

ATIC

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CRYPTOCOCCAL MENINGITIS

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BACKGROUND

HIV-associated cryptococcal meningitis (CM), an AIDS-defining illness, is the leading cause of meningitis in Sub-Saharan Africa (SSA) and is responsible for 10-15% of AIDS-associated deaths.¹ The development of clinical CM is preceded by an asymptomatic phase characterised by the presence of cryptococcal antigen (CrAg) in the serum of an infected individual for a median period of 3 weeks.^{2,3} Cryptococcal antigen screening alongside antifungal pre-emptive therapy entails the testing of at risk HIV-infected patients for cryptococcal antigen and treating those found positive with fluconazole.⁴ Cryptococcal antigen can be detected in whole blood, plasma or serum.⁵ There is evidence suggesting that CrAg screening and pre-emptive therapy is an excellent public health strategy to reduce

morbidity and mortality due to cryptococcal disease.^{4,6}

Epidemiology of Cryptococcal Disease

The estimated prevalence of cryptococcal antigenemia in ART naive patients with CD4 below 100cells/ml in the world, SSA and Uganda is 6%, 3-19% and 8.2% respectively.^{1,3,4}

An estimated 223,100 (95% CI 150,600–282,400) incident cases of CM occurred globally in 2014, of which 73% (162,500) were in SSA.¹ Annual global deaths from CM were estimated at 181,100 (95% CI 119,400–234,300), with 75% (135,900 [95% CI 93,900 – 163,900) of these deaths in SSA. There are an estimated 120,000 people at risk of CM in Uganda with an estimated 12,000 cases annually.¹

The acute mortality rates of CM range from 17-43% in various health facilities across SSA.⁷⁻⁸ Patients at risk of cryptococcal infection include

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DEAR READER,

Greetings from ATIC!

We are glad to be back with yet another exciting and educational issue of the quarterly Advanced Treatment Information Centre (ATIC) newsletter.

In this issue, we focus on Cryptococcal Meningitis (CM) – the leading cause of meningitis in HIV. Dr Edward Mpoza explains the management and prevention of this disease with the latest guidelines from the Uganda Ministry of Health, and the World Health Organisation (WHO).

In our “ASK ATIC” column Dr Paul Buyego, together with Dr Eve Ahairwomugisha, answer your questions on CM. We hope that this can translate into better patient management and that you’ll share the knowledge therein with your colleagues.

Have you called our toll-free clinical helpline yet? No? Well, our expert clinical team is waiting to answer all your questions on any health condition – free of charge – to enable you manage your patients better. See back of newsletter for details.

We would love to hear from you: Email us: queries@idi.co.ug and elearningidi.mak@gmail.com or call our toll-free line: 0800200055. Let’s together ensure a healthy Africa free from the burden of disease.

Enjoy!

Carolyne Amuge,
ATIC Research and Communications Officer

ART naïve HIV patients with CD4 counts below 100cells/ μ L and the ART-experienced HIV patients with virologic failure. CrAg screening is recommended in countries where the CM prevalence is above 3%.⁹ Current estimates are that only 20% and 30% of eligible patients are receiving CrAg screening in Uganda and worldwide respectively.¹⁰ Data from implementing partners suggests 20% of those eligible are CrAg-screened and only 65% CrAg-positive receive fluconazole. We still need data outcomes and this will be best done by incorporating facility-based data into the Health Management Information System and Open Medical Record System.

