THE REPUBLIC OF UGANDA
MINISTRY OF HEALTH

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GLOBAL HEALTH

MAKERERE UNIVERSITY

INFECTIOUS DISEASES INSTITUTE

Emergency approach to Adult Meningitis

(Current guidelines, new drug regimens, completed trials and ongoing trials)

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- With the introduction of pneumococcal vaccine/ over use of the antibiotics for other infections – Rapid reduction bacterial meningitis

- ~ 60 to 80% of meningitis in sub-Saharan Africa is HIV-associated, with (CM) ~ 60% and (TBM) ~ 6 to 17%.

- Most HIV associated meningitis require LP and Csf for diagnosis

Introduction and Background

WHO definition of Advanced HIV Disease (AHD)

- For **adults and adolescents**, and **children five years or older**, advanced HIV disease is defined as **CD4 cell count <200cells/mm3** or with a **current WHO stage 3 or 4** event
- **All children younger than five years of age with HIV** regardless of CD4 count are **considered as having advanced HIV disease** due to high viremia and rapid disease progression with high mortality

1/3rd of people initiating ART have CD4<200

~25,000 PLHIV suffer from AHD annually

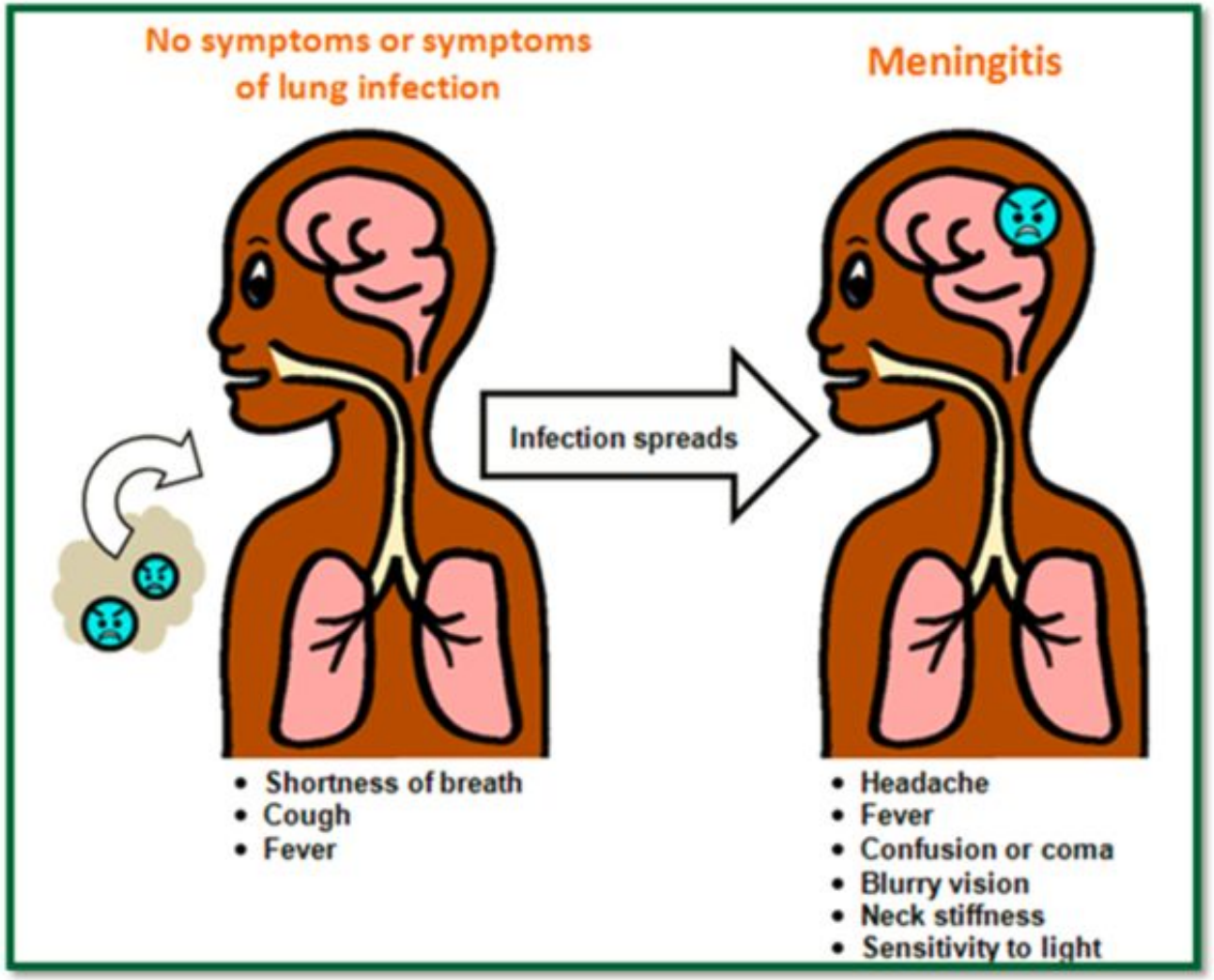
~11% of PLHIV in care experience **treatment failure to ART regimens** and a growing number of PLHIV are returning to care with AHD after treatment interruption

