Cryptococcal Meningitis: Diagnosis and Management in Resource Limited Settings

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Case 1

• TN is a 42yoM who is admitted with severe headache, fatigue and weight loss over the last 2 months. He reports that he has never been tested for HIV before.

• His exam is notable for meningismus and a sixth nerve palsy

• An LP is done. Opening pressure is not measured but fluid is noted to be “under pressure”.
Case 1 continued

- His labs are notable for a Na 128, a WBC of 1.8, Hgb 7g/dl, Plt 152
- His CSF is notable for a cell count of 3cells/mm³, total protein 85g/dL, glucose nl. India ink and CSF CrAg are positive.
- He is commenced on antifungal therapy.
Key Clinical Questions

• What is the best way to diagnose cryptococcal disease?
• What is the most appropriate antifungal therapy?
• When should antiretroviral therapy be initiated?
Overview

• Cryptococcal Biology and Epidemiology
• Diagnosis
• Management
  – Resource limited settings
• Primary and secondary prophylaxis
Cryptococcal Biology

- There are four different types of *C. neoformans* - A to D based on serotyping
- Types B & C are called *C neoformans var. gattii*
- Type A – *C neoformans var. grubii*
- Type D – *C. neoformans var. neoformans*
- Type A is the most common cause of disease in sub-Saharan Africa
Human Cryptococcosis

• Previously a rare pathogen, with <300 cases reported before 1955
• Cryptococcal infection is likely acquired in childhood as a minor respiratory infection that is contained by host immune responses with activation in the setting of defects in cell mediated immunity.
  – A study in New York showed children <2 years had no crypto specific Ab
  – 56% of children ages 2-5 years; 71% of children>5 years

Human Cryptococciosis and HIV infection

• In non-AIDS patients in the US, incidence 0.2-0.8 per 100,000
• In the US 6-10% of patients with AIDS developed cryptococciosis
• Introduction of HAART decreased incidence significantly
  – Atlanta: 66/1000 in 1992, to 7/1000 in 2000
  – Texas: 24/1000 in 1993 to 2/1000 in 2000
Human Cryptococcosis in Africa

• Surveillance study over 3 year period
  – 1 per 100,000 cases of cryptococcal disease in children in the general population
  – 19 per 100,000 cases in adults in the general population

• Higher incidence among people with HIV
  – 47 per 100,000 among children
  – 120 per 100,000 among adults

Meiring et. Al GERMS-SA AIDS 2012
C. *Neofomans* is the leading cause of meningitis in sub-Saharan Africa

- 406 patients with suspected meningitis
- 200 confirmed meningitis
- 45% had CM
- 12% with TB meningitis
- In hospital mortality from CM was 38.8%

### Table 1. Diagnostic categories and HIV seropositivity in 406 suspected cases of meningitis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
<th>HIV tests carried out (n)</th>
<th>HIV seropositive [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcal</td>
<td>89 (45)</td>
<td>80</td>
<td>80 (100)</td>
</tr>
<tr>
<td>Mononuclear</td>
<td>54 (27)</td>
<td>51</td>
<td>43 (83)</td>
</tr>
<tr>
<td>Pyogenic</td>
<td>31 (16)</td>
<td>31</td>
<td>25 (81)</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>24 (12)</td>
<td>24</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Undefined</td>
<td>2 (1)</td>
<td>2</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>200 (100)</td>
<td>188</td>
<td>170 (90)</td>
</tr>
<tr>
<td>Non-meningitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septicaemia</td>
<td>43 (21)</td>
<td>42</td>
<td>31 (74)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>41 (20)</td>
<td>38</td>
<td>32 (84)</td>
</tr>
<tr>
<td>PUO</td>
<td>33 (16)</td>
<td>32</td>
<td>28 (88)</td>
</tr>
<tr>
<td>Malaria</td>
<td>17 (8)</td>
<td>14</td>
<td>11 (79)</td>
</tr>
<tr>
<td>Fits</td>
<td>13 (6)</td>
<td>13</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Other</td>
<td>34 (17)</td>
<td>33</td>
<td>22 (67)</td>
</tr>
<tr>
<td>Unknown</td>
<td>25 (12)</td>
<td>24</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Total</td>
<td>206 (100)</td>
<td>196</td>
<td>156 (80)</td>
</tr>
</tbody>
</table>

PUO, pyrexia of unknown origin.