Asymptomatic Cryptococcal Antigenemia

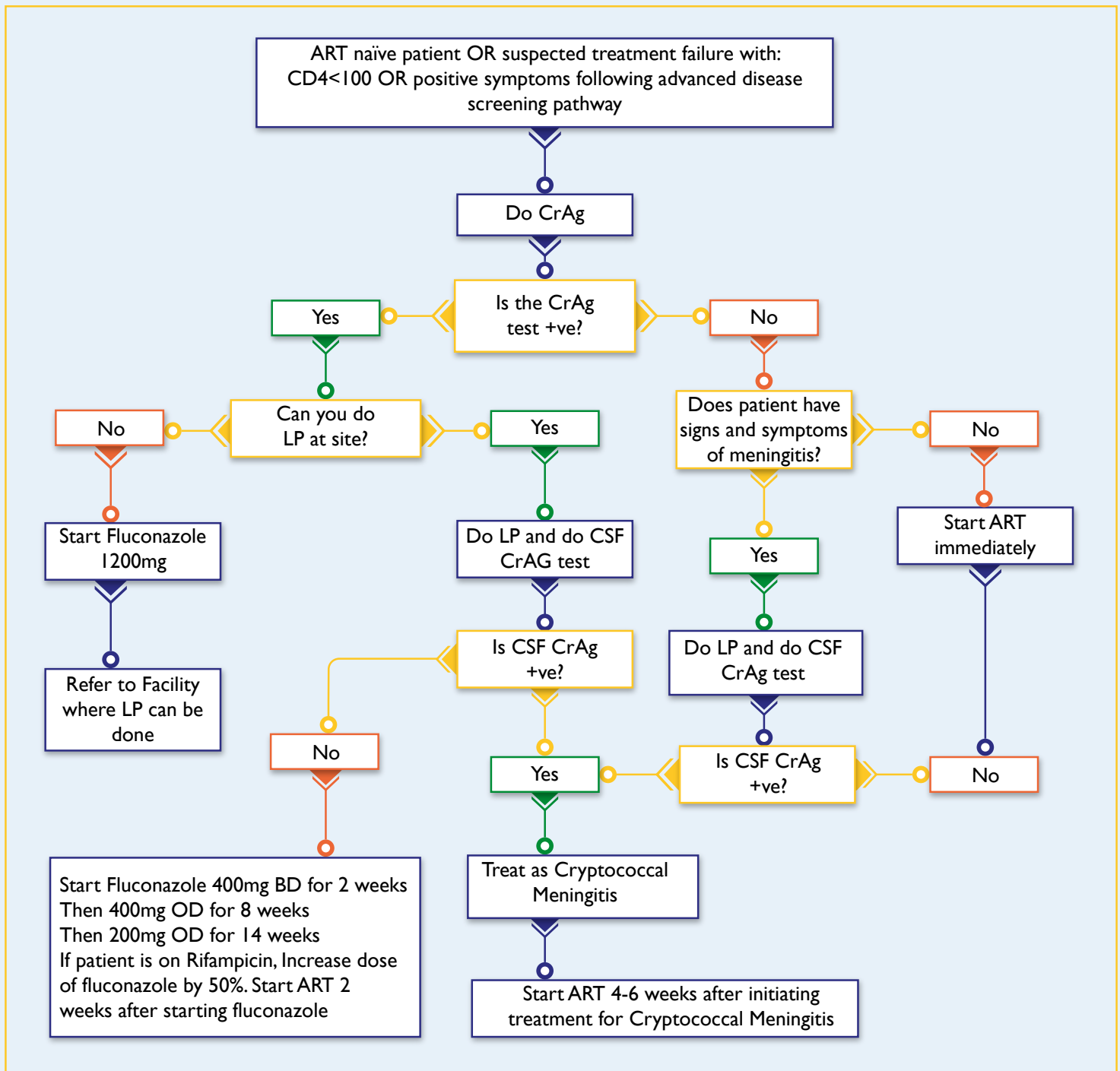
Asymptomatic cryptococcal antigenemia is a phase in which the polysaccharide CrAg can be detected in the serum prior to onset of symptoms. If untreated this can progress to CM.³ Cryptococcal antigenemia is an independent predictor of mortality.^{3,4} Screening asymptomatic patients for CrAg provides a window for pre-emptive fluconazole therapy. It was noted during a retrospective cohort of CrAg patients in 2004-2006, prior to the introduction of pre-emptive fluconazole therapy, that the mortality rate was 100%.⁴ Between 2012-2014 in a cohort of 151 CrAg-positive patients treated with fluconazole, the all-cause six months’ mortality was 14%.¹¹ Independent predictors of positive serum cryptococcal antigenemia are CD4⁺ T cell counts of less than 50 cells/mm, low body mass index, neck pain, signs of meningeal irritation, and a recent diagnosis of HIV infection.¹²

Who should have CrAg Screening per the Uganda HIV Treatment Guidelines 2018?

