HIV-associated Cryptococcal Disease

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Overview

• CrAg screening + pre-emptive treatment

• New treatment strategies
  • ACTA trial
  • WHO guidelines

• Management of raised intracranial pressure
WHO recommendations 2018: screening and pre-emptive therapy

Overarching principle
Screening for **cryptococcal antigen** is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying infection when managing people presenting with advanced HIV disease.

Recommendations
Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among **cryptococcal antigen–positive people** to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a **CD4 cell count <100 cells/mm³** (*strong recommendation; moderate-certainty evidence*) and may be considered at a higher **CD4 cell count threshold of <200 cells/mm³** (*conditional recommendation; moderate-certainty evidence*).

*Screening not recommended for children, given the low incidence of cryptococcal meningitis in this age group.*
Antigenemia precedes meningitis

In a Ugandan study: Antigenemia preceded meningitis by median 22 days (>100 days in 11%)

French, AIDS 2002;16:1031
Retrospective testing of plasma of 707 patients who started ART 2002-2005

- 336 with CD4 ≤ 100
  - 42 CrAg + (13%)
- 21 no history of CM
- 21 history of CM
- 6 (29%) developed CM on ART
- 4 (19%) others died or lost to follow-up

Among those who were CrAg negative none developed CM
Systematic review and meta-analysis:
CrAg positivity prevalence at CD4 <100 cells/mm³

6.4% (95% CI 5.7 – 7.2%)
CrAg Lateral Flow Assay

1. ADD 1 DROP LF SPECIMEN DILUENT TO TUBE
2. ADD 40 µL PATIENT SPECIMEN TO TUBE
3. INSERT STRIP AS SHOWN
4. WAIT 10 MINUTES
5. POSITIVE / NEGATIVE

Source: Immy CrAg LFA package insert
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

Soyoki Mfinanga, Duncan Chanda, Sokoline L. Kivuyo, Lorna Guinness, Christian Bottomley, Victoria Simms, Carol Chijoka, Ayubu Masasi, Godfather Kimaro, Bernard Ngowi, Amos Kahwa, Peter Mwaba, Thomas S Harrison, Saidi Egwaga, Shabbar Jaffar, on behalf of the REMSTART trial team

28% reduction in mortality

Mfinanga, Lancet 2015
# Systematic review and meta-analysis:
CrAg positivity prevalence at CD4 100-200 cells/mm³

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>% (95% CI)</th>
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<tbody>
<tr>
<td>Vidal</td>
<td>Brazil</td>
<td>4.05 (0.15, 12.81)</td>
</tr>
<tr>
<td>Alemu</td>
<td>Ethiopia</td>
<td>7.28 (4.42, 10.79)</td>
</tr>
<tr>
<td>Beyene</td>
<td>Ethiopia</td>
<td>15.21 (7.78, 24.57)</td>
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<tr>
<td>Ezeanolue</td>
<td>Nigeria</td>
<td>0.96 (0.50, 1.56)</td>
</tr>
<tr>
<td>MSF Kenya</td>
<td></td>
<td>13.40 (3.30, 28.85)</td>
</tr>
<tr>
<td>Jarvis</td>
<td></td>
<td>1.21 (0.35, 2.56)</td>
</tr>
<tr>
<td>Govender</td>
<td></td>
<td>1.74 (0.67, 3.32)</td>
</tr>
<tr>
<td>Kwan</td>
<td></td>
<td>0.20 (0.18, 1.73)</td>
</tr>
<tr>
<td>MSF DRC</td>
<td></td>
<td>13.73 (4.96, 25.95)</td>
</tr>
<tr>
<td>Magambo</td>
<td></td>
<td>6.60 (1.97, 13.66)</td>
</tr>
<tr>
<td>Micol</td>
<td></td>
<td>3.17 (0.12, 10.11)</td>
</tr>
<tr>
<td>Oladele</td>
<td></td>
<td>5.54 (1.65, 11.53)</td>
</tr>
<tr>
<td>Osazuwa</td>
<td></td>
<td>3.54 (0.52, 9.09)</td>
</tr>
<tr>
<td>Pongsai</td>
<td>Thailand</td>
<td>5.03 (0.20, 15.76)</td>
</tr>
<tr>
<td>Reepalu</td>
<td>Ethiopia</td>
<td>0.87 (0.78, 7.39)</td>
</tr>
<tr>
<td>Mfinanga</td>
<td>Tanzania &amp; Zambia</td>
<td>2.04 (0.70, 4.07)</td>
</tr>
<tr>
<td>Rugemalila</td>
<td>Tanzania</td>
<td>1.53 (0.06, 4.97)</td>
</tr>
<tr>
<td>Sawadogo</td>
<td>Namibia</td>
<td>2.47 (1.03, 4.52)</td>
</tr>
<tr>
<td>Guha</td>
<td>India</td>
<td>7.52 (2.64, 14.63)</td>
</tr>
<tr>
<td>Katchanov</td>
<td>Germany</td>
<td>1.18 (0.55, 2.04)</td>
</tr>
<tr>
<td>Ogouyémi-Hounto</td>
<td>Cameroon</td>
<td>0.12 (0.11, 1.09)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.98 (1.24, 2.72)</td>
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</table>