Hakim, James; Gangaidzo, Innocent; Heyderman, Robert; Mielke, Jens; Mushangi, Ebbah; Taziwa, Albert; Robertson, Valerie; Musvaire, Praise; Mason, Peter

High ongoing burden despite ART Roll Out

Jarvis JN, AIDS 2009, 23(9):1182
Cryptococcosis is a leading cause of Mortality in Sub-Saharan Africa

Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. Park, Benjamin; Wannemuehler, Kathleen; Marston, Barbara; Govender, Nelesh; Pappas, Peter; Chiller, Tom

DOI: 10.1097/QAD.0b013e328322ffac

Fig. 1. Comparison of deaths in sub-Saharan Africa due to HIV-related cryptococcosis, as estimated in present study, and common infectious diseases excluding HIV, as estimated by World Health Organization. STD, sexually transmitted disease.
Clinical Presentation of Cryptococcal Disease
Clinical Presentation

- Cutaneous Cryptococcomas
- Lesions may be single or multiple
- Present as small papules, pustules, nodules, or ulcers with a base of granulation tissue.
Pulmonary cryptococcosis
Neurologic Manifestations

• CNS Cryptococcomas
• Meningoencephalitis
• 123 patients with CM in 12 month period (9/06-9/07) in Harare, Zimbabwe
  – 89% presented with a headache with mean duration of headache being 14 days (IQR 6, 21)
  – Fever relatively uncommon – 18% of patients
  – Confusion – 26%
  – Seizures – 22%
  – Focal neurological signs – 6th nerve palsies, hearing loss, loss of vision, hemi-paralysis – 20%
Figure 13b. Cryptococcoma in a 25-year-old HIV-infected patient who presented with increasing headache, nausea, and vomiting.

Smith A B et al. Radiographics 2008;28:2033-2058
Figure 11a. Cryptococcal meningoencephalitis in a 42-year-old man with AIDS who became progressively obtunded.

Smith A B et al. Radiographics 2008;28:2033-2058
Diagnosis

- **India Ink**
  - Sensitivity is user dependent
  - Depends on antigen load. Sensitivity can be as low as 68%.
- **Cryptococcal Antigen Test**
  - Latex cryptococcal antigen tests or EIA Meridian
  - Serum Sensitivity 97%, Specificity 95%
  - CSF sensitivity 100% and Specificity 96%
- **Lateral Flow Assay**

Tanner, DC J Clin Micro (1994) 32:1680
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. Control test.
Results

- LFA had >96% sensitivity in both CSF and plasma samples.
- LFA had high specificity for both CSF and Plasma.
- 70% specificity of CSF LFA compared to CSF culture in 2006-2009 likely reflected culture procedures and likely false negative by culture. In 27 LFA+/Cx neg, 46% were India Ink +ve and 85% were CSF latex +.

Rolfes et al. CROI 2012
LFA is an accurate POC diagnostic for Cryptococcal Meningitis

- LFA is an accurate, simple, inexpensive POC diagnostic for Cryptococcal meningitis
  - Stable at room temperature
  - 2 year shelf life
  - $2/test
- High sensitivity in CSF and plasma samples
- Validation of LFA on whole blood, saliva needed if it is to be used for screening ART eligible individuals.
CSF Characteristics

• Low to normal cell counts (84/123 patients had CSF cell counts available)
  – 67% with cell counts <5 cells/mm³
  – 27% with cell counts between 6-100 cells/mm³
  – 6 patients had CSF cell counts >101cells/mm³

• CSF protein may be normal or modestly elevated
  – 27% nl CSF protein (15-60g/dL)
  – 61% CSF protein of 61-200g/dL