- ART naïve individuals with CD4 less than 100 cells/ μ L.
- HIV patients on ART with suspected virologic failure (viral load above 1000 copies/ml) with a stage III/IV clinical event.

To screen for cryptococcal disease, health workers should do a CrAg test using the Lateral Flow Assay (LFA) on plasma, serum or finger-prick blood. See the algorithm below that summarises the steps to follow for a CrAg test:

Screening for Cryptococcal Meningitis



Cryptococcal Antigen Detection

Cryptococcal antigenemia diagnosis was simplified in July 2011 following the approval by FDA of a CrAg lateral flow assay, CrAg LFA (Immy, Inc., Norman, OK, USA). This assay is a rapid diagnostic test that provides a definitive result in ≤ 10 min.⁵ It is a more sensitive, highly specific test, cheaper and easier to use than other modalities e.g. cultures, India ink or ELISA. It is now the standard of diagnostic care in cryptococcal disease.^{5,14}

Management of Asymptomatic Cryptococcal Antigenemia

CrAg screening and pre-emptive therapy guidelines for Uganda recommend fluconazole 400mg twice daily for 2 weeks, then 400mg once daily for 8 weeks and then 200mg for 14 weeks.¹³

The maintenance fluconazole dose at 200mg was recommended after observing continued mortality and CM development past the initial 10 weeks for those CrAg positive patients with high titre ($>1:160$) and CD4 below 50 cells/ μ L.^{11,13}

Cryptococcal Meningitis in Children

CM is much less common in children than in adults. Screening and primary prophylaxis are not recommended for children, given the low incidence of cryptococcal meningitis in this age group.

Cryptococcal Meningitis in other Age Groups

All people living with HIV with a positive cryptococcal antigen result on screening should be carefully evaluated for signs and symptoms of meningitis, and undergo a lumbar puncture with CSF examination and India ink or CSF cryptococcal antigen assay to exclude active cryptococcal meningitis. Health facilities where a lumbar puncture is not possible, start 1200mg of fluconazole and refer the patients to a facility that can do it.

Cost Effectiveness of CrAg Screening and Reduction in Mortality.

Asymptomatic CrAg-positive HIV-infected adults have a 20% higher mortality than CrAg-negative adults.^{6,15} CrAg screening and pre-emptive therapy has proven survival benefit and could result in 44% relative reduction in cryptococcal-associated deaths.^{4,16}

The number needed to test and treat with CrAg screening and fluconazole to prevent one CM case is 11.3 (95% CI, 7.9–17.1) at costs of \$190 (95% CI, \$132–\$287). The number needed to test and treat to save one life is 15.9 (95% CI, 11.1–24.0) at costs of \$266 (95% CI, \$185–\$402) yet the per patient cost of CM treatment in Uganda with amphotericin B and fluconazole is US \$400 for two weeks.⁴ CrAg screening with pre-emptive therapy could save Uganda \$5M annually.¹

The incremental health system cost of the CrAg screening intervention in the base case scenario for Uganda (i.e. 100% implementation of CrAg screening for one year total costs inclusive of a 5-year time period of downstream costs) was estimated to be \$1.52 more than 'no screening' per patient.¹⁶ CrAg screening and pre-emptive therapy was found highly cost effective than no CrAg screening (25 DALYS averted per 100 PLWH, at \$6.14 per DALY averted). It is estimated that a CrAg screening programme, including preemptive treatment, costs approximately \$10.76 per person per year in Uganda yet amphotericin is \$7 per day.^{6,16}