Uganda consolidated guidelines for prevention and management of HIV recommend a package of interventions, similar to those recommended by WHO, aimed at reducing HIV-associated morbidity and mortality

Cryptococcal infection/disease

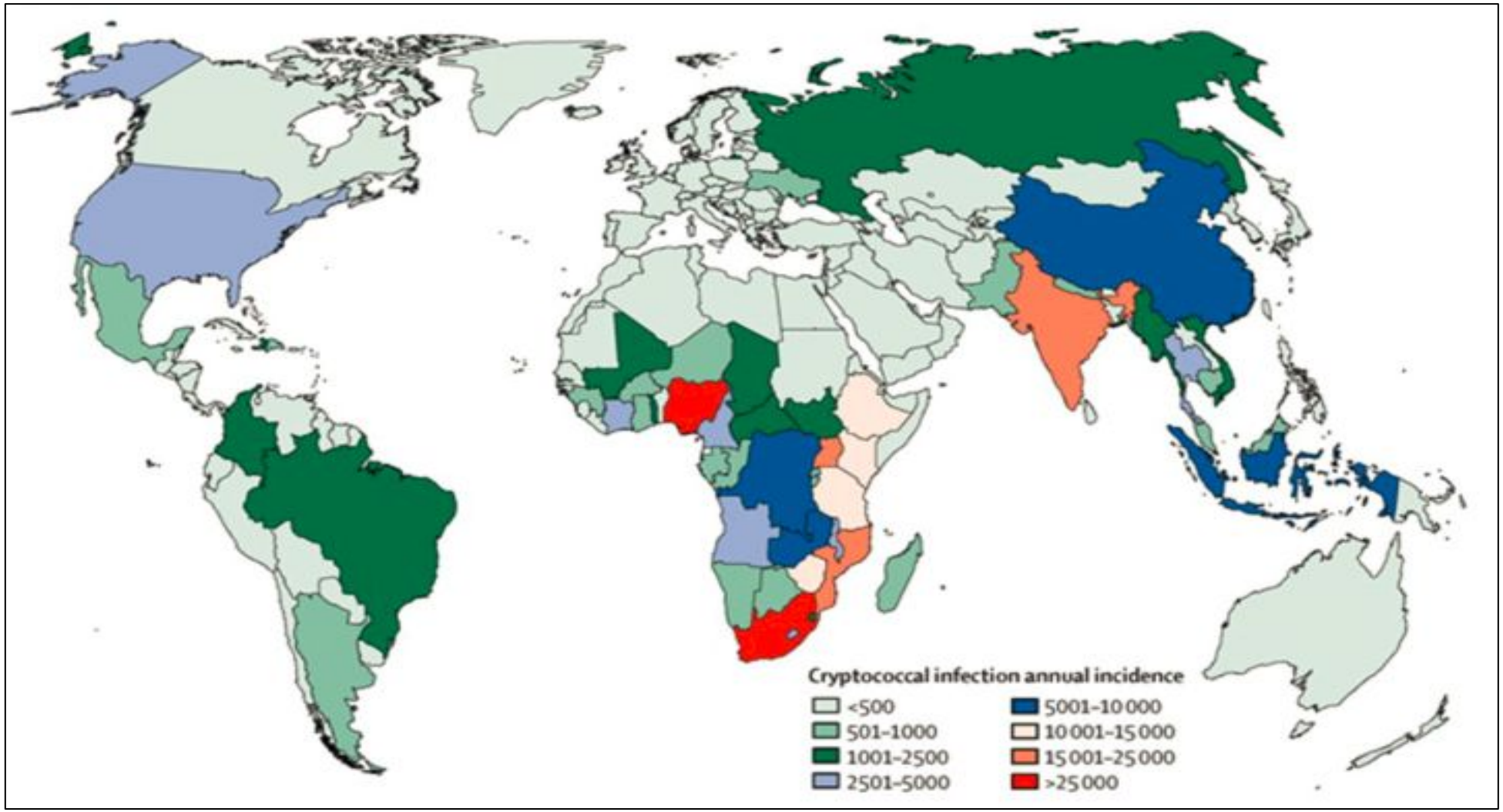
- **NO** person–person transmission

- **NB:** This is a ‘time lapse diagram showing infection spreading within the same patient



Source: *South African National Department of Health and NICD/Nelesh Govender*

Global burden of disease of HIV associated cryptococcal meningitis: an updated analysis – Annual incidence of cryptococcal infection



Source: *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):873–881. doi:10.1016/S1473-3099(17)30243-8*