• CSF glucose typically normal

• Elevated opening pressures
Treatment of Cryptococcal Meningitis
Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Human Immunodeficiency Virus–Infected Individuals.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)(^a)</td>
<td>2 weeks</td>
<td>A-I</td>
</tr>
<tr>
<td>Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)(^a)</td>
<td>2 weeks</td>
<td>B-II</td>
</tr>
<tr>
<td>AmBd (0.7–1.0 mg/kg per day) or liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)</td>
<td>4–6 weeks</td>
<td>B-II</td>
</tr>
<tr>
<td><strong>Alternatives for induction therapy(^b)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmBd plus fluconazole</td>
<td>...</td>
<td>B-I</td>
</tr>
<tr>
<td>Fluconazole plus flucytosine</td>
<td>...</td>
<td>B-II</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>...</td>
<td>B-II</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>...</td>
<td>C-II</td>
</tr>
<tr>
<td><strong>Consolidation therapy: flucytosine (400 mg per day)</strong></td>
<td>8 weeks</td>
<td>A-I</td>
</tr>
<tr>
<td><strong>Maintenance therapy: flucytosine (200 mg per day)(^a)</strong></td>
<td>(\geq 1) year(^c)</td>
<td>A-I</td>
</tr>
<tr>
<td><strong>Alternatives for maintenance therapy(^b)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole (400 mg per day)(^d)</td>
<td>(\geq 1) year(^c)</td>
<td>C-I</td>
</tr>
<tr>
<td>AmBd (1 mg/kg per week)(^d)</td>
<td>(\geq 1) year(^c)</td>
<td>C-I</td>
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**NOTE.** ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate; HAART, highly active antiretroviral therapy.

\(^a\) Begin HAART 2–10 weeks after the start of initial antifungal treatment.

\(^b\) In unique clinical situations in which primary recommendations are not available, consideration of alternative regimens may be made—but not encouraged—as substitutes. See text for dosages.

\(^c\) With successful introduction of HAART, a CD4 cell count \(\geq 100\) cells/\(\mu\)L, and low or nondetectable viral load for \(\geq 3\) months with minimum of 1 year of antifungal therapy.

\(^d\) Inferior to the primary recommendation.

Treatment in Resource Limited Settings
<table>
<thead>
<tr>
<th>Target Population</th>
<th>Drugs available</th>
<th>Pre-hydration + electrolyte replacement + toxicity monitoring/management</th>
<th>Induction phase options(^{14})</th>
<th>Consolidation phase options</th>
<th>Maintenance/secondary prophylaxis options</th>
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| **Adults**        | Amphotericin B\(^15\) ± flucytosine | Available | a. Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day  
                   b. Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day | Fluconazole 400-800 mg/day | Fluconazole 200 mg daily |
|                   | Amphotericin B\(^15\) | Not available for full 2 week induction period | Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 800 mg/day (2 weeks) | Fluconazole 800 mg/day | |
|                   | Amphotericin B not available | Not available | a. Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day  
                   b. Fluconazole 1200 mg/day alone | Fluconazole 800 mg/day | |

WHO, 2011
Amphotericin B and Flucytosine

- Randomized (2 step), double blind multicenter study
  - Amphotericin B (0.7mg/kg) with flucytosine x 2 weeks
  - Amphotericin B (0.7mg/kg) without flucytosine x 2 weeks
  - Consolidation: 8 weeks of fluconazole or itraconazole

Primary end-points CSF clearance rates at 2 and 10 weeks

- CSF clearance at 2 weeks
  - 60% in patients receiving amphotericin + flucytosine
  - 51% in patients receiving amphotericin only (p=0.06)

- 72% of those in the fluconazole group, and 60% in the itraconazole group had negative cultures at 10 weeks (ns)

- Overall mortality was comparable between the two groups

- Multivariate analysis addition of flucytosine in the induction period, and treatment with fluconazole for 8 weeks in the consolidation period were independently associated with CSF sterilization

Van der Horst et al. NEJM 1997, 337:15
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<td></td>
<td></td>
<td>b. Fluconazole 1200 mg/day alone</td>
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</table>