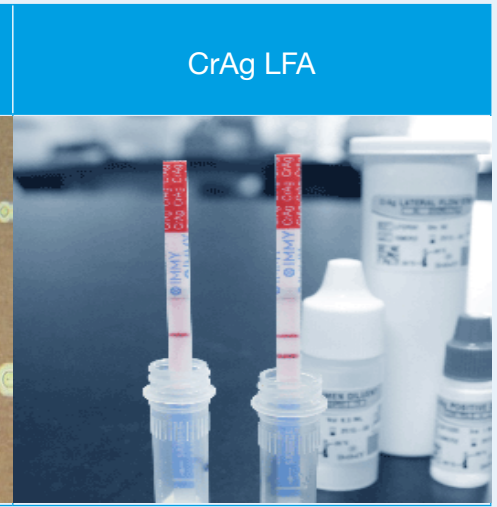
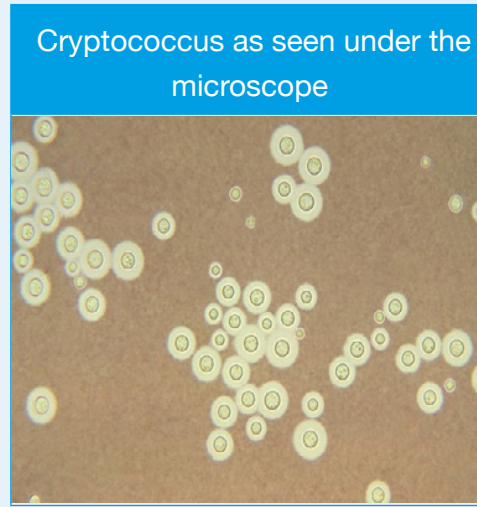
Clinical Presentation of Cryptococcal Meningitis

CM presents as a sub-acute meningitis with the following features:

- Severe headache and neck stiffness or pain
- Photophobia
- Vomiting
- Convulsions
- Cranial neuropathy
- Altered mental state, confusion, coma

- Low grade fever

Other uncommon presentations of cryptococcal disease include pulmonary masses or infiltrates; abdominal features, that is hepato-splenomegaly, lymph nodes, splenic infiltrates; skin lesions.



Updates In Cryptococcal Meningitis WHO Guidelines 2018

Timing of ART after First Cryptococcal Meningitis Episode

Immediate ART initiation is not recommended among adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred 4-6 weeks from the initiation of antifungal treatment.

Diagnosis of cryptococcal meningitis

Lumbar puncture + rapid CSF cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) is the preferred diagnostic approach. If rapid CrAg assays are unavailable, then India ink can be used.



