CRYPTOCOCCAL MENINGITIS: DIAGNOSIS AND MANAGEMENT IN RESOURCE LIMITED SETTINGS

A. Tariro Makadzange, MD PhD
Case

- AT is a 53yoM who notes that over the last 6 months he has had progressive weight loss, and recurrent upper respiratory infections. He had an HIV test 4 years ago at the end of his last marriage and had tested HIV negative. He is now concerned and presents to the OI clinic for HIV testing. His HIV test returns positive and his CD4 count is 64 cells/mm3. What tests would you do to screen him for cryptococcal disease?
Screening before ART initiation

A. No screening is required as screening for cryptococcal disease is not necessary
B. Serum cryptococcal antigen
C. Serum LFA
D. Recommend LP and CSF cryptococcal antigen
E. Urine LFA
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.
ART has significantly reduced the burden of disease in western cohorts

- 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 cryptococcosis
- 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
High ongoing burden despite ART Roll Out in sub-Saharan Africa

Jarvis JN, AIDS 2009, 23(9):1182
Screening for Cryptococcal Antigen prior to initiation of ART may decrease mortality

• 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
Cryptococcal antigen tests

- Latex agglutination or EIA
  - Serum Sensitivity 97%, Specificity 95%
  - CSF sensitivity 100% and Specificity 96%
- Lateral Flow Assay
  - >96% sensitivity and specificity
  - Affordable, point of care tests
  - May have similar sensitivity with whole blood
  - Sensitivity and specificity in urine to be determined
Follow up visit

AT returns and of note his serum LFA test was positive. On symptom screening he denies any fevers, headaches, confusion. What would you recommend next?

A. Do nothing and initiate ART immediately
B. Start on Fluconazole at 200mg once daily
C. Start on Fluconazole 800mg once daily for 2 weeks followed by 400mg once daily for 8 weeks, then 200mg once daily thereafter
D. Hospitalize and start on Amphotericin B
E. Recommend a Lumbar puncture
Do nothing, initiate ART immediately?

- 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 et al. CID (2010) 51:448
Management of screened patients

Cryptococcal antigen screening when CD4+ T-lymphocyte count <100 cells/µl

- Contact patient for urgent follow-up
- Screen for symptoms of meningitis*
- Check for special situations

Symptomatic

Start fluconazole 1 200 mg daily and refer immediately for lumbar puncture

Lumbar puncture (+)

Amphotericin B plus fluconazole 800 mg daily for 2 weeks in hospital

Initiate ART
No fluconazole

Lumbar puncture (-)

Asymptomatic

Fluconazole 800 mg daily for 2 weeks as outpatient

Fluconazole 400 mg daily for 2 months then 200 mg daily
Continue fluconazole for minimum of 1 year in total and discontinue when patient has had 2 CD4 counts >200 cells/µl taken at least 6 months apart

Start ART after 6–6 weeks of antifungal therapy

Start ART after 2 weeks of antifungal therapy
meningoencephalitis. Serum CrAg is usually positive in both meningeal and non-meningeal infection and may be present weeks to months before symptom onset. A positive serum CrAg should prompt a lumbar puncture to rule out meningeal disease. Three methods exist for antigen detection: latex agglutination, enzyme immunoassays, and lateral flow assay (a newly developed dipstick test). Testing for the antigen is a useful initial screening tool in diagnosing cryptococcosis in HIV-infected patients, and it may be particularly useful when lumbar punctures need to be delayed or are refused.

Follow up visit

AT returns and of note his serum LFA test was positive. On symptom screening he denies any fevers, headaches, confusion. What would you recommend next?

