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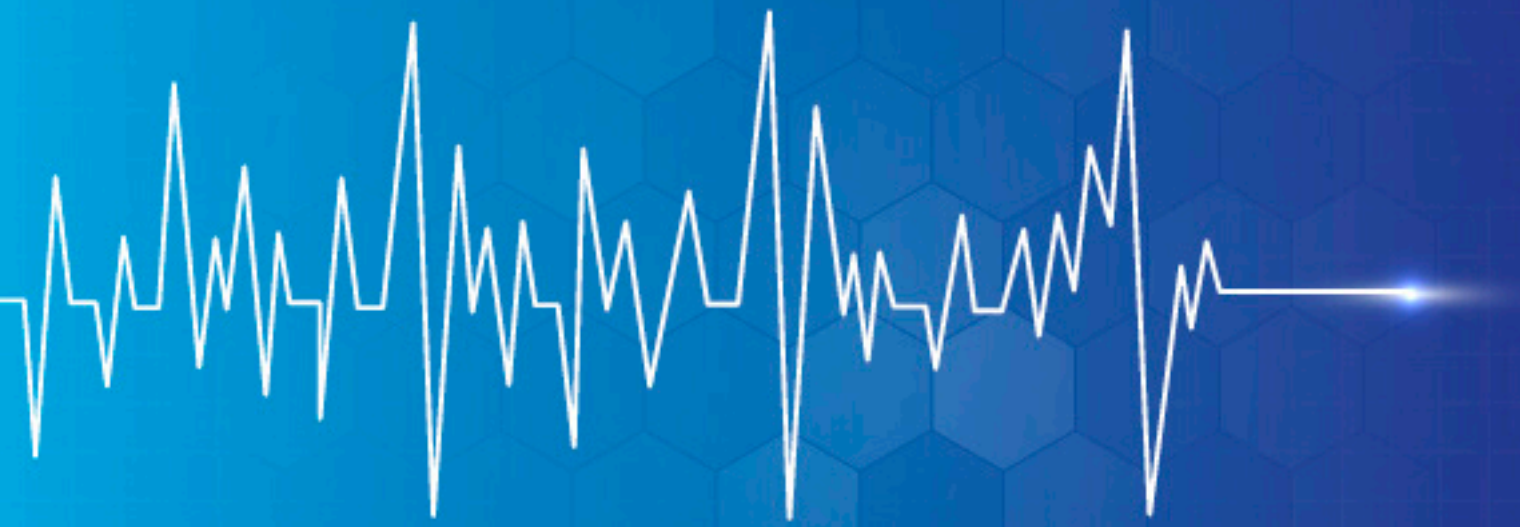

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CNS Recovery in Severe Cryptococcal Meningitis in Advanced HIV Following Re-Establishment of Fungicidal Amphotericin-Based Therapy in an Older Adult

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ABSTRACT

Cryptococcal meningitis (CCM) remains a major cause of mortality among adults with advanced HIV disease. Globally, approximately one million cases of cryptococcosis are reported each year, with an estimated 625,000 annual deaths. Sub-Saharan Africa, where the population burden of HIV is up to 60%, accounts for nearly three-quarters (73%) of these deaths. The treatment of CCM involves the induction, consolidation, and maintenance of fungal clearance, with concurrent immune reconstitution. Rapid induction-phase fungal clearance is strongly associated with improved survival, and current guidelines recommend amphotericin-based combination therapy where feasible. Fluconazole monotherapy may be used in the induction phase, but is often associated with poor and slower fungal clearance. However, it is the backbone of the consolidation and maintenance phases of CCM treatment. This case is a report of a 69-year-old Kenyan woman, newly diagnosed with HIV, who presented with headache and progressive confusion and was diagnosed with cryptococcal meningoencephalitis. She initially received high-dose fluconazole, followed by amphotericin B deoxycholate. The treatment was complicated by severe febrile reactions and persistent hypokalemia, necessitating the discontinuation of the amphotericin. Her clinical status, especially the neurological function, subsequently deteriorated on fluconazole monotherapy. Liposomal amphotericin B was then introduced with strict pre-hydration and scheduled electrolyte supplementation, resulting in marked neurological improvement. This case emphasizes the necessity of fungicidal induction therapy, proactive mitigation of amphotericin-associated complications, and sustained clinical vigilance to ensure good patient outcomes.

INTRODUCTION

Cryptococcal meningitis (CCM) is a severe fungal infection that can present with a highly variable range of neuro-ophthalmic and systemic symptoms. Although more commonly associated with immunocompromised individuals, it has increasingly been reported in immunocompetent hosts. *Cryptococcus neoformans* is typically linked to opportunistic infections in immunosuppressed populations, whereas *Cryptococcus gattii* more commonly affects immunocompetent individuals (Nakahira *et al.*, 2025).