WHO, 2011
Amphotericin plus fluconazole

- Phase II randomized trial comparing safety and efficacy of Amphotericin plus fluconazole
- 143 HIV positive patients in US and Thailand were enrolled and randomized to
  - Amphotericin B (AmB) deoxycholate 0.7mg/kg/day x 2 wks then Fluconazole 400mg po qday x 8 weeks
  - AmB 0.7mg/kg/day plus fluconazole 400mg/day x 14 days, then Fluconazole 400mg po qday x 8 weeks
  - AmB 0.7mg/kg/day plus fluconazole 800mg/day x 14 days, then Fluconazole 400mg po qday x 8 weeks

Study Outcomes

• Safety and tolerability
  – 30% of patients in each arm experienced severe toxicities related to AmB or fluconazole
  – Most common side effects – hypomagnesemia, hypokalemia, anemia, AmB infusion intolerance, decreased renal function, psychosis and subdural hematoma
  – No significant differences in adverse events between treatment arms
• Mortality
  – Higher mortality observed in the AmB only arm compared with the combination therapy arms
  – AmB – 22.2% mortality; AmB plus Fluc 400 arm – 17%; Amb plus Fluc 800 arm –18.4%
  – Trend towards improved survival in the AmB plus Fluc 800 arm compared with the AmB arm
  – Most common primary causes of death were sepsis, cryptococcal meningitis and other OIs.
Kaplan Meier estimates of overall survival for the modified intention-to-treat population.

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WHO, 2011
Short Course Amphotericin B with high dose fluconazole

• Cohort in Uganda 30 HIV positive, ART naïve, first episode cryptococcal meningitis
  – High dose fluconazole 1200mg x 2 weeks + AmB (1mg/kg/d) x 5 days then
  – Fluconazole 800mg/d until ART initiation
• Good Early fungicidal activity
• No reduction in the rate of clearance between days 5-14
• No hypokalemia, renal failure, anemia, elevation of ALT
• Mortality 23% at 2 weeks and 28% at 10 weeks

Muzoora et al. J Infect 2012, 64(1):76
Electrolyte management in patients on Amphotericin B
Box 1: Minimum package for amphotericin B toxicity prevention, monitoring and management

Pre-emptive hydration and electrolyte supplementation\textsuperscript{17}

- **Adults:**
  One litre of normal saline solution with one ampoule (20 mmol) of KCL over 2-4 hours before each controlled infusion of amphotericin B (with one litre of 5% dextrose) and one to two 8mEq KCL tablets orally twice daily. An additional one 8mEq KCL tablet twice daily may be added during the second week. If available, magnesium supplementation should also be provided (two 250mg tablets of magnesium trisilicate twice daily).

- **Adolescents and Children:**
  Up to one litre of normal saline solution with one ampoule (20 mmol) of KCL at 10-15 ml/kg over 2-4 hours before each controlled infusion of amphotericin B. If saline is unavailable, then other intravenous rehydration solutions that contain potassium can be used e.g. Darrow’s or Ringer’s Lactate solutions.

- Potassium replacement should not be given patients with pre-existing renal impairment or hyperkalaemia.

- A test dose for amphotericin B is not recommended

**Monitoring**

- Serum potassium and creatinine (baseline and twice weekly), especially in the second week of amphotericin B administration.
- Haemoglobin (baseline and weekly)
- Careful attention to fluid monitoring of intake and output, and daily weight

**Management**

- If significant hypokalaemia (K < 3.3mmol/l), increase potassium supplementation to two KCL ampoules (40 mmol), or one or two 8mEq KCL tablets three times daily. Monitor potassium daily.
- If hypokalaemia remains uncorrected, double magnesium oral supplementation.
- If creatinine increases by $\geq 2$ fold from baseline value, either temporary omission of an amphotericin B dose, or increase pre-hydration to one litre 8 hourly. Once improved, restart at 0.7 mg/kg/day and consider alternate day amphotericin B. If creatinine remains elevated, discontinue amphotericin and continue with fluconazole at 1200mg/day. Monitor creatinine daily.
## Treatment of Cryptococcal Meningitis in Resource Limited Settings

**WHO, 2011**

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                   |                               |                                           | b. Fluconazole 1200 mg/day alone | Fluconazole 800 mg/day               |                                           |

