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THERAPY IN PRACTICE

Therapy for HIV-associated cryptococcal meningitis: a case report demonstrating a new treatment approach emphasizing updated treatment guidelines

David M. Hachey[1] · Brian R. Wood[2] · Martha Buitrago[1] · Anushka Burde[3]

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Abstract

Cryptococcal meningitis (CM) remains a significant global health burden, especially for persons living with HIV. Despite effective antiretroviral and antifungal therapy, mortality rates are still approximately 70% in low- and middle-income countries and 20–30% in high-income countries. Central nervous system symptoms range from mild to severe, depending on burden of disease, and prompt and appropriate therapy is critical to reducing mortality. Treatment consists of three phases: induction, consolidation, and maintenance. Although treatment regimens have largely remained unchanged for decades, recent clinical trials have led the World Health Organization to update guidelines to reflect best practices in resource-limited settings. We review the clinical presentation, diagnosis, and standard therapy for CM, present a case with a challenging diagnostic and treatment course complicated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, and discuss the benefits of a new treatment dosing strategy highlighting potential advantages of adopting this novel dosing option in high-income countries.

Key Points

Cryptococcal meningitis in persons living with HIV carries high mortality globally, despite the existence of effective therapy.

The World Health Organization revised cryptococcal disease treatment guidelines in 2022, informing best practices in low- and middle-income countries by updating the induction regimen to include an option with single, high-dose liposomal amphotericin.

New treatment regimens have led to better outcomes in low- and middle-income countries as well as benefits for certain patients in high-income countries during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

✉ David M. Hachey
hachdavi@isu.edu

[1] Department of Family Medicine, Idaho State University, Pocatello, ID, USA

[2] Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, WA, USA

[3] Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy, Idaho State University, Pocatello, ID, USA

Introduction

Cryptococcus is a fungus with more than 30 identified species readily found in the environment, but only two are known to cause disease in humans, *C. neoformans* and *C. gattii* [1]. *C. neoformans* is responsible for approximately 95% of invasive cryptococcal infections and the majority of these infections occur in immunocompromised persons living with HIV (PLWH) with CD4 T lymphocyte (CD4) cell counts less than 100 cells/mm^3 [2]. Clinically relevant invasive disease results primarily from reactivation of latent infection months to years after initial exposure [3–5].

Prior to widely available antiretroviral therapy (ART), approximately 8% of PLWH in high-income countries (HICs) developed disseminated cryptococcal infection. Mortality from cryptococcal meningitis (CM) has improved in HICs, although annual mortality still persists at 20–30% [6, 7]. In low- and middle-income countries (LMICs), 1-year mortality for PLWH with CM remains a staggering 70% [6]. The difference in mortality between HICs and LMICs is multifactorial, but can be explained by delays in diagnosis secondary to a lack of access to lumbar punctures (LPs) and rapid diagnostic testing, and also by limited availability of

medications for the treatment of CM [4, 5]. Current estimates suggest the global annual case rate of CM for PLWH is 280,000 cases, and CM also accounts for approximately 15% of all AIDS-related deaths [7].

PLWH presenting with disseminated cryptococcal infection may display a spectrum of symptoms, from no overt clinical symptoms to severe neurologic manifestations [8]. When present, clinical symptoms of CM appear around 2 weeks after infection or during immune reconstitution, and most commonly present as subacute meningitis with fever, malaise, and headache developing slowly over weeks [6]. Other symptoms may include neck stiffness and photophobia in about 25% of cases; in patients with increased intracranial pressure, it is common to see lethargy, altered mentation, personality changes, and memory loss. For PLWH who present with CM after starting ART, the illness presentation may be more acute as it can be associated with immune reconstitution inflammatory syndrome (IRIS; manifestations that develop secondary to the inflammatory response to the pathogen with restoration of the CD4 count on ART initiation) [9]. Disseminated disease may also involve other organs such as the lungs, with isolated pulmonary infection possible. Manifestations of pulmonary cryptococcus include cough and dyspnea accompanied by abnormal radiographic findings showing lobar consolidation may occur, and in some cases, nodular infiltrates, especially in the lower lobes [8, 10]. For patients with asymptomatic CM, there is little evidence on the disease course and clinical outcomes [7].

