Further management of HIV-associated cryptococcal meningitis

Raised intracranial pressure, ART initiation and significant drug interactions

Training module structure

- This training module is organised into 7 sections which can be accessed individually.
- This is section 7: Further management of HIV-associated cryptococcal meningitis
- It is recommended to complete all sections and access them sequentially from 1 to 7.
- All references and acknowledgments can be found in the notes section of each slide as well as more information and external links to resources.

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Raised intracranial pressure

- All patients who are obtunded or have focal neurological signs (except VIth cranial nerve palsy which is often a false localising sign) should, if possible, have a contrast enhanced brain CT to identify mass lesions that may increase the risk of lumbar puncture (LP).

- If no CT scan is available, the balance of risk usually favours performing a lumbar puncture.

- Cryptococcal meningitis patients should all have an admission lumbar puncture with CSF opening pressure recorded.

- Where patients have raised intracranial pressure secondary to cryptococcal meningitis, the patient's CSF will be drained by therapeutic LP as often as required until the opening pressure normalises.

CT: Computerised tomography

Raised intracranial pressure

- Defined as a CSF opening pressure > 20 cm H20. A therapeutic LP aims to provide lumbar drainage to achieve a closing pressure ≤ 20 cm H20 or 50% of the initial opening pressure.

- If OP >30 cm H20, daily therapeutic LPs should be undertaken.
- Usually no more than 30mL CSF will be drained at any one therapeutic LP.
- Recheck the CSF pressure after removal of every 10mL CSF.

- No evidence for use of corticosteroids, mannitol or acetazolamide for treatment of raised intracranial pressure. Risk of harm.

Raised intracranial pressure

Identify CSF Opening Pressure at baseline	
Perform CT or MRI brain if impaired mentation or focal neurological signs present at baseline. The use of mannitol and acetazolamide is not indicated for the treatment of raised ICP related to CM.	
If CSF Opening Pressure ≥25cm H_2O, perform therapeutic lumbar puncture	
Reduce opening pressure (OP) by 50% if OP very high or to a normal pressure of ≤20cm H_2O. Repeat lumbar puncture daily until CSF pressure normalised & symptoms stabilised for >2 days.	Do not remove more than 30mL CSF at any therapeutic lumbar puncture. Check CSF pressure after every 10mL CSF removed . *IDSA Guidelines 2010*

See DREAMM CCM poster and Lumbar Puncture workshop for more details

Lumbar puncture clinical workshop. DREAMM training. Dar es Salaam, August 2017.
Images courtesy or Robert Harris, St George's University of London.

Management of seizures

- 1. ABC – Airways, breathing and circulation
- 2. Check random blood glucose
- 3. Treat in line with local site seizure protocol.

Example seizure protocol

- 10mg of diazepam in 8 ml of 5% Glucose or 0.9% saline
- Given by slow IV (given over 2-3 minutes) or rectally if no IV access

- **Repeat if convulsion persists beyond 5 minutes**

- If second dose diazepam fails, treat as status epilepticus
- Oxygen supplementation
- Options include Phenytoin and Phenobarbital

- Once the seizures have stopped, reduce the infusion rate

- Start **Valproate sodium therapy** or alternative anticonvulsant as per local guidelines

Starting ART

- Current WHO 2018 guidance:

Recommendation

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

- 2018 WHO cryptococcal disease guidance
- SA 2013 HIV Clinicians' Society Guidelines:
- 2010 IDSA cryptococcal disease management guidance

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Starting ART

- 2 key RCTs have informed these guidelines:
- RCT performed in Zimbabwe. High dose fluconazole therapy as induction therapy. Randomisation to start ART at ≤72 hours versus 10 weeks. Excess mortality found in immediate ART arm.[1]