*WHO, 2011*
High Dose Fluconazole for Cryptococcal Meningitis

- 60 HIV positive, ART naïve individuals with first episode of CM in Uganda treated with fluconazole
  - 30 treated with Fluconazole 800mg po qday x 2 weeks, then 400mg po qday x 8 weeks
  - 30 treated with Fluconazole 1200mg po qday x 2 weeks then 400mg po qday x 8 weeks
- Lumbar punctures done on days 3, 7 and 14. Additional LPs if opening pressure >35cm water and or headache or other symptoms attributable to increased ICP
- Started on ART 1-8 weeks after start of antifungal therapy (median time to ART 5 weeks)
- Patients followed for 6 months post enrollment.
- Median CD4 count 12 (4-32)

Decrease in CSF Cryptococcus neoformans colony-forming units (CFU) over time, by treatment cohort.

- Decrease in CFU over time by treatment group 1 (800mg) vs. group 2 (1200mg)
- Early fungicidal activity (EFA) shown as the mean rate of decrease in log CFU counts in the first two weeks was significantly higher in patients treated with 1200mg of fluconazole a day compared to those receiving 800mg fluconazole per day (p=0.007)
- The difference in mortality between the two groups at 2 weeks and 10 weeks was not statistically significant.

Fluconazole plus Flucytosine
Combination Flucytosine and High-Dose Fluconazole compared with Fluconazole Monotherapy

• Tertiary hospital in Llongwe, Malawi. 41 individuals HIV seropositive, ART naïve, first episode of CCM randomized to
  – Fluconazole 1200mg po qday alone x 2 weeks
  – Fluconazole 1200mg qday plus flucytosine 100mg/kg per day) x 2 weeks
  – Both treatment groups subsequently received Fluconazole 800mg po qday through to 10 weeks
• Primary end point early fungicidal activity, secondary end point safety and 2 and 10 week mortality
Survival curves by treatment group. One patient lost to follow-up was censored. P=.05 at 2 weeks and P=.25 at 10 weeks, by Cox regression.
## Treatment of Cryptococcal Meningitis in Resource Limited Settings

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WHO, 2011
When to Initiate ART among patients with Cryptococcal Meningitis?
Early vs deferred ART for treatment of acute AIDS OIs

ACTG 5164

• 282 Patients randomized within 14 days of starting treatment for OI.
  – Early: ART initiated within 48hrs of study enrollment.
  – Deferred: ART initiation between week 6 and week 12 of the study.

• Results: 141 patients in each treatment group
  – 63% with PCP, 12% with serious bacterial infections, 12% with cryptococcus

• Cryptococcus group: 13 patients in early group, and 22 in deferred group
Early ART associated with improved survival

- Death or disease progression: 14.2% (n=20) in early vs 24.1% (n=34) in deferred (p=0.035; OR=0.51, 95%CI 0.27-0.94)

Early ART associated with decreased AIDS/Disease Progression in Fungal Infections

Early vs. Delayed Initiation of ART for Cryptococcal Meningitis

Prospective open-label randomized trial. 54 patients randomized to:

- Early initiation of ART w/in 72hrs of diagnosis and initiation of antifungal therapy (Fluconazole 800mg po qday)
- Delayed initiation of ART at 10 weeks after the initiation of antifungal therapy
- Primary end-point mortality
- 28 patients in the early treatment group; 26 patients in the delayed treatment group
  - High overall 3-year mortality rate of 73%
  - 3 year mortality was higher in the early compared with delayed treatment group (88% vs 54%; P <0.006)
  - Median survival was 28 days and 637 days in the early vs delayed treatment group
Early vs Delayed Initiation of ART

- Kaplan-Meier survival estimates by treatment group. Early treatment was associated with increased mortality and a median survival time of 28 days vs. delayed with median survival time of 637 days (log-rank p-value = 0.031).