Cryptococcal infection/disease

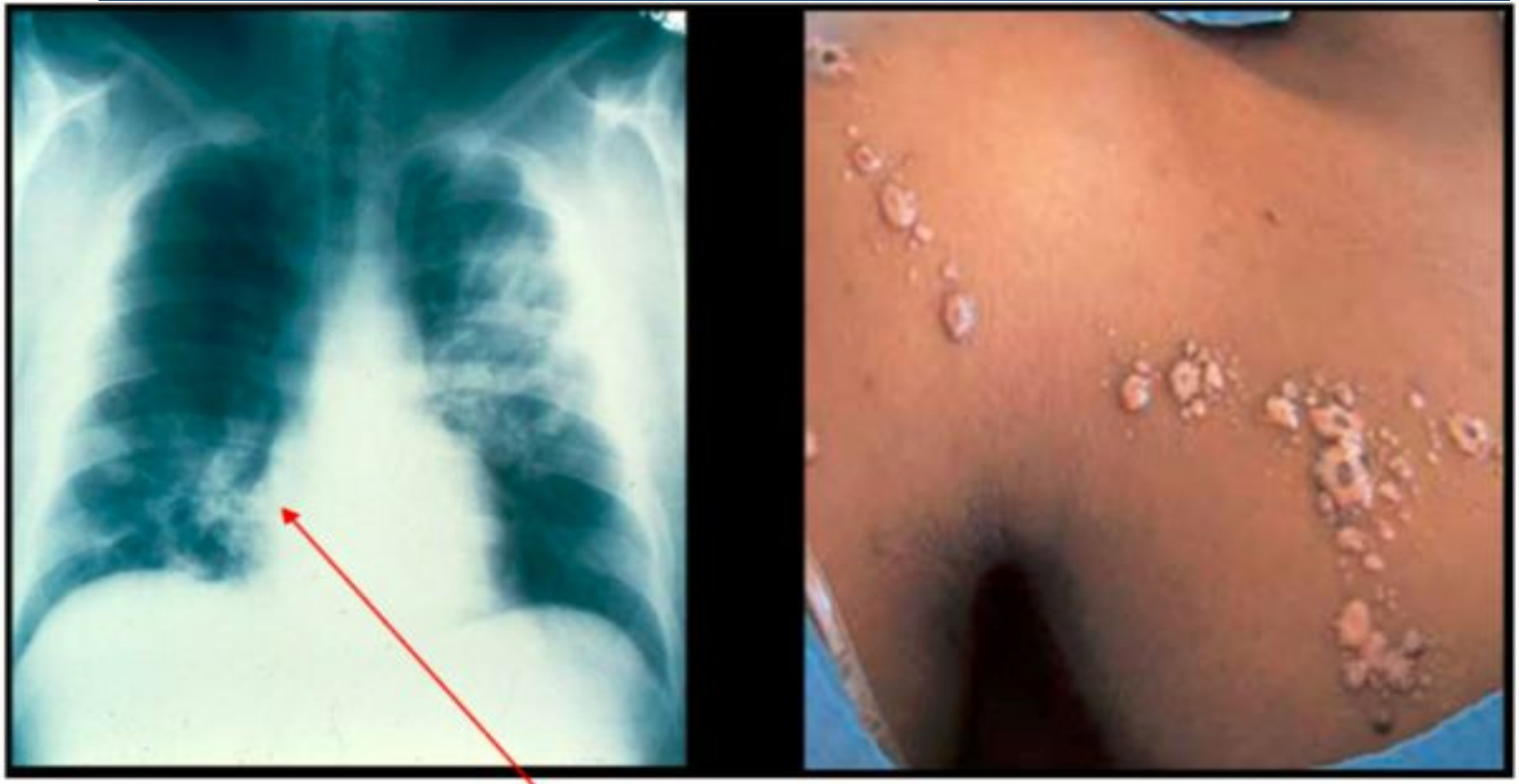
Infection

- Cryptococcus is a fungus found in soil throughout the world.
- After inhalation, the fungus can cause an acute lung infection, or, commonly no symptoms at all.
- The fungus may stay dormant in the body for months to years.
- Reactivation of disease can occur in immune-suppressed people, such as HIV/AIDS patients.
- Adult HIV/AIDS patients with a CD4 count < 100 are at highest risk for reactivation.
- When Cryptococcus reactivates in the body, it can cause disease in the brain, lungs, skin, and bones.

Neurological Manifestations

- Meningitis (inflammation of the tissue surrounding the brain) is the most common form of cryptococcal disease in HIV/AIDS patients.
- Encephalitis (infection of the brain itself) can also occur together with meningitis.
- Cryptococcal meningitis is a common cause of death among HIV/AIDS patients.
- Even when patients are treated with anti-retroviral medications and anti-fungal therapy, 30 to 70 per cent die from their cryptococcal disease.