Cryptococcus neoformans causes CCM and is a leading opportunistic cause of death in people with advanced HIV disease, particularly in sub-Saharan Africa (McHale *et al.*, 2023). Nearly two-thirds of all deaths from HIV-associated CCM occur in Africa, and a 10-week mortality rate has been reported to be as high as 50% of the incident cases in a routine care African setting (Tugume *et al.*, 2023). Clinical features of CCM include fever, headache, neck stiffness, visual disturbances, and altered mental status.

Cryptococcal antigen (CrAg) testing on cerebrospinal fluid (CSF), serum, plasma, or whole blood, performed using a lateral flow assay (LFA), a latex agglutination assay, or an enzyme-linked immunosorbent assay (ELISA), is the cornerstone of prompt invasive cryptococcal diagnosis (Organization, 2022; Tugume *et al.*, 2023).

LITERATURE REVIEW

The current WHO treatment protocol involves an induction phase of two weeks, followed by a consolidation phase of eight weeks, and finally a maintenance phase of 12 months. The preferred induction regimen is 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/day for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) (Jarvis *et al.*, 2022; WHO, 27 June 2022). There are alternative induction regimes when either of the three drugs is not available. For instance, when flucytosine is not available, an alternative induction can include 14 days of liposomal amphotericin B (3–4 mg/kg per day) plus fluconazole (1200 mg daily, or 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily; or 14 days of amphotericin B deoxycholate (1 mg/kg per day) plus fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).

Induction therapy is the most critical step in CCM treatment, as it allows for rapid clearance of the *Cryptococcus neoformans* fungi to control the disease (Liu *et al.*, 2024). Combination regimens using amphotericin B with flucytosine (with or without fluconazole) are associated with improved early fungicidal activity and survival compared with fluconazole monotherapy (Tugume *et*

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al., 2023). Fluconazole monotherapy is associated with suboptimal treatment of CCM. It is fungistatic and is associated with the development of resistance through chromosomal duplication or aneuploidy in the *Cryptococcus spp.*(Hope *et al.*, 2019) resulting in relapse of symptoms and a high likelihood of immune reconstitution syndrome when antiretroviral therapy is initiated (Bicanic *et al.*, 2006).

Amphotericin B deoxycholate is effective but frequently limited by nephrotoxicity and electrolyte disturbances, especially hypokalemia. Liposomal amphotericin B offers improved tolerability but may be less accessible in resource-limited settings. Flucytosine-containing regimens are superior due to their synergistic effects, and steps should be taken to ensure access to this drug since it has generally been inaccessible in resource-limited clinical settings (WHO, 27 June 2022).

MATERIALS AND METHODS

This is a descriptive single-patient case report of a 69-year-old woman diagnosed with cryptococcal meningoencephalitis in the setting of newly diagnosed advanced HIV infection at the Nanyuki Teaching and Referral Hospital, Kenya.

Clinical data were obtained from the patient's records, comprising the clinical history, physical examination findings, diagnostic evaluation process, including the laboratory data and imaging studies. The treatment interventions, progress monitoring, and the evaluation of patient outcomes were done as per the WHO and the IDSA treatment guidelines for CCM. All these have been summarized below.

Patient Clinical History and Physical Examination

A 69-year-old widow, a mother of three adult children, and a small-scale farmer from Nanyuki, Kenya, presented to the hospital in mid-October 2025 with a 2-week history of severe headaches associated with progressive altered mental status. The baseline Glasgow Coma Scale (GCS) was 14/15. She also had recurrent episodes of acute diarrhea, which was mucoid but non-bloody. She appeared unwell and dehydrated, with a blood pressure of 139/86 mmHg and a heart rate of 93 bpm. She was confused, with the characteristic stigmata of immunosuppression, including wasting, oral thrush, and hyperpigmented pruritic papular eruptions on the legs. She was afebrile. HIV testing performed on admission as per local guidelines was positive. CD4 count and HIV viral load testing were not available at the treating facility.