Makadzange, AT CID (2010) 50:1532
Cryptococcal Optimal ART Timing Trial (COAT)

- HIV infected, ART naïve, first diagnosis Cryptococcal meningitis by CSF culture or positive CrAg on Amphotericin based therapy for 7-11 days prior to randomization into

- Early ART: Initiation of ART <48 hours after study entry
- Standard ART group: Initiation of ART at>=4 weeks after study entry
- Primary End-point: Survival at 26 weeks
COAT Study Continued

Treatment

• **Induction**: Amphotericin B (0.7-1mg/kg/day) x 2 weeks with Fluconazole 800mg daily

• **Consolidation**: Fluconazole 400mg daily approx 8 weeks

• **Maintenance**: Fluconazole 200mg daily

• Enrollment target 500, enrollment stopped in April 2012 at 177 enrolled per DSMB recommendation
COAT Study Findings

• Excess 6-month mortality rate in the early ART compared with delayed ART arm
• Hazard Ratio for death for early ART was 1.71 [95% CI (1.03-2.87) ]
• Absolute survival difference was 15%
• High mortality associated with Altered mental status, paucity of CSF inflammation
• Follow up to be complete by Nov 2012
Summary: When to Initiate ART

• Early is associated with High Mortality
• Reasonable to initiate ART about 4 weeks after initiation of anti-fungal therapy and preferably with evidence of CSF clearance
Preventing Cryptococcal Disease
Primary Prophylaxis

- 2005 Cochrane Review. Five randomized controlled trials were identified
  - **Powderly 1995**: US Multicenter ACTG 981 study. 428 patients (09/83-06/93) compared fluconazole 200mg daily vs clotrimazole troches 10mg 5x/day. Median CD4 90 cells/ul. All patients on AZT. Primary endpoint invasive fungal infection, secondary death
  - **MccKinsey 1999**: 295 pts from areas with endemic histoplasmosis. US multicenter randomized double blind placebo controlled trial from 06/93-4/96. Intervention Itraconazole 200mg po daily. Median CD4 57 cells/ul. 65% with hx of ART use. Primary endpoint histoplasmosis infection, secondary any other fungal infection
  - **Smith 2001**: Multinational, double blind randomized placebo controlled trial 01/94-10/97. Intervention itraconazole 200mg po daily. Eligible if CD4<300. 79% with hx of ART use. Mean CD4 in both groups 200 cells/ul. 1o endpoint invasive fungal infection.
  - **Chariyalertsak 2002**: 129 Thai patients, single center, double-blind, randomized, placebo-controlled trial from 03/98 to 02/2000. Intervention itraconazole 200mg po daily. Eligible if CD4<200, mean CD4 78 cells/ul. History of ART use in 7.6%. Primary end point invasive fungal infection

Primary prophylaxis for CCM

- Thai multicentre randomized double-blind placebo trial of fluconazole for primary prophylaxis
- 90 patients with CD4<100 enrolled
  - 44 received fluconazole 400mg po once a week
  - 46 received placebo
- 3 cases of CCM in the fluconazole group, 7 cases in the placebo group
- Patients in the placebo group were more likely to develop CCM than in the fluconazole group (HR 2.23; 95%CI: 0.58-8.63; P 0.245)
- 2.7 deaths per 10,000 person days in fluconazole group; 11.7 deaths per 10,000 person days in placebo group (rate difference =9, 95% CI: 0.4-17.5, P=0.046)
- Placebo group was 4.3x more likely to die than fluconazole group (95% CI: 0.9-19.8; P=0.065)

Primary prophylaxis for CM

• In the five studies N=1316 when analyzed as a single group
  – Primary prophylaxis decreases the incidence of cryptococcal disease compared to placebo (RR 0.21, 95% CI 0.09-0.46)
  – There was no significant difference in overall mortality observed (RR 1.01, 95% CI 0.71-1.44)
• Itraconazole prophylaxis (N=798)
  – The incidence of cryptococcal disease was decreased with itraconazole compared with placebo (RR 0.12; 95% CI 0.03-0.51)
  – No significant difference in overall mortality (RR 1.12; 95% CI 0.7-1.8)
• Fluconazole prophylaxis (N=518)
  – Incidence of cryptococcal disease was decreased in those taking fluconazole for primary prophylaxis compared with placebo (RR 0.25; 95% CI 0.07-0.87)
  – There was no significant difference in overall mortality (RR 0.59; 95% CI 0.01-2.62)
Screening for Cryptococcal Antigen prior to initiation of ART