Additional CM presentations



Chest X-ray of cryptococcal infiltrate

Cryptococcal skin lesions

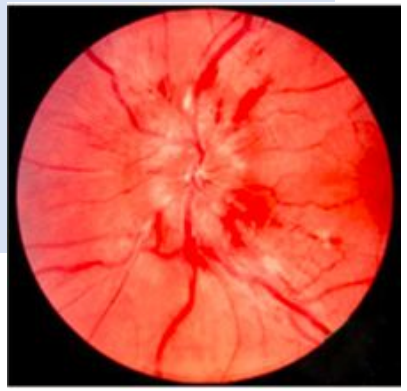
Recognizing Cryptococcal disease

Symptoms:

- Headache
- Fever
- Change in mental status (ranging from confusion to lethargy to coma)
- Double vision (and other cranial nerve deficits)
- Neck stiffness
- Sensitivity to light
- Nausea and vomiting

Signs

- Seizures
- VIth cranial nerve palsy
- Reduced level of consciousness
- Meningism
- Papilloedema (blurred optic disk margin on fundoscopy)



- *Refer to Cryptococcus Screening for OI among PLHIV CDC fact sheet*

Differential diagnoses

1. **TB meningitis is the most common**
2. **Cerebral Malaria**
3. **Meningoencephalitis** caused by other organisms (mycobacterial, viral, bacterial, *Toxoplasma gondii*, neurosyphilis etc.) – see other modules for details
4. **Space-occupying lesions** (lymphoma, *T. gondii*, abscess, etc.)
5. **HIV encephalopathy**
6. **Other conditions** (toxic, metabolic, autoimmune, intracranial bleed, etc.)

CSF parameters

- **CSF samples for PLHIV presenting with meningoencephalitis need a basic CSF analysis with White Cell Count and differential, CSF protein and glucose**
  - CSF opening pressure not useful to distinguish meningitis cause but often elevated in CM patients (can be normal)
  - Total CSF white cell count is of limited use for immunocompromised (HIV+) patients: it may be below 10 cells/ul or 10-500 cells/ul
  - CSF glucose levels may be normal or low
  - CSF protein levels may be normal or slightly elevated
  - Low CSF WBC may be a poor prognostic sign

CrAg LFA, Culture, and India Ink

1

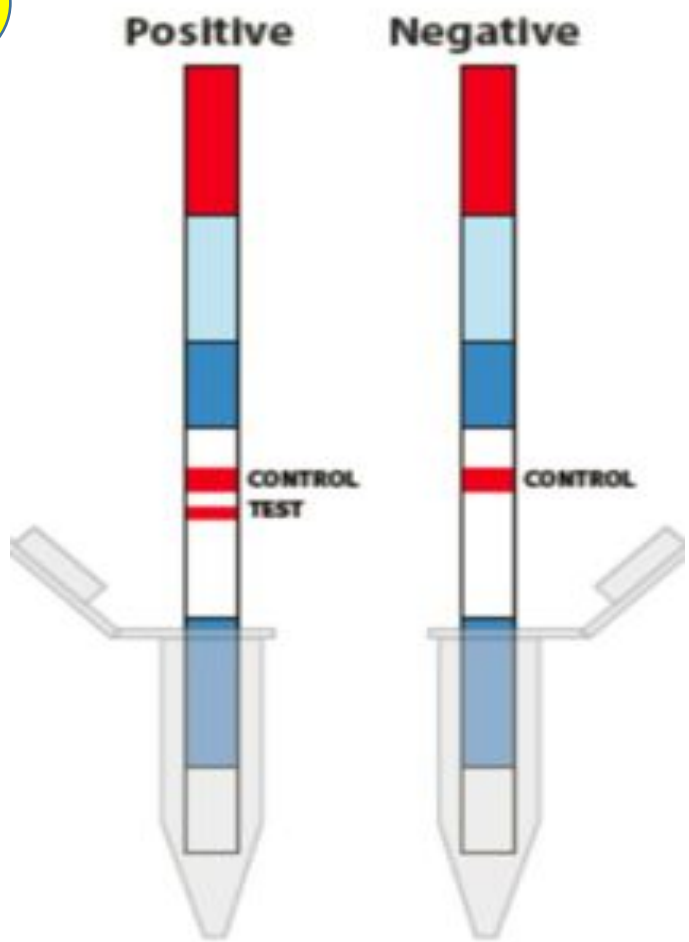
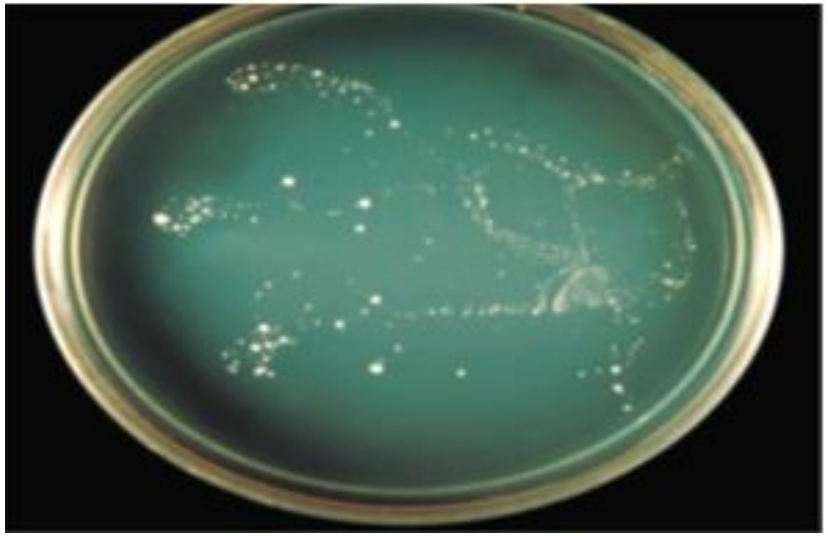