Rapid diagnosis of CM is critical to reducing mortality, but access to adequate resources may be challenging in LMICs. The World Health Organization (WHO) currently recommends prompt LP, with measurement of cerebrospinal fluid (CSF) opening pressure and cryptococcal antigen (CrAg) assay as the preferred approach for diagnosing CM [4, 5]. However, if a CSF CrAg assay is not available, the CSF India ink test is an alternative, and if LP and/or microscopy are not available, rapid serum, plasma, or whole-blood CrAg assay should be performed for diagnosing CM. Similarly, opportunistic infection guidelines in the United States (US) suggest conducting an LP to capture opening and closing pressures and to collect CSF for analysis that includes protein, glucose, cultures, and CrAg assay [8]. In PLWH with CM, the CSF opening pressure may be elevated, with pressures ≥25 cm H_2O occurring in 60–80% of patients. An estimated 50% of fungal blood cultures will be positive and 80% of fungal CSF cultures will be positive [8, 11]. Finally, it is important to test serum the CrAg assay in an immunocompromised individual with symptoms of CM, as the presence of *cryptococcus* may not be identified in the CSF in the early stages of infection [12].

Treatment of CM in PLWH is distributed into three phases: induction, consolidation, and maintenance. The treatment options differ based on medication availability, patient symptoms, geographic location, and other clinical variables, and are reviewed in the Discussion [4, 5, 8, 13–15]. Several treatment nuances exist for PLWH who develop CM. First, immediate ART initiation is not recommended because of the increased risk of mortality (probably due to intracranial IRIS) and should be deferred by 4–6 weeks from the initiation of antifungal treatment [4, 5, 8, 16, 17]. Second, corticosteroids should not be used routinely during induction therapy unless used for the management of IRIS. Finally, corticosteroids and mannitol are ineffective in reducing intracranial pressure and are thus not recommended [4, 5, 8].

Case report

In September 2020, at the start of a significant spike in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections (COVID-19 illness) in the US, a 69-year-old Caucasian male presented to a rural hospital with shortness of breath for 4 weeks, oral candidiasis for 4 months, and unintentional 50-pound weight loss over the previous 8 months. His past medical history was significant for coronary artery disease (eight stents), gastroparesis, and seasonal allergies. He was married, semi-retired, working part-time, and denied alcohol or tobacco use. During his 5-day hospital stay, the patient had a normal physical examination with the exception of white oropharyngeal plaques, cachexia, visible increased work of breathing, decreased breath sounds on chest auscultation bilaterally, and evidence of loss of short-term memory recall. The patient had reactive HIV screening and confirmatory tests, with a CD4 count of less than 20 cells/mm^3 (2%) and a viral load of 2,080,000 copies/mL (6.31 logs). Further testing revealed a negative QuantiFERON gold™ test for tuberculosis, negative antibodies for hepatitis A and C, and negative hepatitis B surface antibodies, a negative respiratory panel for 19 pathogens including SARS-CoV-2, pancytopenia, and computed tomographic (CT) scan of the lungs and two-view chest x-ray that did not identify any pulmonary infectious processes. The patient was given supplemental oxygen, placed on a course of prednisone 20 mg daily (initially for suspected *Pneumocystis* pneumonia) and fluconazole 100 mg daily for thrush for 3 weeks, and trimethoprim/sulfamethoxazole 160/800 mg three times weekly for pneumocystis prophylaxis until CD4 count increased above 200 cells/mm^3 for more than 3 months in response to HIV medication. He was the discharged at day 5.

The patient was connected to HIV care at day 11 after diagnosis and prescribed bictegravir/tenofovir alafenamide/emtricitabine for HIV treatment. At day 25 after diagnosis,

the oral candidiasis resolved and the patient stopped fluconazole and began to taper the prednisone over 2 weeks. His weight loss began to stabilize at this point but he was still experiencing dyspnea on exertion. On day 39 after diagnosis, after taking antiretroviral medication for 4 weeks, it was incidentally discovered that the patient had a serum CrAg assay while in the hospital that resulted as >1:4096 (semi-quantitative enzyme immunoassay method); the assay was conducted by an outside laboratory. The patient was contacted and reported no symptoms suggestive of disseminated cryptococcal disease or meningitis. His appetite had returned and weight was stable and he had no shortness of breath. A repeat serum CrAg assay (semi-quantitative enzyme immunoassay method) at that time was lower but still reactive at 1:100. The patient was immediately referred to a regional medical center for a CT scan of the head and LP.