Lumbar puncture being performed

SUMMARY OF MANAGEMENT OF CRYPTOCOCCAL MENINGITIS

Phase	Drug	Comments
Newly Diagnosed Patient		
Induction Phase (2 weeks)	<p>Recommended: Amphotericin B 0.7-1mg/kg/day + flucytocine (100mg/kg/day in four divided doses Or Amphotericin B 0.7-1mg/kg/day + high dose fluconazole 800mg/day</p> <hr/> <p>Or Amphotericin B short course (1 mg/kg/day) for 5-7 days+ high dose fluconazole (1200mg/day)</p> <hr/> <p>Alternative: Fluconazole 1200 mg/day (or 6-12mg/kg/day in children)</p>	<p>Preventing amphotericin toxicity: To prevent nephrotoxicity and hypokalemia, do the following:</p> <ul style="list-style-type: none"> • Pre-hydration with 1L normal saline before starting the daily amphotericin • Monitor serum potassium and creatinine levels at initiation and at least twice weekly to detect changes in renal function • Routine administration of 40 mEq/day of potassium chloride can decrease the incidence of amphotericin-related hypokalemia • Consider alternate day amphotericin if creatinine is >3 mg/dl
Consolidation Phase (8 weeks)	If amphotericin B is used in induction phase: fluconazole 400-800mg/day (or 12mg/kg/day in children and adolescents < 19 yrs.)	Initiate ART 4-6 weeks after starting CM treatment and there is clinical response to antifungal therapy
Maintenance Phase (1 year)	Fluconazole 200mg/day (or 6mg/kg/day up to 200mg in children and adolescents <19 yrs.)	<p>Criteria to stop after a minimum of 1 year of maintenance phase adults VL<1,000 copies/mm³ & CD4≥100 for 6 months or CD4≥200 if viral load not available Children: If CD4>25% or viral suppressed</p>
Relapse Disease		
<p>Presents with a recurrence of symptoms of meningitis and have a positive cerebrospinal fluid culture following a prior confirmed diagnosis of cryptococcal meningitis</p> <ul style="list-style-type: none"> • Evaluate for drug resistance; Send CSF to microbiology reference laboratory at the College of Health Sciences, Makerere University for culture and sensitivity testing. • If there are no drug resistance results, reinstitute the induction therapy for two weeks and complete other phases of treatment • Other options for treatment are a combination of flucytosine (100mg/kg/day in four divided doses) and fluconazole 800-1200mg/day. For patients on rifampicin increase fluconazole dose by 50% 		
Adequate Control of Elevated CSF Pressure		
<ul style="list-style-type: none"> • Control of increased intracranial pressure improves survival by 25% in persons with cryptococcal meningitis • All patients with a CSF pressure>250mm H₂O will need a therapeutic LP the following day to reduce the CSF pressure to <200mm • In the absence of a manometer, one may use an IV giving set to create an improvised manometer measuring the height with a meter stick. • Removing 20-30 mL of CSF (even in the absence of a manometer) may be adequate to decrease CSF pressure. Most patients will need LPs during the induction phase. 		

SUMMARY OF CHANGES IN THE 2018 GUIDELINES

This issue of the ATIC newsletter has focused on cryptococcal meningitis, however, with the ongoing country-wide rollout of the 2018 HIV guidelines, we felt the need to bring to your attention, a summary of the overall changes in the guidelines.

These changes include:

- Dolutegravir, a new drug, has been introduced and combined with Tenofovir and Lamivudine to get the preferred first line drug regimen for eligible PLHIV.
- HIV/syphilis SD Bio-line duo kit introduced for HIV and syphilis screening in pregnant and breastfeeding mothers; Statpak to be used as a confirmatory test.
- For clients whose results are inconclusive after the recommended 14 days following a first inconclusive test result, a DBS sample should be collected, labelled “2nd INC” and sent to CPHL for testing.
- APN (Assisted Partner Notification), a process through which HIV-positive index clients are interviewed to trace the partners on their sexual next work has been emphasised and documented.
- CPT prophylaxis is only recommended for particular categories of PLHIV and not everyone who is HIV positive as in the old guidance.
- Comprehensive package for intervention for advanced disease management; Urine-LAM kits have been introduced to screen for tuberculosis in patients with CD4 below 100cells/ul.
- All populations are targeted for psychosocial support across the continuum of HIV response unlike the the 2016 guidelines that focused on adolescents only.
- There has been changes in the first, second line ART regimens for children, adolescents and adults including the introduction of ABC/3TC/LPV/r syrup for children below three months and Dolutegravir for PLHIV weighing above 25kg.
- Viral load monitoring for newly initiated patients on ART has changed. The first VL being done after six months. If VL <1000 copies/ml repeat VL at 12 months then every 12 months thereafter for adults, and every 6 months for children, adolescents and pregnant/breastfeeding mothers until they are discharged from the mother baby care point (MBCP).
- Differentiated service delivery(DSD) model which is client-centred with emphasis on differentiated HIV testing services and differentiated HIV care and treatment service.



**For details of the changes, refer to Consolidated Guidelines for Prevention and Treatment of HIV in Uganda 2018.*

ASK ATIC

Dear doctor, I have a breastfeeding mother not on HAART with a 9 months old baby who did not get the eMTCT services. What should I do?