RESULTS AND DISCUSSION

Diagnostic Assessment

Laboratory investigations done included a complete blood count, which showed a hemoglobin of 12.9 g/dL, a total leukocyte count of 3.1 x 10^9/L (4-10) with normal differential counts, and platelets of 272 x 10^9/L; the renal function tests showed a serum urea of 3.12 mmol/L, a creatinine of 97.31µmol/L with a baseline K+ of 3.43 mmol/L and Na+ of 135.2 mmol/L. A blood slide for malaria parasites was negative, and stool analysis for ova and parasites was unremarkable. A brain CT scan ruled out any space-occupying lesion. A lumbar puncture and CSF analysis showed an elevated opening pressure at 50 drops per minute (normal should be < 40 drops/min). It was clear in appearance, and the CSF biochemistry showed an elevated protein of 6.4 g/L (0.14-4), and a low glucose of 0.43 mmol/L (2.5-4.0); the India ink study was positive, the CSF CrAg was positive, and the CSF culture showed no organisms. The CD4 count was not possible to do in the facility at the time. Screening for tuberculosis was done by doing a chest X-ray, a urine TB-LAM, and a sputum GeneXpert, all of which were negative.

Therapeutic Intervention

The patient was initially started on high-dose oral fluconazole 1200 mg once daily. Amphotericin B deoxycholate at 1 mg/kg per day was started four days later as part of induction therapy when it became available, but she developed severe febrile reactions and persistent hypokalemia despite the corrective interventions, requiring cessation of the amphotericin B deoxycholate after 3 doses. She continued on high-dose fluconazole monotherapy but clinically deteriorated with worsening confusion. Adjunctive therapeutic lumbar punctures were performed to reduce the elevated intracranial pressures. The repeat CSF analyses showed persistently positive CSF Indian ink tests before the re-initiation of amphotericin therapy. One week since starting treatment for CCM, liposomal amphotericin B was obtained and started at 3 mg/kg/day with strict hydration with one litre of normal saline bolus before and after the amphotericin infusions and scheduled intravenous potassium infusion at 20 mmol/L in 5% dextrose 500 ml to maintain serum potassium levels above 3.5 mmol/L, with close ongoing clinical and electrolyte monitoring.

Management and follow-up

Table 1 below shows a summary of clinical events from admission to discharge. The graph predominantly depicts changes in potassium levels.

Discussion

Confirmation of Cryptococcal Meningitis

Cryptococcal meningitis (CCM) is a life-threatening opportunistic infection that predominantly affects individuals with advanced HIV infection and remains a major contributor to AIDS-related mortality worldwide, particularly in sub-Saharan Africa (Mohamed *et al.*, 2022; Tugume *et al.*, 2023). Diagnosis is typically established through detection of Cryptococcus neoformans species in cerebrospinal fluid (CSF) using cryptococcal antigen testing (CrAg), India ink microscopy, or fungal culture. CrAg detection, particularly using lateral flow assays, has a high sensitivity and specificity of 99% and is widely recommended for rapid diagnosis (McHale *et al.*, 2023; Tugume *et al.*, 2023).

Table 1: Timeline of key clinical events and management

Date	Event / Findings	Intervention / Outcome
17/10/2025	Presented to the hospital and diagnosed with CCM in a newly diagnosed HIV.	Admitted for evaluation and management of CCM in advanced HIV.
17–20/10/2025	Progressive neurological symptoms; cryptococcal meningitis confirmed on CSF (opening pressure recorded >50 drops/min). CXR normal, urine TB-LAM and Sputum GeneXpert negative.	Started induction planning; high-dose fluconazole 1200 mg daily initiated.
Late October 2025	Amphotericin B deoxycholate was commenced together with high dose oral fluconazole; she developed amphotericin B-related severe febrile reactions and persistent hypokalemia despite corrective interventions.	Amphotericin B deoxycholate stopped; continued on fluconazole monotherapy.
17/10/2025 to 01/11/2025	Raised intracranial pressure was suspected clinically by the Cushing's reaction, and headaches; therapeutic interventions performed.	Serial therapeutic lumbar punctures.
25/10/2025	Clinical deterioration with worsening confusion on fluconazole monotherapy.	Liposomal amphotericin B infusion restarted at 3 mg/kg/day with strict pre-hydration and scheduled potassium supplementation and close monitoring.
28/10/2025	K^+ 3.43 mmol/L.	Electrolyte replacement continued.
02/11/2025	K^+ 2.80 mmol/L.	Escalated supplementation; monitoring.
04/11/2025	K^+ 2.88 mmol/L.	Ongoing supplementation.
08/11/2025	K^+ 2.20 mmol/L (nadir).	Aggressive replacement; continued Liposomal Amphotericin B infusion under protocol.
11/11/2025	K^+ 3.45 mmol/L.	Improving stability.
19/11/2025	K^+ 3.80 mmol/L.	Stable on protocol.
26/11/2025	K^+ 4.50 mmol/L.	Normalized potassium.
03/12/2025	K^+ 4.47 mmol/L.	Maintained normalization.
~3 weeks after discharge	Clinical improvement sustained; commenced ART.	Engaged in routine HIV care and follow-up.
February 2026	Routine Review	Patient is doing well after initiation of antiretrovirals (Tenofovir alafenamide, lamivudine, and dolutegravir). She is also on fluconazole 200 mg once a day maintenance dosage.