- Positive serum CrAg can precede the onset of clinical symptoms
  - In Uganda a positive CrAg preceded clinical symptoms by a median of 22 days (range 5-234 days) French N AIDS (2002) 16:1031

- Screening most beneficial for patients with CD4<100

- Asymptomatic HIV positive ART naïve outpatients in Thailand
  - 9.2% with positive cryptococcal antigen
  - Stratified by CD4 count: CD4>200 – 0%; CD4 100-199 – 3.4%; CD4 <100 – 12.9%

- Positive cryptococcal antigen is an independent predictor of mortality
  - South African study – 7% of outpatients were serum CrAg positive. Positive sCrAg was associated with a 3 fold increase risk of mortality (HR 3.2 (95%CI 1.5-6.6)) Jarvis J CID (2009) 48:856

- Antifungal treatment likely decreases mortality
  - In Kampala, Uganda – 295 patients with CD4<100 initiating ART, 26 (12.6%) were sCrAg positive
    - 21 were treated with fluconazole; 3 developed CM. 30 month survival was 71%
    - 5 started on ART without any antifungal therapy – all died within 2 months of therapy. Meya DB CID (2010) 51:448
Fluconazole treatment of asymptomatic +sCrAg is associated with improved survival

Meya et al. CID (2010) 51:448
Management of Asymptomatic antigenemia?

4. Localized non-meningeal disease

For localized non-meningeal disease, or in patients with isolated serum CrAg positivity (where active cryptococcal meningitis has been excluded), fluconazole 800 mg/day (or 12 mg/kg/day up to 800 mg/day if below 19 years) for two weeks, then 400 mg/day (or 6 mg/kg/day up to 400-800 mg/day if below 19 years) for eight weeks, and continued maintenance with fluconazole 200 mg/day is recommended. The optimal antifungal regimen in this population remains to be determined.

[Conditional recommendation, low quality of evidence]
<table>
<thead>
<tr>
<th>Target Population</th>
<th>Drugs available</th>
<th>Pre-hydration + electrolyte replacement + toxicity monitoring/management</th>
<th>Induction phase options(^\text{14}) (2 weeks)</th>
<th>Consolidation phase options (8 weeks)</th>
<th>Maintenance/secondary prophylaxis options</th>
</tr>
</thead>
</table>
| Adults            | Amphotericin B\(^\text{15}\) ± flucytosine | Available                                                              | **a.** Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day  
**b.** Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day | Fluconazole 400-800 mg/day | Fluconazole 200 mg daily |
|                   | Amphotericin B\(^\text{15}\) | Not available for full 2 week induction period | Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 800 mg/day (2 weeks) | Fluconazole 800 mg/day | |
|                   | Amphotericin B not available | Not available                                                          | **a.** Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day  
**b.** Fluconazole 1200 mg/day alone | Fluconazole 800 mg/day | |

WHO, 2011
Secondary prophylaxis for CCM

- European study to assess the safety of interrupting maintenance therapy for CMV, MAC, toxoplasmosis and Cryptococcal meningitis
  - 39 patients with cryptococcal disease
  - Mean CD4 count at diagnosis 48 cells/µL (11-94)
  - Mean CD4 count at interruption 297 cells/µL (180-392)
  - Time after initial opportunistic infection 29 months (17-21)
  - Duration of antiretroviral therapy 25 months (17-21)
  - 0 relapses in cryptococcal disease

- Thai prospective multicenter randomized study
  - 42 Patients successfully treated for acute cryptococcal meningitis all initially ART naïve.
  - Initiated on AZT/3TC/EFV
  - 22 patients randomized to continue Fluconazole
  - 20 patients randomized to discontinue secondary prophylaxis when CD4 count >100 cell/µL and undetectable HIV RNA and sustained for 3 months
  - Median duration of follow up after randomization 48 weeks (24-60)
  - 0 relapses of CCM were detected in both groups

Summary

- **Treatment:** Amphotericin Based regimens preferred
- **Timing of ART:** Early is harmful, 4 weeks is probably best, 2-4 weeks may be reasonable.
- **Prevention:** Key. Early treatment initiation.
- **Identification of individuals who are CrAg or LFA positive and initiation of Fluconazole prophylaxis.**
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