The CT scan was normal and an LP was completed (normal opening pressure) and CSF sent for analysis (see Table 1). The patient had no neurological findings, normal CT scan, and a CSF CrAg assay that grew *C. neoformans* at 48 h. Due to the potential for exposure to SARS-CoV-2 if hospitalized (with risk factors for developing severe SARS-CoV-2 illness), it was decided to treat the patient conservatively as an outpatient with high-dose fluconazole (800 mg daily) for 2 weeks starting at day 45. At the end of the treatment course, laboratory tests indicated a normal serum creatinine 0.9 (0.8–1.5 mg/dL) and potassium 3.5 mEq/L (3.5–5.1), and the repeat LP on day 62 resulted in 1+ *cryptococcus* on CSF fungal culture at 48 h, indicating treatment failure. Under consultation with infectious disease specialists and consent from the patient, it was decided to treat the patient with an experimental high-dose liposomal-amphotericin B (L-AmB) approach. On day 81 after diagnosis, he was premedicated with 500 mL of normal saline and treated with a single infusion of high-dose L-AmB at 10 mg/kg (total 630 mg) followed by 2 weeks of fluconazole 1200 mg daily. The patient did not report any adverse effects from the infusion in the subsequent days. The decision not to admit the patient for daily liposomal amphotericin or for clinical monitoring was influenced by the high levels of SARS-CoV-2 in the community. Furthermore, because of his age and increased risk of adverse effects, coupled with a lack of clinical symptoms and apparent low burden of disease, the use of flucytosine was avoided. After 2 weeks, repeat complete metabolic panel showed normal creatinine, potassium and magnesium, and another repeat LP showed no growth of *cryptococcus* and the patient remained asymptomatic. The patient completed consolidation with 400 mg fluconazole once-daily for 8 weeks, and then decreased to a maintenance dose of 200 mg daily for 1 year. During the maintenance phase, the patient remained asymptomatic, the HIV RNA level (viral load) attained undetectable levels (<20 copies/mL), and the CD4 count climbed to over 200 cells/mm^3 (see Table 2).

Records from a previous provider were discovered and indicated that the patient had a known 2.2 cm right lower lung mass for several years prior to HIV diagnosis, which had remained unchanged in size and was never biopsied. At the time this was discovered in the records, which was approximately 10 months after starting ART and 8 months after completing CM induction treatment, the patient was referred for a biopsy of the mass and pathology revealed "necrotizing granulomatous inflammatory reaction with numerous fungal hyphal organisms with morphologic features most suggestive of *Cryptococcus neoformans*". Repeat chest CT 6 months later, at the end of CM maintenance therapy, showed no change in the mass and the patient ended his maintenance therapy and remains clinically stable 2 years later, with no evidence of CM relapse.

Discussion

The diagnosis and treatment of CM in PLWH poses many challenges for clinicians in both LMICs and HICs. This case highlights some unique facets of diagnosis and treatment of CM in the setting of the SARS-CoV-2 pandemic in an HIC. First, during hospitalization at the time of HIV diagnosis, the cryptococcal antigen result was not identified and the patient was initiated on ART. Although data are not available for HICs, missed diagnosis of CM is common in LMICs

Table 1 LP and CSF results of the patient with HIV-associated cryptococcal meningitis

Day after HIV diagnosis	Serum CrAg assay titer	*Cryptococcus* growth on CSF fungal culture	CSF CrAg assay titer	Glucose [40–70]	Protein [15–40]	Color [clear]	WBCs [0–10]	RBCs [0–10]	Opening pressure [<25 cm]
5	>1:4096	ND	ND	ND	ND	ND	ND	ND	ND
39	1:100	2+	ND	48	37	Clear	0	20	7 cm
62	ND	1+	ND	52	62	Clear	0	13	5 cm
95	ND	None	1:32	54	113	Clear	3	13	14 cm

