Treatment Rates for Cryptococcal Meningitis in Malawi

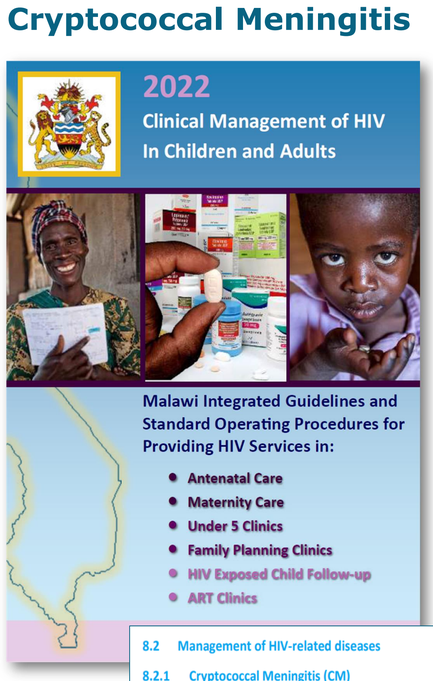
*Yamikani Gumulira, ** Gabriel Saemisch, *Dyson Telela, *Elinat Matupa, **Ikechukwu Amamilo, **Ana Moore, ***Bilaal Wilson, **Paul Nyasulu, ***Rose Nyirenda

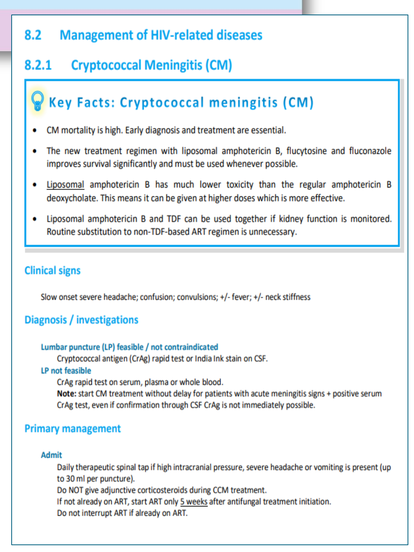
*Clinton Health Access Initiative, Malawi, **Clinton Health Access Initiative, Global, ***Department of HIV & AIDS, Ministry of Health, Malawi

BACKGROUND

Cryptococcal Meningitis (CM) is one of the lead causes of death among people living with HIV (PLHIV). Guidance from World Health Organization (WHO) in 2022 recommends optimized treatment for patients with CM utilizing flucytosine (5FC) and Liposomal amphotericin B (L-AmB), which is estimated to improve survival by up to 70% over fluconazole monotherapy. However, drug toxicity and side effects are known barriers to clinician adoption of this optimal regimen over historically utilized fluconazole. In August of 2020, the Department of HIV and AIDS (DHA) in Malawi scaled CM screening and treatment to 118 sites across 28 districts and included 5FC and L-AmB as the preferred induction treatment regimen in the National HIV Clinical Guidelines. We documented our approach utilizing WhatsApp communications to improve HCW adoption of the WHO recommended optimal CM treatment regimen.

Malawi HIV Clinical Guidelines: Cryptococcal Meningitis




8.2 Management of HIV-related diseases

8.2.1 Cryptococcal Meningitis (CM)

Key Facts: Cryptococcal meningitis (CM)

- CM mortality is high. Early diagnosis and treatment are essential.
- The new treatment regimen with liposomal amphotericin B, flucytosine and fluconazole improves survival significantly and must be used whenever possible.
- Liposomal amphotericin B has much lower toxicity than the regular amphotericin B deoxycholate. This means it can be given at higher doses which is more effective.
- Liposomal amphotericin B and TDF can be used together if kidney function is monitored. Routine substitution to non-TDF-based ART regimen is unnecessary.

Clinical signs

Slow onset severe headache; confusion; convulsions; +/- fever; +/- neck stiffness

Diagnosis / investigations

Lumbar puncture (LP) feasible / not contraindicated
Cryptococcal antigen (CrAg) rapid test or India Ink stain on CSF.

LP not feasible
CrAg rapid test on serum, plasma or whole blood.
Note: start CM treatment without delay for patients with acute meningitis signs + positive serum CrAg test, even if confirmation through CSF CrAg is not immediately possible.

Primary management

Admit
Daily therapeutic spinal tap if high intracranial pressure, severe headache or vomiting is present (up to 30 ml per puncture).
Do NOT give adjunctive corticosteroids during CCM treatment.
If not already on ART, start ART only 5 weeks after antifungal treatment initiation.
Do not interrupt ART if already on ART.