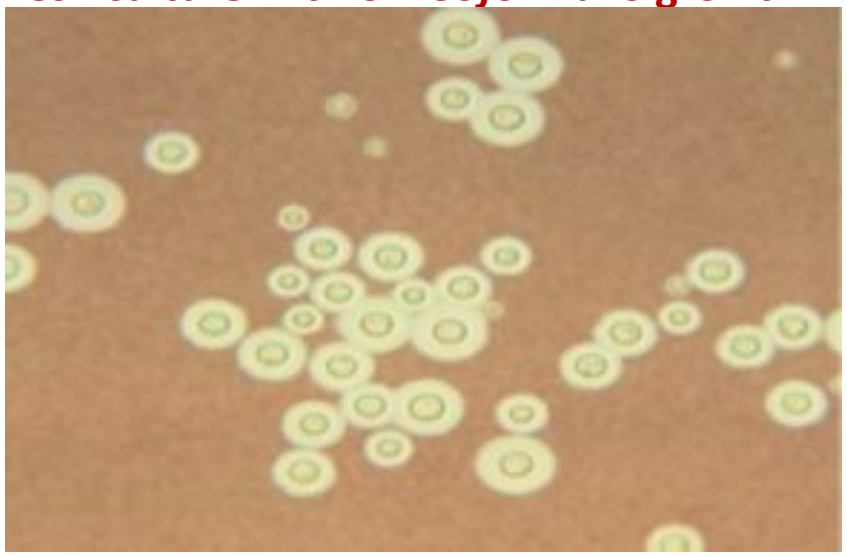
Illustration of CrAg LFA dipstick tests

2



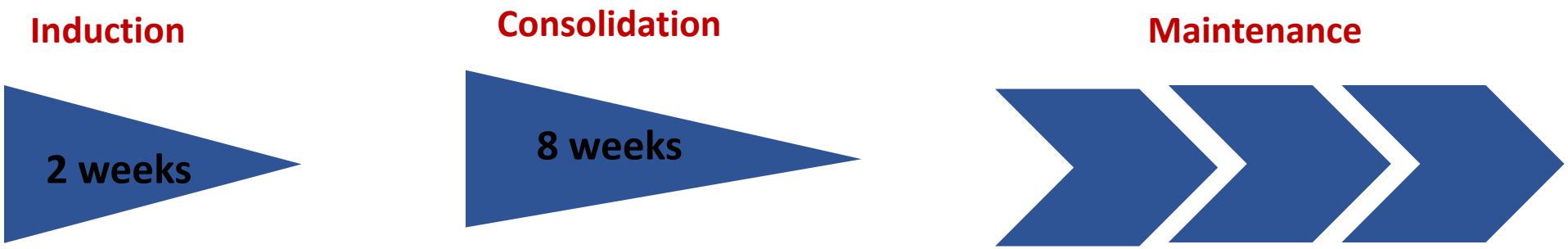
CSF culture with *C. neoformans* growth

3



India Ink stain with *C. neoformans* visible

CM Treatment principles



1. **<u>Induction phase</u> (2 weeks):** Rapidly clear the organism from the body
2. **<u>Consolidation phase</u> (8 weeks):** Ensure disease is fully suppressed
3. **<u>Maintenance phase</u>:** Prevents recurrence of disease after treatment; this phase is also known as secondary prophylaxis

   Continue until:

   - The person is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥200 cells/mm^3 and a fully suppressed viral load.
   - Where VL not available: The person is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥200 cells/mm^3

Ambition trial results:

- **Single, high-dose AmBisome** given with flucytosine and fluconazole for 14 days was non-inferior to one week IV Amphotericin and flucytosine and then one week of fluconazole for HIV associated cryptococcal meningitis.

- The AmBisome regimen was associated with a significant reduction in adverse events including significantly lower rates of anemia, a reduced need for blood transfusions, and a significantly smaller increase in creatinine.

- This regimen offers a practical, easier-to-administer, and better tolerated treatment for HIV-associated cryptococcal meningitis in Africa.

- There is an urgent need to broaden access to AmBisome and flucytosine.