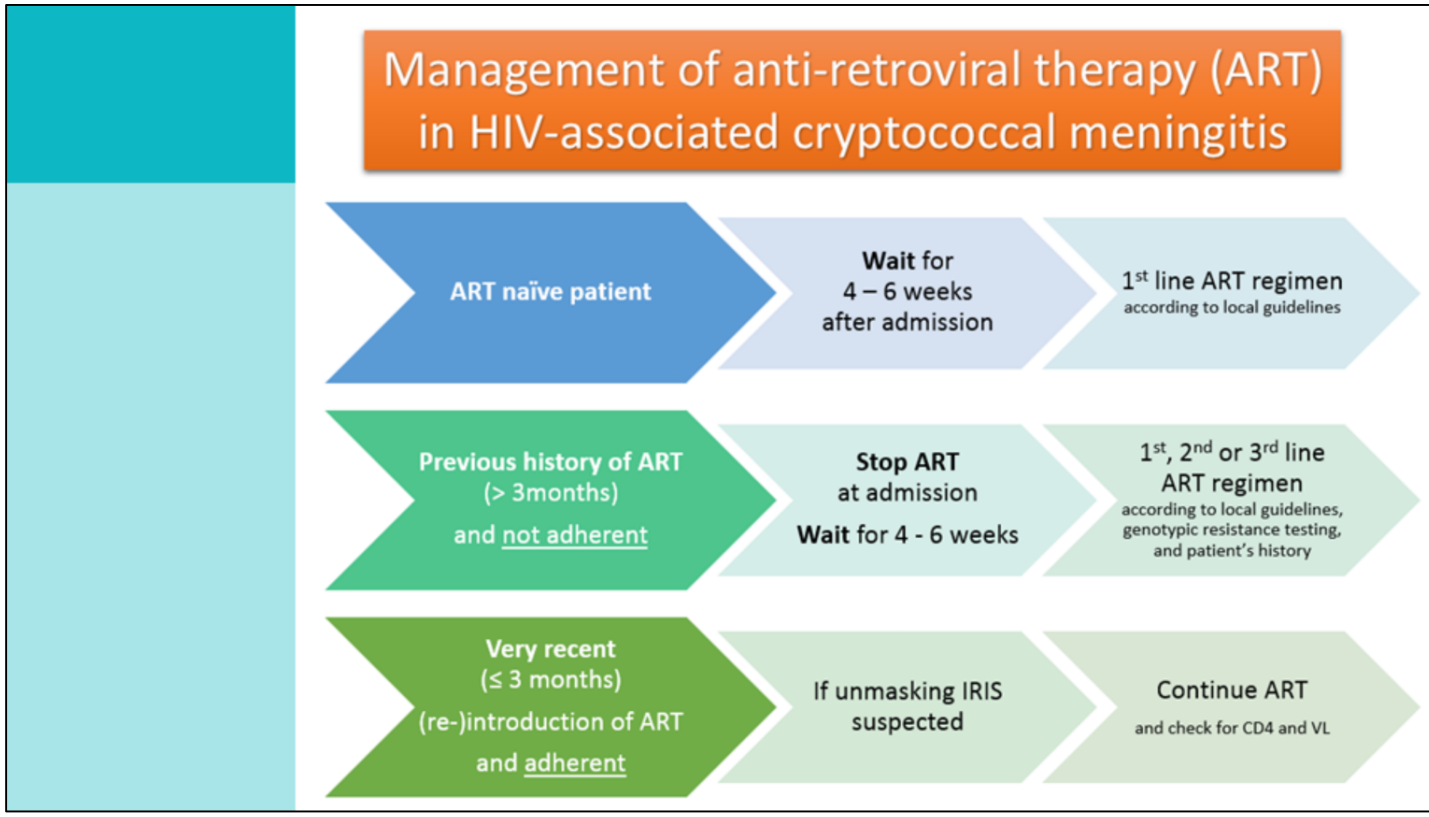
- The COAT trial performed in SA and Uganda. AmB-based induction therapy. Randomisation to start ART: 'early'-1-2 weeks (median 8 days) or 'deferred'-4-6 weeks (median 36 days). 26 week mortality was significantly higher in 'early' arm, particularly in patients with few white cells in their CSF. However the incidence of CM IRIS did not differ between the two arms.[2]

- Lack of data on intermediate time points (2, 3 and 4 weeks) for starting ART.

Reference:1 Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. Clin Infect Dis 2010;50(11):1532-1538. [http://dx.doi.org/10.1086/652652]

Reference:2 D.R Boulware, DB Meya, C Muzoora et al. NEJM 2014; 370: 2487-98.

RCT: randomised controlled trial
ART: antiretroviral therapy



Most cases of cryptococcal meningitis in African LMICs now occur in antiretroviral therapy (ART) experienced people living with HIV (PLHIV).

PLHIV presenting with cryptococcal meningitis are commonly either non-adherent to or failing ART. In such patients ART should usually be withheld until 4-6 weeks at which point either their initial ART regimen (usually) in cases of straightforward non-adherence, or switched to either 2nd or 3rd line therapy in cases of ART failure.

However in cases of unmasking IRIS it is usually recommended to continue the prescribed ART regimen.

CCM and IRIS

▹The term Immune Reconstitution Inflammatory Syndrome (IRIS) can refer to:

- 'Unmasking IRIS'-usually represents a new diagnosis of CCM in a patient started (if ART naïve) or restarted on ART (if ART experienced and treatment interrupted).

- 'Paradoxical IRIS'-a deterioration in a patient's condition in an already diagnosed CCM patient.