A. Do nothing and initiate ART immediately
B. Start on Fluconazole at 200mg once daily
C. Start on Fluconazole 800mg once daily for 2 weeks followed by 400mg once daily for 8 weeks, then 200mg once daily thereafter.
D. Hospitalize and start on Amphotericin B
E. Recommend a Lumbar puncture
Case

• AT says that he feels well. He notes that a distant aunt died a few years ago after having had a lumbar puncture and declines to have a lumbar puncture. You recommend that he should be initiated on antifungal therapy.
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year</th>
<th>Fluconazole Dosing</th>
<th>ART Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Health Organization*</td>
<td>2011</td>
<td>800mg/d X 2 weeks, then 400mg/d X 8 weeks*</td>
<td>After 4 weeks of therapy*</td>
</tr>
<tr>
<td>Southern African HIV Clinicians Society</td>
<td>2013</td>
<td>800mg/d X 2 weeks, then 400mg/d X 2 months, then 200mg/d for 1 year and CD4&gt;100</td>
<td>After 2 weeks of therapy</td>
</tr>
<tr>
<td>Infectious Diseases Society of America</td>
<td>2010</td>
<td>Not clearly defined. 400mg/d 6-12 months</td>
<td>Not discussed</td>
</tr>
</tbody>
</table>

*WHO guidelines grade recommendations as “conditional” because of the lack of data to support them.
Case

- AT was placed on Fluconazole 800mg po daily x 2 weeks, then 400mg po daily x 8 weeks, followed by 200mg daily thereafter. He tolerated the fluconazole well.
- 2 weeks after starting his fluconazole therapy he was initiated on ART with TDF/FTC/EFV.
- He has done well.
Case 2

- TC is a 17yoF with chronic HIV infection on ART since 2008, who presents with a frontal throbbing headache.
- She notes that over the last month she has had an intermittent headache which has progressively worsened over the last few days. She complains of nausea, vomiting, neck pain, no photophobia. She notes that she has lost about 7kg over the last 1 month. She also notes that she has not taken her ARVs, on average 7 days out of each month.
- She is afebrile, BP 97/61, HR 104, RR 20. GCS 14/15. Her physical examination is notable for oral thrush, marked neck stiffness.
- PMH: is notable for HIV diagnosed in 2008. Her baseline CD4 count was 154, she does not recall her most recent CD4 count. She lives with her twin sister who is also HIV positive and both parents are deceased.
Case 2

• Her labs are notable for a Na\(^+\) 133, K\(^+\) 3.6, BUN 2.4, Cr 52, eGFR >90.
• She had a WBC of 2.5 (62\%N, 22\%L), Hgb 8.8g/dL, Plt 387
• Her CxR is clear
• Her CSF is notable for a cell count of 3cells/mm\(^3\), total protein 85g/dL, glucose nl. India ink and CSF CrAg are positive.
• She is commenced on antifungal therapy. What antifungal therapy would you begin?
Treatment options

A. Amphotericin B 0.7-1mg/kg IV qday x 14 days of induction followed by Fluconazole 800mg po od x 8 weeks

B. Amphotericin B 0.7-1mg/kg IV qday + Fluconazole 400mg po od x 14 days of induction followed by Fluconazole 400mg po od x 8 weeks

C. Amphotericin B 0.7-1mg/kg IV qday + Fluconazole 600mg po od x 14 days of induction followed by Fluconazole 600mg po od x 8 weeks

D. Amphotericin B 0.7-1mg/kg IV qday + Fluconazole 800mg po od x 14 days of induction followed by Fluconazole 400mg po od x 8 weeks

E. Amphotericin B 0.7mg-1/kg IV qday + Fluconazole 600mg po bd x 14 days of induction followed by Fluconazole 600mg po bd x 8 weeks
However …

- TC is admitted to Parirenyatwa Hospital, there are no relatives around, and when they do arrive they cannot afford $15/day for the amphotericin, or the $20 every few days for the U+Es. What would you treat her with?
Alternative options

A. Fluconazole 400mg po od x 2 weeks of induction then 200mg po od
B. Fluconazole 600mg po od x 2 weeks of induction then 400mg po od x 8 weeks
C. Fluconazole 800mg po od x 2 weeks of induction then 400mg po od x 8 weeks
D. Fluconazole 600mg po bd x 2 weeks of induction then 800mg po od x 8 weeks
E. Fluconazole 600mg po bd x 10 weeks
**Table 3. Summary of recommendation 3: Management of first episode of CM**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>2 weeks</td>
<td>• Amphotericin B (1 mg/kg/day IV) and fluconazole (800 mg daily PO)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>8 weeks</td>
<td>• Fluconazole (400 mg daily PO)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Until the CD4+ T-lymphocyte count &gt;200 cells/μl for 6 months on ART and most recent viral load is suppressed (minimum 10 months)</td>
<td>• Fluconazole (200 mg daily PO)</td>
</tr>
</tbody>
</table>