OBJECTIVES

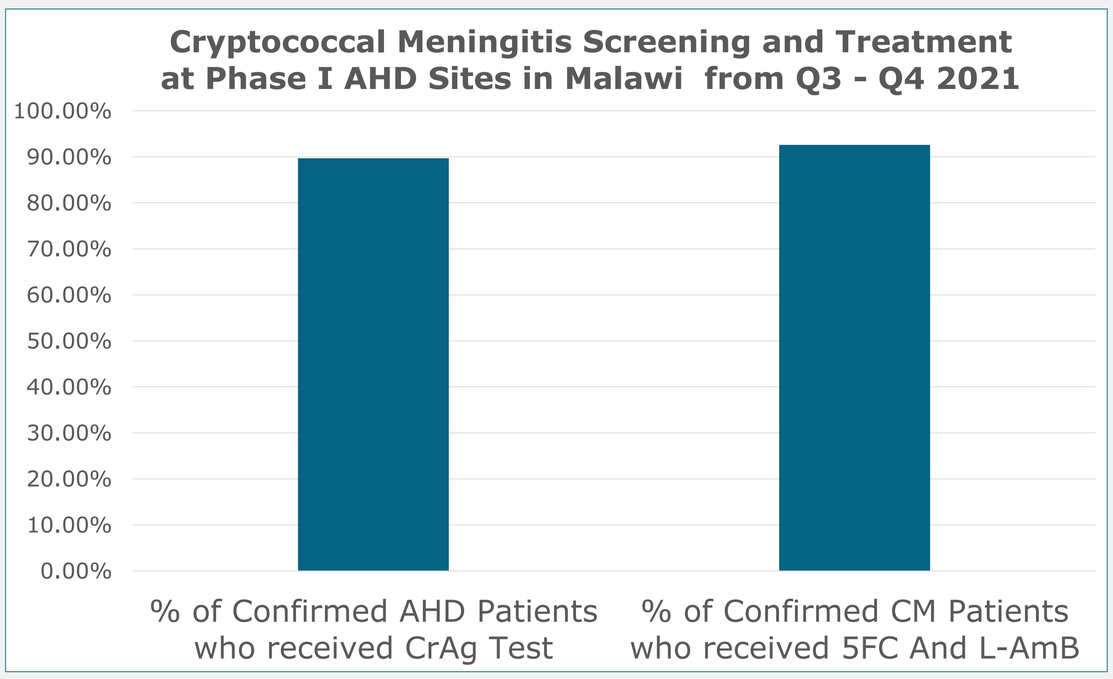
1. Address known barriers to L-AmB and 5FC through development of best practices, lessons learnt, and job aide materials

2. Disseminate best practices and lessons learnt nationally through virtual communication platforms ensuring patients have access to optimal treatment for CM in Malawi

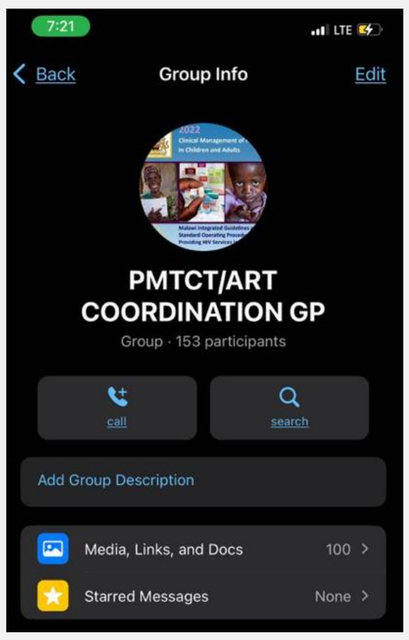
METHODS

In July 2021, the team collected CM treatment data via the HIV patient treatment registers at CM treatment sites. Utilizing a Microsoft Excel AHD capture tool, the primary outcome data collected was the proportion of PLHIV with confirmed CM via lumbar puncture with rapid cerebral spinal fluid (CSF) cryptococcal antigen assay who were managed with the optimal regimen. Following this analysis, the team utilized the DHA antiretroviral treatment (ART) WhatsApp communication platform to disseminate updated guidelines, job aides, and instructional videos to sites where patients were not being managed optimally. Additionally, the team opened a CM clinical hotline available to ART coordinators at hospitals who were treating CM patients to address clinical case questions, support the management of side effects, and immediately address stock outs of CM commodities.