▹The differential diagnosis of a patient who presents with a recurrence of symptoms and signs includes:

- Non-adherence to fluconazole secondary prophylaxis
- Fluconazole resistance (less common)

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IRIS diagnosis and management

Consider a diagnosis of IRIS if:

- a. Temporal association between starting ART and clinical presentation (median is one month post ART).
- b. Evidence of rapid immune restoration (ie sharp rise in peripheral CD4 cell count from low baseline).
- c. Exclusion of alternative explanations eg. non-compliance or resistance to fluconazole, second diagnosis.
- d. Clinical features (ie new or increased lymphadenopathy) or cytology (ie CSF WCC)

- Management of raised ICP is an important aspect of IRIS.

- Steroids may be considered if CCM IRIS is considered likely in the absence of an alternative diagnosis and raised ICP is not a persistent issue.

ART: Antiretroviral therapy
WCC: White cell count
ICP: Intracranial pressure

Significant drug interactions:
AMPHOTERICIN B / TENOFOVIR

- Amphotericin B and Tenofovir have shared **renal toxicity**.
- Particular attention should be paid to hydration and saline fluid loading in any patients on AmB and Tenofovir.
- Doses of Tenofovir should be adjusted if there is significant renal impairment according to standard guidance.
- Note – there are no interactions between Dolutegravir or Co-trimoxazole and antifungals

Significant drug interactions:
LAMIVUDINE (3TC), EMTRICITABINE (FTC), ZIDOVUDINE (AZT), TENOFOVIR

- May potentiate the **haematological toxicity** of **FLUCYTOSINE** and worsen neutropenia and thrombocytopenia.

- Consider **reducing dose or switching** to an alternative antiretroviral, if grade III or IV neutropenia, or thrombocytopoenia develop.

- All the above are renally excreted, and **dose adjustment may be needed if renal impairment develops**.

- Given that renal impairment may be transient, it may be worth waiting a short period (for example 1-3 days for measures such as hydration to take effect), depending on level of creatinine rise, to avoid making unnecessary and short term dose adjustments.

- Any such adjustment needs to be regularly reviewed as renal function recovers.

Significant drug interactions:
ZIDOVUDINE (AZT)

- Zidovudine has some bone marrow suppressive effects and therefore **the potential to exacerbate the anaemia associated with Amphotericin B**.

- Full blood counts need to be monitored.
- Consideration switching AZT to an alternative antiretroviral, if grade III or IV anaemia develops.

- **Fluconazole increases AZT levels.**
- Dose adjustment is not recommended on this basis
- However concomitant fluconazole may, at the discretion of local PIs, lower the threshold for switching away from AZT if anaemia, develops.

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Summary

- WHO has issued new guidance for the management of CCM in LMICs with new regimen recommendations: 1 week AmB + 5FC and alternative two weeks' of Fluconazole and 5FC.
- Safe drug administration, laboratory monitoring and management of common treatment toxicities is essential for good outcomes for PLHIV with CCM who have a good prognosis with effective antifungal therapy and timely ART
- Raised intracranial pressure is a common complication that must be managed by repeat therapeutic lumbar punctures and guidance on performing these to be followed.
- ART should not be started before 4-6 weeks

2018 WHO cryptococcal disease guidance

SA 2013 HIV Clinicians' Society Guidelines:

2010 IDSA cryptococcal disease management guidance

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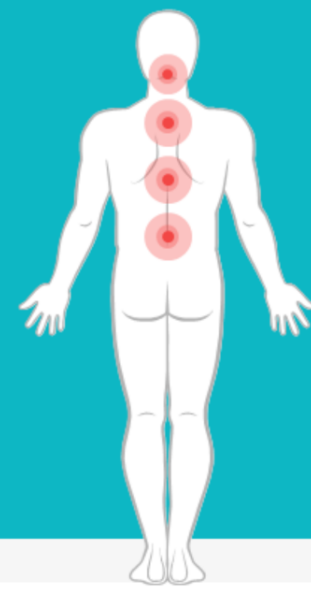

Authors and affiliations

▹St George's University of London
Mr Muirgen Stack – Education lead
Dr Angela Loyse – Academic lead
Prof Tom Harrison
Prof Anne-Marie Reid (previous Dean of Education)
Ms Sarah Burton
Dr Tihana Bicanic
Dr Sile Molloy
Ms Ida Kolte

▹Institut Pasteur, France
Ms Aude Sturny-Leclère - Laboratory lead
Dr Timothée Boyer-Chammard – Clinical lead
Prof Olivier Lortholary

▹National Institute Communicable Diseases, South Africa
Dr Nelesh Govender

▹UNC Project Lilongwe, Malawi
Dr Cecilia Kanyama

▹National Institute for Medical Research, Tanzania
Dr Sayoki Mfinanga

Hôpital Central Yaoundé, Cameroon/ANRS
Dr Charles Kouanfack

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Education programme topics

- General meningo-encephalitis patient management
- Cryptococcal meningitis - CCM
- Tuberculous meningitis – TBM
- Bacterial meningitis – BM
- Toxoplasmic encephalitis - Toxo
- Neurosyphilis – NS