ANSWER

The Consolidated Guidelines for Prevention and Treatment of HIV in Uganda, 2018, insist that before starting anyone on ART, their HIV status should be confirmed. In this regard, it is important to run an HIV test for this mother using the newly introduced HIV/syphilis duo kit/test. If her HIV status is confirmed as positive, this mother should be started on ART immediately for the good of her health and also to reduce the risk of transmitting the HIV to the breastfeeding baby.

The infant should be screened for any opportunistic infections, the first PCR done immediately and as recommended in the 2018 HIV prevention and treatment guidelines. For any baby that presents after six weeks, ART should be started, that is, AZT+3TC+NVP for six weeks as this is a high risk baby. If the PCR is negative, the infant should be given Nevirapine for six weeks after completing six weeks of HAART(AZT/3TC/NVP). If the test turns out positive, the guidance is to stop AZT/3TC/NVP straight away and give the recommended first line which is ABC/3TC/LPV/r.

Dear doctor, my patient is on second line ART (Tenofovir, Lamivudine and Alluvia). He was diagnosed with smear positive pulmonary tuberculosis. What should we give our patient?

ANSWER

This patient should be maintained on his current regimen and have anti-TBs initiated immediately. The challenge though is that there is a drug-drug interaction between the anti-TB drug Rifampicin and Lopinavir. In this scenario the best option, if

available, is to substitute Rifampicin with Rifabutin as recommended in the 2018 guidelines.

If Rifabutin is unavailable:

- a) We can do a SUPERBOOST, where we double the dose of Ritonavir in Alluvia if the health facility has separates of Lopinavir and Ritonavir that is LPV/r (400mg/400mg) twice daily.
- b) Most health facilities do not have separates of the drugs so we can DOUBLE THE DOSE OF ALLUVIA to LPV/r (800mg/200mg) twice daily. This gives lots of GIT-associated side-effects so the patient should be monitored closely.

Dear Doctor, my patient has got liver toxicity on his first line Efavirenz. What should I do?

ANSWER

It is important to note that the Revised Consolidated Guidelines for the Prevention and Treatment of HIV in Uganda, 2018, mentions Dolutegravir (DTG) as the first line drug instead of Efavirenz. If the patient is intolerant to Efavirenz and DTG is contraindicated, a protein inhibitor can be considered to substitute EFV.

Dear doctor, my patient has a positive serum CrAg but a negative CSF CrAg and a negative zn stain. How do I manage them?

ANSWER

This patient has a diagnosis of cryptococcal antigenemia so Fluconazole 400mg BD for two weeks, then 400 mg OD for eight weeks, then 200 mg for 14 weeks as recommended in the Consolidated Guidelines for Treatment and Prevention of HIV in Uganda 2018.

Doctor, can we use ketoconazole for cryptococcal prophylaxis if we run out of fluconazole?

ANSWER

The goal of treatment is cure of the infection (CSF sterilization) and prevention of long-term CNS system sequelae. Ketoconazole is generally ineffective in the treatment of cryptococcosis because it does not cross an intact blood brain barrier and crosses to only a limited extent in fungal meningitis. Ketoconazole should not be used even for prophylaxis.

Dear doctor is it true that, we can stop fluconazole in the prophylaxis for cryptococcal meningitis?

ANSWER

Yes, it can be stopped after a minimum of one year of maintenance phase:

- In adults if viral load is < 1,000 copies and CD4 is >100 for 6 months or CD4>200 if viral load not available.
- In children if CD4 > 25% or viral load suppressed

Dear doctor, we have a pregnant woman with cryptococcal meningitis, should we give fluconazole?

ANSWER

Standard therapy for CM relies on prolonged use of azole antifungal compounds like fluconazole which are teratogenic and hence cannot be used in pregnancy. There are no standard guidelines on the management of cryptococcal meningitis in pregnancy. However, drug prescription during pregnancy requires a careful evaluation of the balance between maternal benefit and foetal risks.