CrAg cryptococcal antigen, *CSF* cerebrospinal fluid, *LP* lumbar puncture, *ND* not done, *RBC* red blood cell *WBC* white blood cell

Table 2 CD4 counts, viral load results, and weight metrics of the patient with HIV-associated cryptococcal meningitis

	Day 0	Day 39	Day 60	Day 81	Day 111	Day 171	Day 211	Day 293	Day 370	Day 475
CD4 Absolute (cells/mm^3)	<20	ND	152	ND	87	124	ND	178	ND	229
CD4 percentage	2%	ND	12%	ND	9%	7%	ND	10%	ND	9%
Viral load (copies/mL)	2,080,000	252	ND	105	64	52	75	46	<20	<20
Weight (kg)	65	63	66	ND	ND	76	77	82	84	91
BMI	19.4	19.0	19.8	ND	ND	22.8	23.1	24.7	25.1	27.7

BMI body mass index, *ND* not done

due to various factors, including lack of education, seeking care multiple times, misdiagnosis, and cultural factors [18]. Circumstances in our case report that may have led to a missed diagnosis include an asymptomatic presentation for CM, laboratory results resulting after discharge not seen by providers, and multiple other medical problems that were being addressed.

Starting ART before CM treatment is generally not advised because of an increased risk of mortality [4, 5, 8, 16, 17]; ART is generally deferred for 4–6 weeks after the initiation of antifungal treatment. Our patient started ART 11 days after the HIV diagnosis and approximately 1 month before the CM was identified. Taking fluconazole for severe oral thrush may have reduced the fungal burden and perhaps the risk of IRIS. Furthermore, after the patient initiated ART, he was monitored clinically and never manifested symptoms of CM on physical examination, although the CSF analysis demonstrated evidence of asymptomatic central nervous system infection.

As the US was in the midst of the SARS-CoV-2 pandemic, and patients had risk factors for severe COVID-19 illness, providers were not comfortable admitting the patient to the hospital for 2 weeks of intravenous CM treatment. Flucytosine was avoided because of the patient's age and the potential for significant adverse effects. Furthermore, because he lived in a rural environment, daily outpatient parenteral therapy was not an option. Therefore, given the clinical stability of the patient, providers opted to attempt a course of fluconazole monotherapy for 2 weeks, which failed. Then, based on the results from a phase II clinical trial performed in an LMIC setting, the patient and providers agreed to treat the patient with a single, high dose of L-AmB, followed by 1200 mg/day of oral fluconazole for 2 weeks (not endorsed by guidelines), ultimately leading to a successful outcome [19]. This approach of using high-dose oral fluconazole is supported when flucytosine is not available or contraindicated [15].

Although guidelines for the treatment of CM in PLWH in HICs have not changed, the WHO guidelines were modified in 2022 to reflect the results from a phase III clinical trial from the Ambition Study Group (see Table 3) [20]. The study, conducted in five sub-Saharan countries, evaluated single, high-dose L-AmB 10 mg/kg administered with 14 days of flucytosine 100 mg/kg/day and fluconazole 1200 mg/day (L-AmB group) or the 2018 WHO-recommended treatment of seven daily doses of amphotericin B deoxycholate (1 mg/kg/day) plus flucytosine (100 mg/kg/day), followed by 7 days of fluconazole 1200 mg/day (control group). The primary endpoint was all-cause mortality at 10 weeks, and the results of the primary intention-to-treat analysis showed a mortality rate of 24.8% (101/407, 95% CI 20.7–29.3%) in the L-AmB group and 28.7% (117/407, 95% CI 24.4–33.4%) in the control group. There were also fewer significant adverse drug reactions in the L-AmB treatment group [5, 20]. When our patient was treated, only results from phase II of this clinical trial were available, although the phase III findings have now been published.