KEY: CCM = cryptococcal meningitis, TB-LAM = tuberculosis lipoarabinomannan, ART = antiretroviral therapy
Figure 1 below shows the serum potassium trends and management during the amphotericin-based treatment.

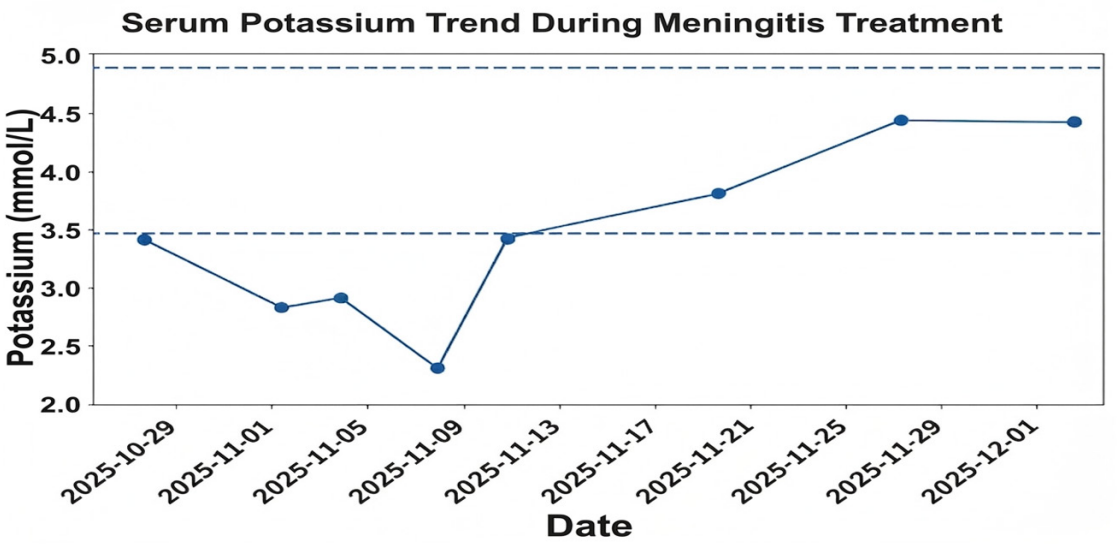

Figure 1: Serum potassium trends during amphotericin-based CCM treatment

In our patient, the diagnosis of CCM was supported by the presence of the stigmata of advanced HIV disease combined with a positive HIV rapid test and a confirmatory positive CSF India ink stain and positive CSF CrAg tests. Advanced immunosuppression represents the most significant risk factor for CCM due to impaired cell-mediated immunity and diminished T-cell–mediated fungal clearance (Tugume *et al.*, 2023; WHO, 27 June 2022).

Guideline-Based Treatment and the Role of Combination Therapy

International treatment guidelines recommend induction therapy with fungicidal agents for the initial management of cryptococcal meningitis. Both the World Health Organization and the Infectious Diseases Society of America guidelines emphasize amphotericin-based regimens combined with flucytosine or fluconazole as first-line therapy during the induction phase (McHale *et al.*, 2023; Perfect *et al.*, 2010; WHO, 27 June 2022).

Combination therapy is recommended because amphotericin B and flucytosine demonstrate synergistic fungicidal activity, enabling rapid reduction in fungal burden. In contrast, fluconazole is fungistatic and therefore produces slower clearance of cryptococci from the CSF (Liu *et al.*, 2024). Rapid fungal clearance during induction therapy is strongly associated with improved survival outcomes (WHO, 27 June 2022).

In our resource-limited case, treatment decisions were guided by available resources and international guideline recommendations to achieve rapid fungal clearance while minimizing drug toxicity.

Amphotericin B Toxicity and Management

Despite its efficacy, amphotericin B deoxycholate is frequently associated with significant toxicity, particularly nephrotoxicity and electrolyte disturbances such as hypokalemia and hypomagnesemia. These toxicities can limit treatment adherence or necessitate temporary discontinuation of therapy (McHale *et al.*, 2023).