2.0% (95% CI 1.2 – 2.7%)

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*Note: The above table and graph illustrate the prevalence of CrAg positivity among individuals with CD4 counts between 100-200 cells/mm³ across various studies and countries.*
Asymptomatic CrAg+ patient outcomes in Uganda (n=151)

Fluconazole 800mg for 2 weeks then 400mg for 8 weeks then stopped

Overall 78% survival at 6 months

Morawski, CROI 2016, Abstract 159
CrAg screen-and-treat algorithm

**Cryptococcal antigen screening when CD4, T-lymphocyte count <200 cells/μL regardless if ART-naïve or -experienced**

Blood CrAg-positive

- Lumbar puncture
- Start fluconazole 1200 mg daily immediately if any delays to hospital
- **Preferred regimen**: 1 week of amphotericin B deoxycholate 1 mg/kg/day + 5-FC 100 mg/kg/day in 4 divided doses then 1-week fluconazole 1200 mg/day
- **If amphotericin B is unavailable**: 2 weeks of fluconazole 1200 mg/day + 5-FC 100 mg/kg/day in 4 divided doses
- **If 5-FC is unavailable**: 2 weeks of amphotericin B 1 mg/kg/day + fluconazole 1200 mg/day

Fluconazole 800 mg daily for 8 weeks then 200 mg daily
- Continue fluconazole for minimum of 1 year in total and discontinue when patient has had at least 1 CD4 count >200 cells/μL and virologic suppression

Fluconazole 800 mg daily for 8 weeks then 200 mg daily

**Confirmed CM**: Start ART after 4-6 weeks of antifungal therapy

Blood CrAg-negative

- Lumbar puncture
- CSF negative for CrAg

- CSF negative for CrAg
  - Start fluconazole 1200 mg daily immediately if any delays to hospital
  - Preferred regimen: 1 week of amphotericin B deoxycholate 1 mg/kg/day + 5-FC 100 mg/kg/day in 4 divided doses then 1-week fluconazole 1200 mg/day
  - **If amphotericin B is unavailable**: 2 weeks of fluconazole 1200 mg/day + 5-FC 100 mg/kg/day in 4 divided doses
  - **If 5-FC is unavailable**: 2 weeks of amphotericin B 1 mg/kg/day + fluconazole 1200 mg/day

Fluconazole 800 mg daily for 8 weeks then 200 mg daily
- Continue fluconazole for minimum of 1 year in total and discontinue when patient has had at least 1 CD4 count >200 cells/μL and virologic suppression

**CSF CrAg-negative**: Start ART immediately

**Initiate ART** No antifungal treatment

**Screen for other OIs**

**Lumbar puncture**

**Asymptomatic**

- Symptoms of meningitis (headache and confusion)

**No consent for lumbar puncture**

**Treat for CSF+ cryptococcal meningitis**

**No consent for lumbar puncture**

**Blood CrAg-negative**

1. Consider special situations: prior cryptococcal meningitis; pregnancy or breastfeeding mothers; clinical liver disease; initiation of ART prior to obtaining blood CrAg+ result
2. If symptoms of meningitis are present but CSF CrAg test is negative/ LP declined, consider alternative diagnoses (such as TB meningitis) and/or treat as cryptococcal meningitis
3. A blood CrAg titre >160 may indicate a high risk of CM and mortality in asymptomatic CrAg-positive patients. Monitor carefully for signs/symptoms of CM and consider empirical CM treatment.
4. There is no evidence for appropriate ART timing in these groups
Cryptococcal meningitis treatments

**Amphotericin B (IVI)**
Forms transmembrane channels

**Fluconazole (PO/IVI)**
Inhibits membrane ergosterol synthesis

**Flucytosine (PO/IVI)**
Interferes with RNA and DNA synthesis
CM treatment paradigm

<table>
<thead>
<tr>
<th>PHASE</th>
<th>Duration</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>INDUCTION</strong></td>
<td>2 weeks</td>
<td></td>
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<tr>
<td><strong>CONTINUATION</strong></td>
<td>8 weeks</td>
<td></td>
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<tr>
<td><strong>MAINTENANCE</strong></td>
<td>Until immune recovery</td>
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Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa


Recruitment

Jan 2013 to Dec 2016

**Sites:**
- 9 sites in 4 countries in SSA

**Inclusion:**
- HIV seropositive adults (≥18 yrs)
- 1st episode of CM, CSF Positive

**Exclusion:**
- >1 dose AmB or FLU (1200mg) or >7 low doses FLU (200mg) in 2 weeks prior to screening
- Pregnant / lactating

**Late exclusion:**
- ALT >5 times ULN, Leukocytes <500 x 10^6/L, Platelets <50,000 x 10^6/L
- Repeat creatinine above 220 μmol/L, despite rehydration
ACTA: 5 treatments arms

• Regimen 1: Fluconazole + flucytosine (no AmB; oral)
• Regimen 2a: 1 week AmB + fluconazole
• Regimen 2b: 1 week AmB + flucytosine
• Regimen 3a: 2 weeks AmB + fluconazole
• Regimen 3b: 2 weeks AmB + flucytosine