Treatment of cryptococcal meningitis during pregnancy is paramount to avoid the high mortality associated with untreated cryptococcal disease as well as to decrease the risk of vertical transmission which has been documented. Amphotericin B is the only antifungal agent with US Food and Drug Administration (FDA) category B rating in pregnancy hence can be used in pregnancy.¹⁷ However, it has toxicities that include anaemia, electrolyte abnormalities, and renal dysfunction. Patients

on amphotericin will need close monitoring. The ideal period of treatment with amphotericin B for cryptococcosis in pregnancy is unknown and depends on clinical response, CSF sterilization, and decrease of cryptococcal antigen titres. Therefore, such patient should be referred and managed in highly facilitated health centres.

The recommended options used in treatment of cryptococcal disease include Amphotericin B based intravenous therapy, oral flucytosine and oral fluconazole.

The Infectious Diseases Society of America (IDSA) guidelines on the treatment of disseminated cryptococcal disease in pregnancy recommends Amphotericin B with or without flucytosine.¹⁶ Amphotericin B is a category B pregnancy drug, meaning that there is no evidence of pregnancy risk in humans from its use following extensive clinical use for both cryptococcosis and other infections.^{17,18}

Perfect et al (2010) highlights that Flucytosine is a category C pregnancy drug indicating that not enough research has been done to determine its safety in pregnancy. Flucytosine crosses the placenta and animal studies have shown the potential for teratogenicity at doses lower than the human dose.¹⁹

Lopez and colleagues guide that Fluconazole treatment of more than a single 150mg dose is a category D pregnancy drug yet the recommended dose to treat CM is 1200mg/day during the induction phase, suggesting that there is evidence that it poses risk to the fetus. It is teratogenic and results in a characteristic pattern of malformations especially during the first half of pregnancy. Ely et al recommend avoiding fluconazole during the first trimester^{17,18,20}

Ely et al suggest 4 to 6 weeks of treatment with intravenous AmpoB with co-administration of oral flucytosine, followed by oral fluconazole after delivery.²⁰

Interesting Facts...

- ❖ Cryptococcal disease is an opportunistic infection that occurs primarily among people with advanced HIV disease
- ❖ CM causes 15% of all HIV-related deaths that occur globally, 3 quarters of which occur in Sub-Saharan Africa
- ❖ 223,100 estimated cases of cryptococcal meningitis result in 181,000 deaths among PLHIV
- ❖ Cryptococcal disease is rare among children with HIV even in areas with a high disease burden in adults.
- ❖ Mortality from cryptococcal meningitis is highest in low income countries.
- ❖ CD4 cell count testing remains important in order to identify people with advanced HIV disease so that they can be offered the cryptococcal package of care.

LEAD WRITER PROFILE



**Dr Mpoza Edward,
MBChB, MMed.**

Edward is a physician and upcoming researcher with the Meningitis research team at the Infectious Diseases Institute. He is under the mentorship of David Meya PhD, Abdu Musubire MMed, Joshua Rhein MD, David Boulware PhD and Radha Rajasingham MD. He is currently a Fogarty Global Health fellow looking at Cryptococcal antigenemia in ART experienced HIV patients with virologic failure. He hopes to pursue a career in translational HIV research with specific interest in CNS infection especially cryptococcal meningitis. Edward continues to advocate for cryptococcal antigen screening and evidence based pre-emptive therapy to reduce the incidence and mortality due to cryptococcal meningitis.