Uganda Treatment Protocols for CM (1/2)

Phase	Drug	Comments
	Newly Diagnosed Patient	
Induction Phase (2 weeks)	**Recommended:** SINGLE high dose Amphotericin B liposomal (10mg/kg) AND Flucytosine (100mg/kg/day in four divided doses) + Fluconazole 1200mg/day for 14 days Or Amphotericin B deoxycholate (1mg/kg/day) + Flucytosine (100mg/kg/day in four divided doses) for 1 week, followed by 1 week of fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents). Or Fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents) + Flucytosine (100 mg/kg/day, divided into four doses per day for 14 days. Or Amphotericin B deoxycholate (1mg/kg/day) + high-dose Fluconazole 1200mg/day for 14 days Alternative: Fluconazole 1200mg/day (or 6-12mg/kg/day in children)	**Preventing Amphotericin toxicity:** To prevent nephrotoxicity and hypokalaemia, do the following: • Pre-hydration with 1L normal saline before starting the daily Amphotericin dose. • 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 >3mg/dl.
Consolidation phase (8 weeks)	Fluconazole 800mg/day (or 6-12mg/kg/day in children and adolescents)	Initiate ART 4–6 weeks after starting CM treatment and there is clinical response to antifungal therapy.
Maintenance Phase (18 months)	Fluconazole 200mg/day (or 6 mg/kg/day up to 200mg in children and adolescents)	Criteria to stop after a minimum of 18 months of maintenance phase: Adults: VL<1,000 copies/mm^3 & CD4 ≥ 200 or CD4 ≥200 (if viral load not available) after 12

How to administer 5-FC?

- Dosing for the induction stage is 100mg/kg/day in 4 divided doses. 5-FC is administered **ORALLY, 6 hourly** periods.
- Nausea and vomiting may occur; this can be prevented by giving capsules individually during a 15-minute window.
- Please note that 5-FC level monitoring for HIV-associated CM is not routinely required.
- Flucytosine can cause bone marrow depression leading to **neutropenia and thrombocytopenia**. Monitor CBC, Creatinine, Electrolytes.
- **FDA pregnancy Category C: Species-specific teratogenicity in animal models.**

Renal Toxicity Management –5-FC

- Ensure adequate hydration.
- If creatinine remains high or climbs despite increased hydration then switch to second line induction regimen: 2 weeks fluconazole + 5FC. Adjust 5FC dose as needed.
- Avoid nephrotoxic drugs such as NSAIDs (Non steroidal anti-inflammatory drugs) including ibuprofen and aminoglycosides.
- Monitor electrolytes closely –acute renal failure can lead to life threatening hyperkalaemia.

Please refer to the CCM poster and safe 5-FC administration poster

5-FC dose interval adjustment for renal impairment

- 5-FC may accumulate in renally impaired patients due to poor levels of excretion.
- The half life of 5-FC is prolonged in patients with renal insufficiency; the average half-life being 85 hours(compared to 2.4-4.8 in normal patients).
- 5-FC blood concentrations should be observed closely in these patients to monitor excretion.
- If creatinine clearance reduces to < 50mL/min, give the same initial 25mg/kg dose but increase the interval between 5-FC doses as per the adjacent table.

5-FC dose interval adjustment in renal impairment

Creatinine Clearance	Individual dose (mg/kg)	Dose Interval (hours)
>40	25	6
20-40	25	12
10-20	25	24
<10	25	>24

Est. Creatinine Clearance = (140 - age) * (weight in kg)

/ (72 *serum Cr in mg/dL) [Multiply result by **0.85** for women]

5-FC dosing in case of neutropaenia

- Always repeat neutrophil count the next day if a grade 3 (500-749 10_6/L) or 4 (<500 10_6/L) case of neutropaenia has been recorded.
- If a patient has a sustained Grade 3 neutropenia (confirmed the following day), monitor carefully and if trend worsens halve the dose of 5-FC.
- If Grade 4 neutropaenia, or neutropenia-related complications develop, stop 5-FC immediately.
- Consider re-introduction of 5-FC if the neutrophil count the following day is grade 3 or better. If grade 3, re-introduce at half dose.

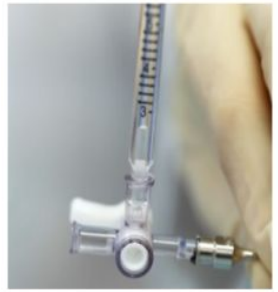
Platelets < 50,000 cells/mm^3 or Neutrophils < 750 cells/mm^3	If grade III range* monitor closely + if worsens then halve the dose of flucytosine (50%).
Platelets < 25,000 cells/mm^3 or Neutrophils < 500 cells/mm^3	Monitor closely and halve dose of flucytosine (50%).