The single-dose treatment was preferred by patients and providers because there were fewer doses, it was less time-consuming to administer, and there was less need for supportive treatment for adverse effects (e.g., rehydration or electrolyte supplementation). There was also less monitoring required, as patients had a lower risk of anemia and hypokalemia. Despite these recommendations from WHO and the inclusion of L-AmB in the WHO Model List of Essential Medicines, many LMICs do not include it in their national guidelines due to higher cost when compared with amphotericin B deoxycholate, or due to challenges accessing the medication [5, 21]. It is expected that single, high-dose L-AmB would increase treatment equity if made available at an affordable price, which has not happened to date.

As the majority of clinical trials for the treatment of CM in PLWH take place in LMICs, research is advancing the care for PLWH in these settings. Unfortunately, there are limited data from HICs to compare clinical and safety outcomes for newer dosing strategies, and patients in HICs may be at risk of receiving suboptimal care by continuing to use potentially more toxic treatments for the induction of CM [22]. Now may be the time to examine the treatment of CM with outpatient parenteral therapy, as in the case with our patient. Changes in reimbursement for care, improved safety profiles of medication, and the desire to discharge patients

Table 3 Summary of recommended cryptococcal meningitis treatment for low- and middle-income and high-income countries

Phase	Low-and middle-income countries [4, 5]	High-income countries [8, 13–15]
Induction	A single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg/day divided into four doses per day) and fluconazole (1200 mg/daily for adults)[a]	Two weeks of liposomal amphotericin B 3–4 mg/kg intravenously once daily plus flucytosine 25 mg/kg orally four times per day
Consolidation	Eight weeks of fluconazole 800 mg orally once daily	Eight weeks of fluconazole 400–800 mg orally once daily, or, for clinically stable patients with negative CSF cultures, the dose can be reduced to 400 mg orally once daily
Maintenance	Fluconazole 200 mg orally once daily for adults	Fluconazole 200 mg orally once daily for ≥1 year from the initiation of antifungal therapy
Discontinuing maintenance	If HIV viral load monitoring is available: the person is stable on and adherent to ART and antifungal maintenance treatment for at least 1 year and has a CD4 cell count ≥100 cells/mm^3 and a fully suppressed viral load If HIV viral load monitoring is not available: the person is stable on and adherent to ART and antifungal maintenance treatment for at least 1 year and has a CD4 cell count ≥200 cells/mm^3	At least 1 year from initiation of antifungal therapy, and the patient remains asymptomatic from cryptococcal infection, and CD4 count ≥100 cells/mm^3 and suppressed HIV RNA in response to effective ART

ART antiretroviral therapy

[a]The previous World Health Organization-recommended alternative regimens remain valid. However, the Guideline Development Group noted that fluconazole plus flucytosine is associated with lower mortality than amphotericin B deoxycholate plus fluconazole, and efforts should be made to ensure access to a flucytosine-containing regimen [5]

who are stable but only remaining in hospitals to complete therapy should be foundations for future research [23].

Extrapolating research from LMICs allowed our patient in an HIC to reduce hospitalization time and exposure risk to SARS-CoV-2, which demonstrates the value of re-examining CM treatment options globally. Despite a successful outcome, we acknowledge a limitation of the case study is the generalizability of management to all PLWH with CM. If the patient was symptomatic or needed flucytosine, they would most likely have been hospitalized for closer clinical and laboratory monitoring. However, the single, high-dose L-AMB option offers numerous potential benefits, including improved safety and logistical advantages, and, as for our patient, potential outpatient management for individuals with evidence of asymptomatic CM who can be safely monitored at home.

Conclusions

Diagnostic and treatment challenges of CM in PLWH still exist in both LMICs and HICs. Ongoing clinical trials in LMICs are advancing the care for PLWH, leading organizations such as the WHO to update treatment guidelines to reflect best practices. As highlighted in this case, future research should be aimed at ways to make treatment more affordable, equitable and translatable in all settings [22].

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Declarations

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Conflicts of Interest David M. Hachey, Brian R. Wood, Martha Buitrago and Anushka Burde have no conflicts of interest to declare.

Ethics Approval This case report does not require Institutional Review Board (IRB) approval and the authors have received a certificate of exemption from Idaho State University.

Consent to Participate/Publication The authors have received approval from the patient to publish this case.

Availability of data and materials De-identified data for this manuscript was extracted directly from a patient's medical record and is not available for public viewing.

Code Availability Not applicable.

