to essential medicines for cryptococcal meningitis

Barriers to accessing antifungal medications for treating cryptococcal meningitis can be overcome by:

- increasing advocacy for reducing drug prices and promoting generic production, especially for liposomal amphotericin B and oral flucytosine;
- prioritizing quality assurance of newly available generic formulations;
- ensuring national registration of all cryptococcal meningitis drugs and including them in national essential medicine lists (amphotericin B deoxycholate, liposomal amphotericin B, flucytosine and fluconazole are all included in the WHO Model List of Essential Medicines);
- ensuring adequate supply chains at the national level;
- developing proper drug-forecasting and -monitoring systems; and
- improving access to liposomal amphotericin B by integrating it into the national package of drugs to treat severe fungal diseases.

Package of care for advanced HIV disease

Preventing invasive cryptococcal disease through cryptococcal antigen screening and pre-emptive fluconazole therapy is a key component of the WHO-recommended package of care for managing advanced HIV disease *(7,8)*. The WHO package of care for advanced HIV disease is a standardized, simplified package of priority interventions that should be offered to all people presenting or re-engaging with care with advanced HIV disease to reduce HIV-associated morbidity and mortality. It includes:

- screening, treatment and prophylaxis for major opportunistic infections (including cryptococcal disease and TB);
- rapid initiation of ART; and
- intensified treatment adherence support.

CD4 cell count remains a central part of clinical care to identify people with advanced HIV disease so that they can be offered the package of care.

Table 1. Comparison of monitoring schedule for single high-dose liposomal amphotericin B and amphotericin B deoxycholate

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

[a] 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily or magnesium chloride 4 mEq twice daily.

[b] If still in hospital.

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

Additional notes:

- Amphotericin B is incompatible with normal saline solution.
- Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia.
- Careful attention should be given to monitoring the intake and output of fluid and daily weight, especially among children.
- Flucytosine: because of concerns about bone marrow suppression, regular monitoring of full blood counts should be considered; guidelines from the Southern African HIV Clinicians Society recommend monitoring full blood counts at baseline and at least weekly for as long as the person is taking flucytosine *(9)*.

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

[a] 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily or 4 mEq magnesium chloride twice daily.

[b] If still in hospital

REFERENCES

1. Ford N, Shubber Z, Meintjes G, Grinsztejn B, Eholie S, Mills EJ et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. Lancet HIV. 2015;2:e438–44.

2. Pasquier E, Kunda J, De Beaudrap P, Loyse A, Temfack E, Molloy S et al. Long-term mortality and disability in cryptococcal meningitis: a systematic literature review. Clin Infect Dis. 2018;66:1122–32.

3. Rajasingham R, Govender NP, Jordan A, Loyse A, et al. An estimate of the global burden of HIV-associated cryptococcal infection in adults in 2020. IAS Abstract EPB045, July 2022

4. Guidelines for diagnosing, preventing and managing cryptococcal disease in adults, adolescents and children living with HIV. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240052178, accessed 1 July 2022).

5. World Health Organization Model List of Essential Medicines: 22nd list (2021). Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/345533, accessed 8 June 2022).

6. Revised Invitation for Expression of Interest (EOI) for medicines against HIV infection and related diseases published. Geneva: World Health Organization; 2022 (https://extranet.who.int/pqweb/news/new-invitation-expression-interest-eoi-hiv-infection-and-related-diseases-medicines-published-1, accessed 1 July 2022).

7. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/342899, accessed 1 July 2022).

8. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/255884, accessed 1 July 2022).

9. Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med. 2019;20:a1030.

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