*Grade III Platelets: 25,000 ≤ 50,000 cells/mm^3

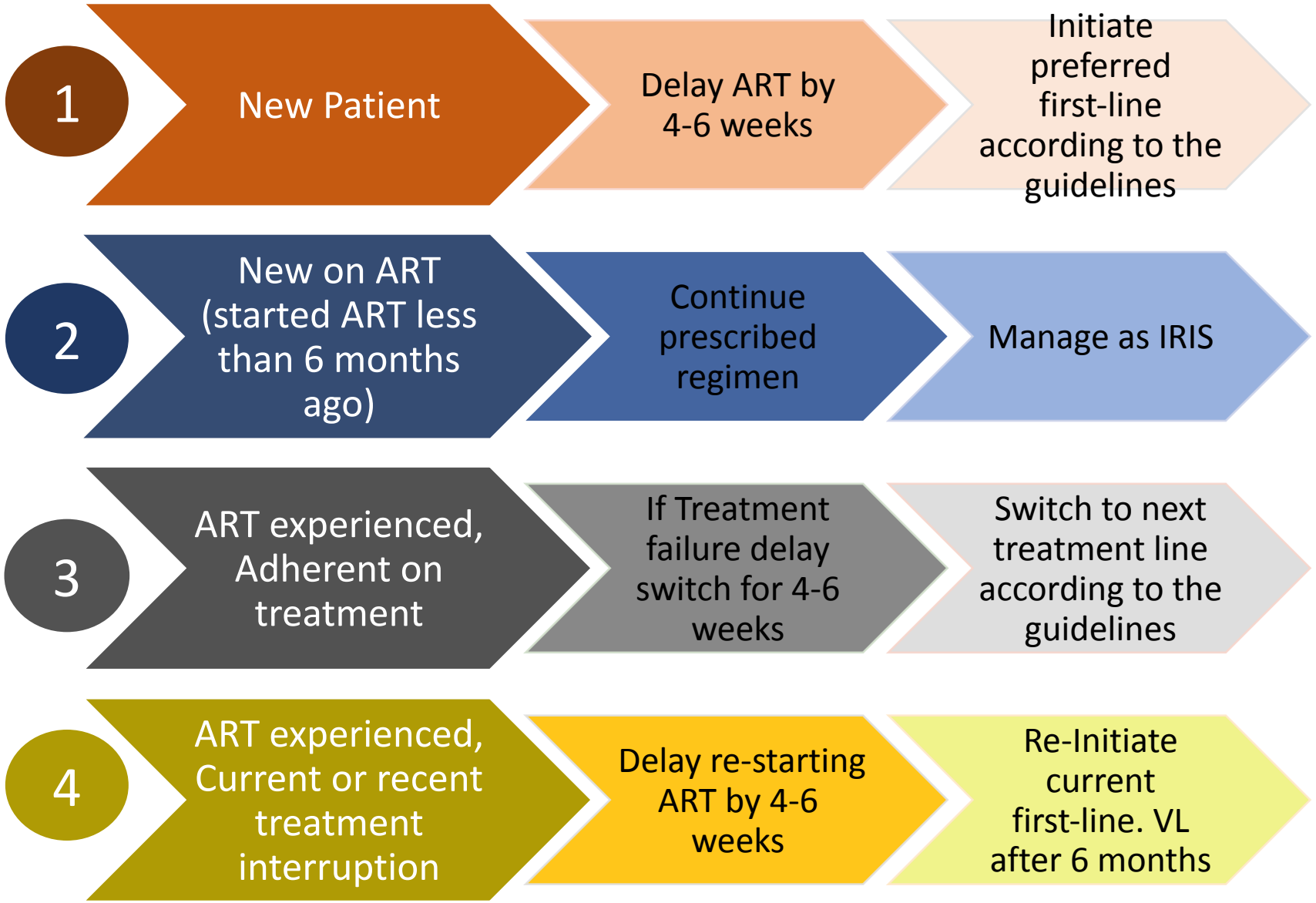
*Grade III Neutrophils: 400—599 cells/mm^3

DAIDS AE Grading Table V2.1 July 17

Managing raised intracranial pressure

Measure CSF (Cerebrospinal Fluid) Opening Pressure (OP) at baseline using a manometer	
If possible perform a computerised tomography (CT) or magnetic resonance imaging (MRI) brain scan, if reduced Glasgow Coma Scale (GCS<10) or focal neurological deficit/cranial nerve abnormality (e.g. VIth nerve palsy). The use of mannitol and acetazolamide is not indicated for the treatment of raised ICP related to cryptococcal meningitis.	
If CSF OP ≥25cm H_2O, perform therapeutic lumbar puncture	
Reduce OP by 50% if OP very high (≥25cm H_20) or to a normal pressure of ≤20cm H_2O. Repeat LP daily until CSF pressure normalised & symptoms stabilised for >2 days.	Remove a maximum volume of 30mL CSF at any therapeutic lumbar puncture (LP). Check CSF pressure after every 10mL CSF removed.  *IDSA Guidelines 2010*

Management of anti-retroviral therapy (ART) in HIV-associated cryptococcal meningitis