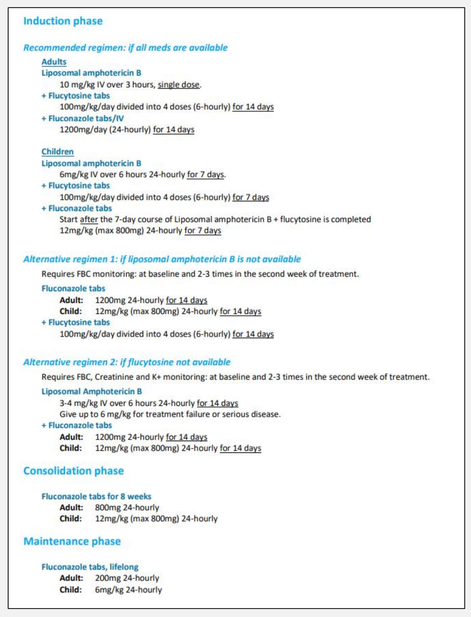
CHAI and the Malawi Department of HIV And AIDS utilized the Malawi antiretroviral treatment WhatsApp communication group to promote optimal management of Cryptococcal Meningitis in Malawi



Malawi antiretroviral treatment (ART) WhatsApp Group



Guidelines and Dosing for Optimal CM Treatment


Induction phase

Recommended regimen: if all meds are available

Adults
Liposomal amphotericin B
10 mg/kg IV over 3 hours, single dose.
+ Flucytosine tabs
100mg/kg/day divided into 4 doses (6-hourly) for 14 days
+ Fluconazole tabs/IV
1200mg/day (24-hourly) for 14 days

Children
Liposomal amphotericin B
6mg/kg IV over 6 hours 24-hourly for 7 days.
+ Flucytosine tabs
100mg/kg/day divided into 4 doses (6-hourly) for 7 days
+ Fluconazole tabs
Start after the 7-day course of Liposomal amphotericin B + flucytosine is completed
12mg/kg (max 800mg) 24-hourly for 7 days

Alternative regimen 1: if liposomal amphotericin B is not available

Requires FBC monitoring: at baseline and 2-3 times in the second week of treatment.
Fluconazole tabs
Adult: 1200mg 24-hourly for 14 days
Child: 12mg/kg (max 800mg) 24-hourly for 14 days
+ Flucytosine tabs
100mg/kg/day divided into 4 doses (6-hourly) for 14 days

Alternative regimen 2: if flucytosine not available

Requires FBC, Creatinine and K+ monitoring: at baseline and 2-3 times in the second week of treatment.
Liposomal Amphotericin B
3-4 mg/kg IV over 6 hours 24-hourly for 14 days
Give up to 6 mg/kg for treatment failure or serious disease.
+ Fluconazole tabs
Adult: 1200mg 24-hourly for 14 days
Child: 12mg/kg (max 800mg) 24-hourly for 14 days

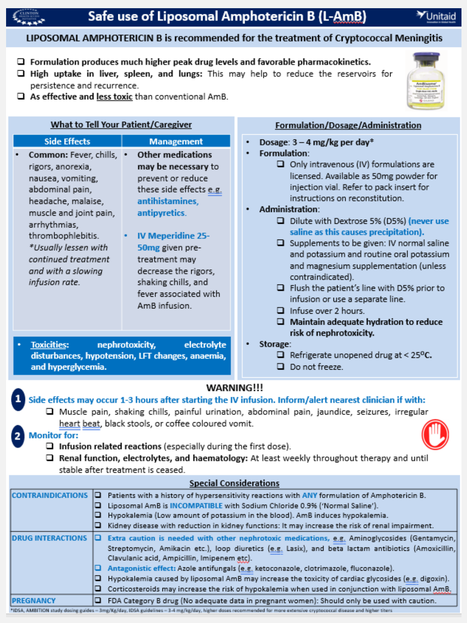
Consolidation phase

Fluconazole tabs for 8 weeks
Adult: 800mg 24-hourly
Child: 12mg/kg (max 800mg) 24-hourly

Maintenance phase

Fluconazole tabs, lifelong
Adult: 200mg 24-hourly
Child: 6mg/kg 24-hourly

Safe use of Liposomal (L-AmB) Job Aide


Safe use of Liposomal Amphotericin B (L-AmB) — Unitaid

LIPOSOMAL AMPHOTERICIN B is recommended for the treatment of Cryptococcal Meningitis

- **Formulation produces much higher peak drug levels and favorable pharmacokinetics.**
- **High uptake in liver, spleen, and lungs:** This may help to reduce the reservoirs for persistence and recurrence.
- **As effective and less toxic** than conventional AmB.

What to Tell Your Patient/Caregiver	
Side Effects	**Management**
• **Common:** Fever, chills, rigors, anorexia, nausea, vomiting, abdominal pain, headache, malaise, muscle and joint pain, arrhythmias, thrombophlebitis. **Usually lessen with continued treatment and with a slowing infusion rate.*	• **Other medications may be necessary** to prevent or reduce these side effects e.g. **antihistamines, antipyretics.** • **IV Meperidine 25-50mg** given pre-treatment may decrease the rigors, shaking chills, and fever associated with AmB infusion.