ATIC welcomes contributions from experts in their respective health fields. Get in touch via our email: queries@idi.co.ug

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REFERENCES

1. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, et al. Global Burden of Disease of HIV-associated Cryptococcal Meningitis: An updated analysis. *The Lancet Infectious Diseases*. 2017.
2. French N, Gray K, Watera C, Nakiyingi J, Lugada E, Moore M, et al. Cryptococcal Infection in a cohort of HIV-1-infected Ugandan Adults. *Aids*. 2002;16(7):1031-8.
3. Liechty CA, Solberg P, Were W, Ekwaru JP, Ransom RL, Weidle PJ, et al. Asymptomatic serum cryptococcal antigenemia and early mortality during antiretroviral therapy in rural Uganda. *Tropical medicine & international health*. 2007;12(8):929-35.
4. Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, et al. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count \leq 100 cells/ μ L who start HIV therapy in resource-limited settings. *Clinical infectious diseases*. 2010;51(4):448-55.
5. Boulware DR, Rolfes MA, Rajasingham R, von Hohenberg M, Qin Z, Taseera K, et al. Multisite validation of cryptococcal antigen lateral flow assay and quantification by laser thermal contrast. *Emerg Infect Dis*. 2014;20(1):45-53.
6. Rajasingham R, Meya DB, Boulware DR. Integrating cryptococcal antigen screening and preemptive treatment into routine HIV care. *Journal of acquired immune deficiency syndromes (1999)*. 2012;59(5):85.
7. Kambugu A, Meya DB, Rhein J, O'Brien M, Janoff EN, Ronald AR, et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. *Clinical infectious diseases*. 2008;46(11):1694-701.
8. Jarvis JN, Bicanic T, Loyse A, Namarika D, Jackson A, Nussbaum JC, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated Cryptococcal meningitis: implications for improving outcomes. *Clinical infectious diseases*. 2013;58(5):736-45.
9. Organization WH. Rapid advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization, 2011. Geneva: World Health Organization. 2011.
10. Pac L, Horwitz M, Namutebi AM, Auerbach BJ, Semeere A, Namulema T, et al. Integrated pre-antiretroviral therapy screening and treatment for tuberculosis and cryptococcal antigenemia. *Journal of acquired immune deficiency syndromes (1999)*. 2015;68(5):e69.
11. Rajasingham R. Operational research in Cryptococcal antigen screening. 2014.
12. Oyella J, Meya D, Bajunirwe F, Kanya MR. Prevalence and factors associated with cryptococcal antigenemia among severely immunosuppressed HIV-infected adults in Uganda: a cross-sectional study. *Journal of the International AIDS Society*. 2012;15(1):15.
13. Uganda-Final-UgandaHIVGuidelines September 2018_.pdf- M. Final-UgandaHIVGuidelines2018_September2018.pdf. 2018.
14. Lindsley MD, Mekha N, Baggett HC, Surinthong Y, Autthateinchai R, Sawatwong P, et al. Evaluation of a newly developed lateral flow immunoassay for the diagnosis of cryptococcosis. *Clinical infectious diseases*. 2011;53(4):321-5.
15. Mfinanga S, Chanda D, Kivuyo SL, Guinness L, Bottomley C, Simms V, et al. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. *The Lancet*. 2015;385(9983):2173-82.
16. Ramachandran A, Manabe Y, Rajasingham R, Shah M. Cost-effectiveness of CRAG-LFA screening for cryptococcal meningitis among people living with HIV in Uganda. *BMC infectious diseases*. 2017;17(1):225.
17. E. Lopez-Rangel, M.I. Van Allen Prenatal Exposure to Fluconazole: An Identifiable Dysmorphic Phenotype Birth Defects Res. A Clin. Mol. Teratol., 73 (11) (2005), pp. 919-923
18. C.T. King, P.D. Rogers, J.D. Cleary, S.W. Chapman'. Antifungal Therapy during Pregnancy Clin. Infect. Dis., 27 (5) (1998), pp. 1151-1160
19. J.R. Perfect, W.E. Dismukes, F. Dromer, D.L. Goldman, J.R. Graybill, R.J. Hamill, et al. Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 update by the Infectious Diseases Society of America Clin. Infect. Dis., 50 (3) (2010), pp. 291-322
20. E.W. Ely, J.E. Peacock, E.F. Haponik, R.G. Washburn. Cryptococcal pneumonia complicating pregnancy *Medicine*, 77 (3) (1998), pp. 153-167

Advanced Treatment Information Centre (ATIC)

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