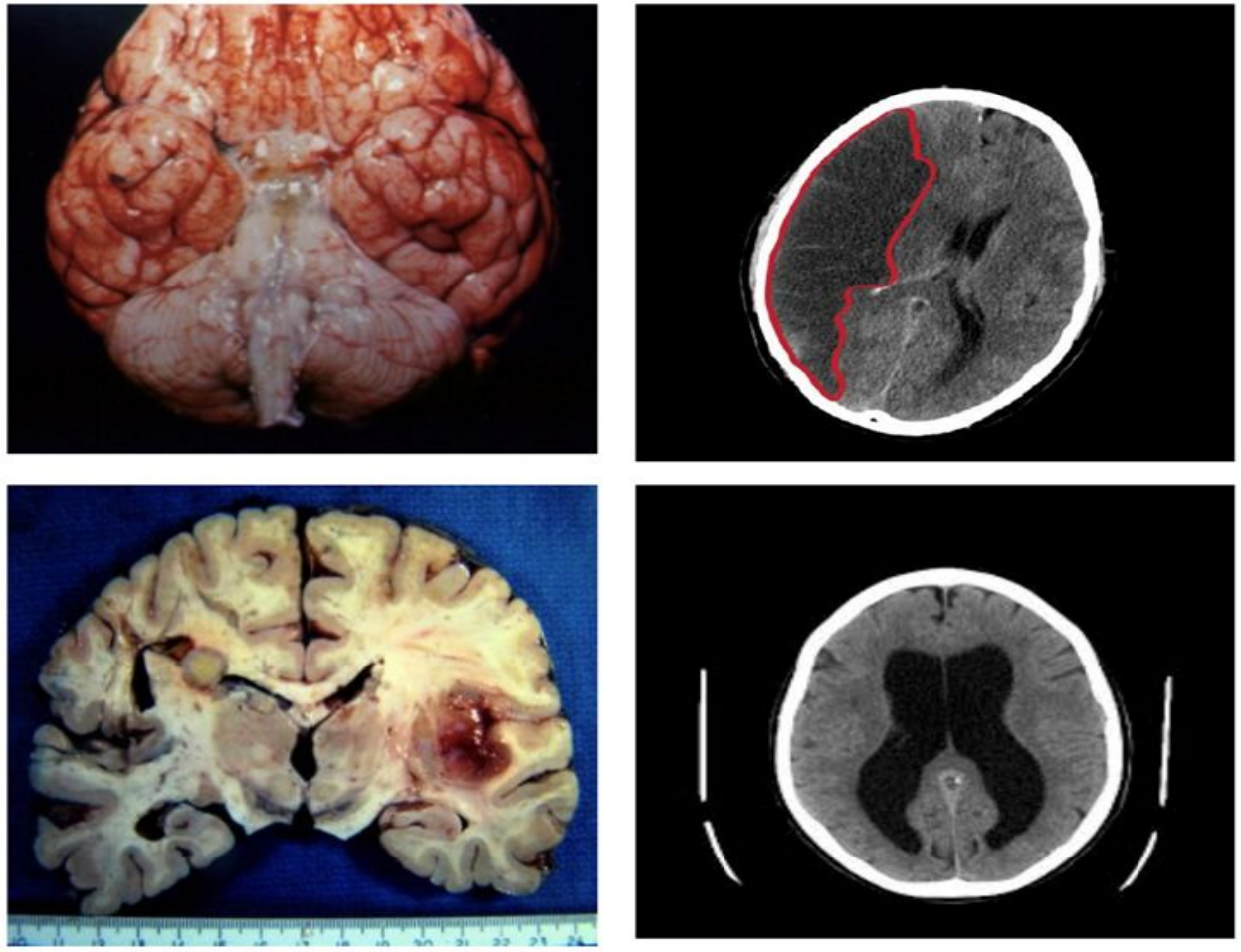


Tuberculous Meningitis (TBM)

- TBM = most severe form of TB and has varied clinical presentation in PLWH

- Mortality averages at 27% but is higher in those with HIV co-infection

Presentation



TBM Cont’

- **Diagnosis**
- Unlike CM, diagnosis of TBM is not straight forward
- **Entails:** - Clinical History
- - Radiological imaging (CXR, Brain imaging, Abd u/s)
- - Bedside CSF parameters (csf gluc, csf Lactate, csf color
- - CSF analysis
- -CSF Xpert/Ultra, CSF MTB culture , CSF Zn staining
-

Treatment

-Anti-TBs

-Steroids : Dexamethasone at 0.4 mg/kg in first week, then 0.3mg/kg in second week. Plan to switch to orals (Prednisolone)

Other

-Aspirin

-Anti-seizures

-Anticoagulant prophylaxis

-PPIs, antacids

-Physio, general care etc

Recently Completed trials

- **Ambition-cm**

- **EnaCT trial-** PK, PD of oral Amphotericin, efficacy and its use as an outpatient. – Preliminary data out, full paper under review in CID

- **RIFT trial** (PK – standard Rif, High dose oral Rif at 35mg/kg, High dose IV Rif at 20mg/kg) in treatment of TBM

On-going trials

- **Improve Trial** – Two arms (& 1HP prophylaxis)
- **HARVEST trial** – Phase 3 (standard anti-Tbs + High dose oral Rifampicin at 35 mg/kg or standard anti-Tbs +Placebo)
- **FLOOR study** – Looking at reduced dose of Flucytosine