Formulation/Dosage/Administration

- **Dosage**: 3 – 4 mg/kg per day*
- **Formulation**:
  - Only intravenous (IV) formulations are licensed. Available as 50mg powder for injection vial. Refer to pack insert for instructions on reconstitution.
- **Administration**:
  - Dilute with Dextrose 5% (D5%) **(never use saline as this causes precipitation).**
  - Supplements to be given: IV normal saline and potassium and routine oral potassium and magnesium supplementation (unless contraindicated).
  - Flush the patient's line with D5% prior to infusion or use a separate line.
  - Infuse over 2 hours.
  - **Maintain adequate hydration to reduce risk of nephrotoxicity.**
- **Storage**:
  - Refrigerate unopened drug at < 25°C.
  - Do not freeze.

Toxicities: nephrotoxicity, electrolyte disturbances, hypotension, LFT changes, anaemia, and hyperglycemia.

WARNING!!!

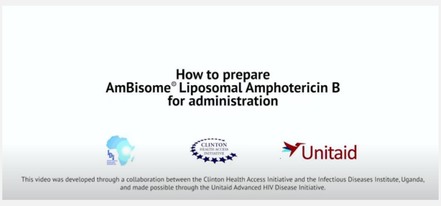
1. **Side effects may occur 1-3 hours after starting the IV infusion. Inform/alert nearest clinician if with:**
   - Muscle pain, shaking chills, painful urination, abdominal pain, jaundice, seizures, irregular heart beat, black stools, or coffee coloured vomit.
2. **Monitor for:**
   - **Infusion related reactions** (especially during the first dose).
   - **Renal function, electrolytes, and haematology:** At least weekly throughout therapy and until stable after treatment is ceased.

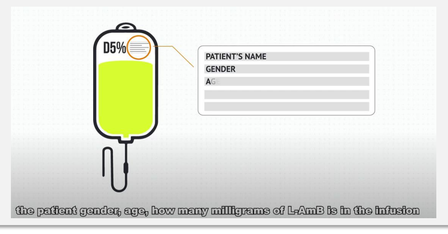
Special Considerations

CONTRAINDICATIONS	❑ Patients with a history of hypersensitivity reactions with ANY formulation of Amphotericin B. ❑ Liposomal AmB is INCOMPATIBLE with Sodium Chloride 0.9% ('Normal Saline'). ❑ Hypokalemia (Low amount of potassium in the blood). AmB induces hypokalemia. ❑ Kidney disease with reduction in kidney functions: It may increase the risk of renal impairment.
DRUG INTERACTIONS	❑ Extra caution is needed with other nephrotoxic medications, e.g. Aminoglycosides (Gentamycin, Streptomycin, Amikacin etc.); loop diuretics (e.g. Lasix), and beta lactam antibiotics (Amoxicillin, Clavulanic acid, Ampicillin, Imipenem etc). ❑ Antagonistic effect: Azole antifungals (e.g. ketoconazole, clotrimazole, fluconazole). ❑ Hypokalemia caused by liposomal AmB may increase the toxicity of cardiac glycosides (e.g. digoxin). ❑ Corticosteroids may increase the risk of hypokalemia when used in conjunction with liposomal AmB.
PREGNANCY	❑ FDA Category B drug (No adequate data in pregnant women): Should only be used with caution.

*IDSA, AMBITION study dosing guides – 3mg/Kg/day. IDSA guidelines – 3-4 mg/kg/day, higher doses recommended for more extensive cryptococcal disease and higher titers

Instructional Video for Prep and Admin of L-AmB





RESULTS

Data collected in July 2021 uncovered most CM patients in Malawi were not receiving optimal treatment consisting of both 5FC And L-AmB. However, following the utilization of the e-communication platforms, 89.7% of eligible AHD patients were screened for CM and 92.6% of patients with confirmed CM received optimal treatment from July – December 2021.

CONCLUSION

Malawi was one of the first low- and middle-income countries to include 5FC and L-AmB as the preferred induction treatment regimen for CM patients in the National HIV Clinical Guidelines and demonstrated how virtual communication platforms can be utilized to drive improvement in the utilization of the optimal regimen for CM patients in resource constrained settings. Now, CrAg screening and CM treatment is being scaled up to an additional 218 facilities starting in in 2022, further increasing access to optimal CM treatment in Malawi. National HIV and CM programs can learn from Malawi's experience utilizing electronic platform communications to improve optimal CM treatment rates, a key component in the global effort to end CM deaths by 2030.

ACKNOWLEDGEMENTS

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