• Comparisons
  • Oral vs 2 weeks
  • 1 week vs 2 weeks
  • Fluconazole vs Flucytosine as adjunct
  • Each of 5 regimens

Fluconazole doses
First 2 weeks: 1200mg
Until 4 weeks: 800mg
Until 10 weeks: 400mg
Thereafter: 200mg
5-FC superior to fluconazole as a partner to AmB: 38% reduced hazards of death at 10 weeks
1-week AmB+5-FC associated with lowest 10-week mortality

<table>
<thead>
<tr>
<th>Oral</th>
<th>1 week AmB + FLU</th>
<th>1 week AmB + 5FC</th>
<th>2 weeks AmB + FLU</th>
<th>2 weeks AmB + 5FC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of death by 10 wks % (95% CI)</td>
<td>35% (29 - 41)</td>
<td>49% (39 - 58)</td>
<td>24% (16 - 32)</td>
<td>41% (32 - 50)</td>
</tr>
<tr>
<td>79/225</td>
<td>54/111</td>
<td>27/113</td>
<td>47/114</td>
<td>44/115</td>
</tr>
</tbody>
</table>
Conclusions from ACTA

• Flucytosine, as adjunct with AmB, led to lower mortality compared with fluconazole

• 1 week AmB + flucytosine associated with better survival compared with all other arms

• May reflect more optimal balance between antifungal effect and tolerability
Induction

- For adults, adolescents and children, a short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day) is the preferred option for treating cryptococcal meningitis among people living with HIV (strong recommendation, moderate-certainty evidence for adults, low-certainty evidence for children and adolescents).

The following induction regimens are recommended as alternative options:

- Two weeks of 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) (strong recommendation, moderate-certainty evidence).

- Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) (strong recommendation, moderate-certainty evidence).
## Consolidation

Fluconazole (800 mg daily for adults, 6–12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) is recommended for the consolidation phase (for eight weeks following the induction phase) *(strong recommendation, low-certainty evidence).*

## Maintenance (or secondary prophylaxis)

Fluconazole (200 mg daily for adults, 6 mg/kg/day for adolescents and children) is recommended for the maintenance phase *(strong recommendation, high-certainty evidence).*

Note: a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management should be provided to minimize treatment toxicity related to amphotericin B and flucytosine.
Flucytosine

- 6 hourly oral dosing

- Bone marrow suppression
  - FBC/differential

- Renal clearance
  - Dose adjust if renal impairment

- Not as monotherapy
Flucytosine largely unavailable in LMIC

Figure 4. Intravenous and/or oral flucytosine availability by country in 2016. Red = not available, green = available and grey = no data. This figure appears in colour in the online version of JAC and at http://www.gaffi.org/antifungal-drug-maps/ and in black and white in the print version of JAC.
Management of raised intracranial pressure
Raised Intracranial Pressure

- Common in CM: 60-80% > 20cmH$_2$O$^{1,2}$
- Patients with OP > 25 have poorer short-term survival
- Pathophysiology: CSF outflow obstruction by organism or polysaccharide capsule at arachnoid villi

1. Graybill et al. CID 2000; 30: 47-54
Obstructed CSF drainage in CM

CSF produced in choroid plexus

CSF reabsorption obstructed in arachnoid granulations
Daily therapeutic lumbar punctures to reduce raised intracranial pressure (Remove up to 30 ml CSF)
Therapeutic LPs and mortality

- Observational study nested in COAT trial
- 248 patients screened for COAT trial
  - Therapeutic LPs advocated if OP>25 or new symptoms
  - 75 (30%) had at least one therapeutic LP

<table>
<thead>
<tr>
<th></th>
<th>11 day mortality</th>
</tr>
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<tbody>
<tr>
<td>No therapeutic LP</td>
<td>18%</td>
</tr>
<tr>
<td>At least one therapeutic LP</td>
<td>7%</td>
</tr>
</tbody>
</table>

- **RR of mortality = 0.31** (95%CI=0.12-0.82) when adjusted for heart rate, CSF quantitative culture & reduced GCS

Rolfes, Clin Infect Dis 2014
### Recommendations

<table>
<thead>
<tr>
<th>Measure baseline opening pressure</th>
</tr>
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<tbody>
<tr>
<td>If opening pressure ( &gt;25 \text{ cm H}_2\text{O} ), remove 10-30 ml CSF</td>
</tr>
<tr>
<td>Repeat LP when there are symptoms/signs of raised intracranial pressure (headache, vomiting, drowsiness/confusion, 6th CN palsy, visual disturbance)</td>
</tr>
<tr>
<td>Daily therapeutic LPs may be required</td>
</tr>
</tbody>
</table>
Key treatment points

• Favored induction regimens
  • 1 week AmB + flucytosine (followed by 1 week fluconazole 1200mg)
  • Fluconazole + flucytosine for 2 weeks where AmB unavailable
  • 2 weeks AmB + fluconazole where flucytosine unavailable

• International efforts to broaden access to flucytosine needed

• ART at 4-6 weeks

• Therapeutic lumbar punctures
2019 update to be published soon
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