Author Contributions DH conceived the idea for the manuscript, collected the data, supported the care of the patient, and wrote the manuscript. BW interpreted and analyzed the clinical data and wrote the manuscript. MB supported the care of the patient, interpreted and analyzed the clinical data and wrote the manuscript. AB supported the care of the patient, interpreted and analyzed the clinical data and wrote the manuscript.

References

1. Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin N Am. 2016;30(1):179–206.
2. Pyrgos V, Seitz AE, Steiner CA, et al. Epidemiology of cryptococcal meningitis in the US: 1997–2009. PLoS ONE. 2013;8(2):e56269. https://doi.org/10.1371/journal.pone.0056269.
3. Garcia-Hermoso D, Janbon G, Dromer F. Epidemiological evidence for dormant Cryptococcus neoformans infection. J Clin Microbiol. 1999;37(10):3204–9.
4. World Health Organization (2018) Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. https://www.who.int/publications/i/item/9789241550277. Accessed 16 May 2023
5. World Health Organization (2002) Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV. https://www.who.int/publications/i/item/9789240052178, Accessed 17 May 17 2023
6. Aberg J, WGP (2002) Cryptococcosis. In: Secondary Aberg J, WGP (eds) Trans. Secondary Cryptococcosis, Vol. ed. Churcill Livingstone, New York, pp 498–510
7. Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017;17(8):873–81.
8. Panel on guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (Pages H1-H21). 2022. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection. Accessed 8 Dec 2022
9. Rhein J, Hullsiek KH, Evans EE, et al. Detrimental outcomes of unmasking cryptococcal meningitis with recent ART initiation. Open Forum Infect Dis. 2018;5(8):ofy122.
10. Kanjanapradit K, Kosjerina Z, Tanomkiat W, et al. Pulmonary cryptococcosis presenting with lung mass: report of 7 cases and review of literature. Clin Med Insights Pathol. 2017. https://doi.org/10.1177/1179555717722962.
11. Bicanic T, Brouwer AE, Meintjes G, et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. AIDS. 2009;23(6):701–6.
12. Ssebambulidde K, Bangdiwala AS, Kwizera R, et al. Symptomatic cryptococcal antigenemia presenting as early cryptococcal meningitis with negative cerebral spinal fluid analysis. Clin Infect Dis. 2019;68(12):2094–8.
13. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. Clin Infect Dis. 2010;50(3):291–322.
14. Nelson M, Dockrell DH, Edwards S, et al. Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals. HIV Med. 2022;12 Suppl 2:1–140.
15. European AIDS Clinical Society. EACS Guidelines version 11.1, October 2022. https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf. Accessed 8 Dec 2022
16. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med. 2014;370(26):2487–98.
17. Scriven JE, Rhein J, Hullsiek KH, et al. Early ART after cryptococcal meningitis is associated with cerebrospinal fluid pleocytosis and macrophage activation in a multisite randomized trial. J Infect Dis. 2015;212(5):769–78.
18. Link A, Okwir M, Nabongo B, et al. Delays in cryptococcal meningitis diagnosis and care: a mixed methods study in rural uganda. Ann Glob Health. 2022;88(1):22.
19. Jarvis JN, Leeme TB, Molefi M, et al. Short-course high-dose liposomal amphotericin B for human immunodeficiency virus-associated cryptococcal meningitis: a phase 2 randomized controlled trial. Clin Infect Dis. 2019;68(3):393–401.
20. Jarvis JN, Lawrence DS, Meya DB, et al. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. N Engl J Med. 2022;386(12):1109–20.
21. Larson B, Shroufi A, Muthoga C, et al. Induction-phase treatment costs for cryptococcal meningitis in high HIV-burden African countries: new opportunities with lower costs. Wellcome Open Res. 2022;6:140.
22. Harrison TS, Lawrence DS, Mwandumba HC, et al. How applicable is the single-dose AMBITION regimen for HIV-associated cryptococcal meningitis to high-income settings? Clin Infect Dis. 2022;76:ciac792.
23. Mahoney MV, Monica V. Wrapping our heads around outpatient parenteral antimicrobial therapy for central nervous system infections. Infec Dis Clin Pract. 2021;29(2):e65–6.