In our patient, amphotericin B–associated hypokalemia presented a significant clinical challenge. Severe hypokalemia may contribute to muscle weakness, arrhythmias, and clinical deterioration. Published management strategies emphasize aggressive electrolyte monitoring, saline pre-hydration and rehydration, avoidance of concomitant nephrotoxic drugs, and prompt potassium and magnesium replacement (Liu *et al.*, 2024; WHO, 27 June 2022).

These toxicity mitigation strategies were implemented during the course of treatment for our patient.

Clinical Deterioration During Fluconazole Monotherapy

Clinical deterioration during fluconazole monotherapy has been described in patients with CCM and is attributed to the drug's fungistatic mechanism and the risk of emerging antifungal resistance. Fluconazole alone results in slower fungal clearance from the CSF compared with amphotericin-based regimens (Hope *et al.*, 2019).

Previous reports have also documented symptomatic relapse following initial fluconazole monotherapy in HIV-associated CCM, highlighting the limitations of this approach in patients with high fungal burden (Bicanic *et al.*, 2006). These findings support current recommendations against fluconazole monotherapy for induction therapy whenever alternative amphotericin-based regimens are available.

In the present case, clinical deterioration observed during fluconazole monotherapy was consistent with these previously described limitations.

Role of Liposomal Amphotericin B

Liposomal amphotericin B represents a lipid formulation designed to improve the therapeutic index of amphotericin while reducing nephrotoxicity. The liposomal formulation alters tissue distribution and reduces renal exposure, thereby allowing effective antifungal activity with an improved safety profile (Liu *et al.*, 2024).

Recent clinical trials have demonstrated that liposomal amphotericin B can achieve effective fungal clearance with fewer adverse effects compared with conventional amphotericin B deoxycholate formulations (Jarvis *et al.*, 2022).

Clinical Improvement After Introduction of Liposomal Amphotericin B

Following the introduction of liposomal amphotericin B and correction of electrolyte disturbances, our patient demonstrated clinical improvement with progressive neurological recovery. This improvement is consistent with clinical evidence demonstrating that amphotericin-based regimens achieve faster fungal clearance and improved clinical outcomes compared with fluconazole monotherapy (Jarvis *et al.*, 2022; McHale *et al.*, 2023).

The patient's recovery emphasizes the necessity of restoring effective fungicidal therapy in cases where initial treatment regimens are interrupted or modified due to drug toxicity.

Challenges Associated with Liposomal Amphotericin B

Despite its improved safety profile, liposomal amphotericin B remains associated with several challenges. The most significant limitation is cost, which restricts its availability in many resource-limited settings, like in our case. In addition, careful monitoring for infusion-related reactions and electrolyte abnormalities remains necessary (Liu *et al.*, 2024). In many low- and middle-income countries, limited access to lipid formulations continues to influence treatment decisions.

Adjunctive Treatment and Comprehensive CCM Management

Optimal management of CCM requires a structured treatment strategy consisting of three antifungal phases: induction, consolidation, and maintenance therapy. Induction therapy aims to achieve rapid fungal clearance, followed by consolidation therapy with fluconazole to eradicate residual infection and prevent relapse. Long-term maintenance therapy is required until immune recovery is achieved with antiretroviral therapy (WHO, 27 June 2022).

In addition to antifungal treatment, adjunctive management includes control of intracranial pressure through serial therapeutic lumbar punctures, correction of electrolyte disturbances, and careful timing of antiretroviral therapy initiation to minimize the risk of immune reconstitution inflammatory syndrome (IRIS) (Tugume *et al.*, 2023).

Neurological Recovery and Current Clinical Status

Neurological recovery following CCM depends on several factors, including fungal clearance, control of intracranial pressure, and restoration of immune function. With optimized antifungal therapy and supportive care, our patient demonstrated progressive improvement in neurological status.

Continued clinical monitoring remains essential during the consolidation and maintenance phases of therapy, particularly during antiretroviral initiation when immune reconstitution may alter the inflammatory response.

CONCLUSION

CCM is a common and serious opportunistic infection in patients with advanced HIV disease. Fluconazole alone is insufficient for effective induction therapy, and combination regimens with fungicidal agents such as amphotericin B and flucytosine are recommended. Although amphotericin B is highly effective, its use is often limited by adverse effects, including renal impairment, hypokalemia, and hypomagnesemia. Liposomal amphotericin B provides a safer alternative, with improved tolerability. Supportive measures such as adequate hydration and potassium replacement are essential in minimizing toxicity. This case demonstrates that, even after intolerance to amphotericin B deoxycholate, successful re-initiation of treatment with liposomal amphotericin B is possible and can lead to clinical recovery.

Ethical Consideration

Written informed consent was obtained from the patient before publishing this report.

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