IV = intravenous; PO = per os.
## 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 fluconazole (100 mg/kg per day)</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 fluconazole (100 mg/kg per day)</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 fluconazole-intolerant patients)</td>
<td>4–6 weeks</td>
<td>B-II</td>
</tr>
<tr>
<td><strong>Alternatives for induction therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmBd plus fluconazole</td>
<td>...</td>
<td>B-I</td>
</tr>
<tr>
<td>Fluconazole plus fluconazole</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: fluconazole (400 mg per day)</strong></td>
<td>8 weeks</td>
<td>A-I</td>
</tr>
<tr>
<td>Maintenance therapy: fluconazole (200 mg per day)</td>
<td>≥1 year</td>
<td>A-I</td>
</tr>
<tr>
<td><strong>Alternatives for maintenance therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole (400 mg per day)</td>
<td>≥1 year</td>
<td>C-I</td>
</tr>
<tr>
<td>AmBd (1 mg/kg per week)</td>
<td>≥1 year</td>
<td>C-I</td>
</tr>
</tbody>
</table>

**NOTE.** ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate; HAART, highly active antiretroviral therapy.

- Begin HAART 2–10 weeks after the start of initial antifungal treatment.
- 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.
- With successful introduction of HAART, a CD4 cell count ≥100 cells/µL, and low or nondetectable viral load for ≥3 months with minimum of 1 year of antifungal therapy.
- Inferior to the primary recommendation.

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Drugs available</th>
<th>Pre-hydration + electrolyte replacement + toxicity monitoring/management</th>
<th>Induction phase options¹⁴</th>
<th>Consolidation phase options</th>
<th>Maintenance/secondary prophylaxis options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Amphotericin B¹⁵ ± flucytosine</td>
<td>Available</td>
<td>a. Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day</td>
<td>Fluconazole 400-800 mg/day</td>
<td>Fluconazole 200 mg daily</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B¹⁵</td>
<td>Not available for full 2 week induction period</td>
<td>b. Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B not available</td>
<td>Not available</td>
<td>a. Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day</td>
<td>Fluconazole 800 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b. Fluconazole 1200 mg/day alone</td>
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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>Available</td>
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<td>Fluconazole 200 mg daily</td>
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<td></td>
<td>Amphotericin B(^1)</td>
<td>Not available for full 2 week induction period</td>
<td>b. Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day</td>
<td>Fluconazole 800 mg/day</td>
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<td>Not available</td>
<td>a. Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b. Fluconazole 1200 mg/day alone</td>
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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

Kaplan Meier estimates of overall survival for the modified intention-to-treat population.

Combination antifungal therapies for HIV-associated cryptococcal meningitis

- Thailand
- 64 patients with first episode of cryptococcal meningitis. Randomized to
  - Amphotericin B only (0.7mg/kg/day)
  - Amphotericin B plus flucytosine (100mg/kg/day)
  - Amphotericin B plus fluconazole (400mg daily)
  - Triple therapy with Amphotericin B, flucytosine and fluconazole
- Primary outcome was CSF sterilization rate
- Outcomes: 2 week mortality of 14%, 10 week mortality of 22%.
  - Not statistically significant across treatment groups (p=0.28, p=0.11 respectively)
- Factors associated with mortality: seizures, decreased level of consciousness, and log cryptococcal CSF CFU/mL

Fungicidal activity

Amphotericin B plus flucytosine had higher early fungicidal activity than:

• Amphotericin B alone (difference $0.23 \log_{10} \text{CFU daily}$ (0.10-0.35, $p=0.0006$)
• Amphotericin B with fluconazole (difference $=0.15 \log_{10} \text{CFU daily}$ (0.01-0.29, $p=0.03$)
• Triple therapy (difference $0.17 \log_{10} \text{CFU daily}$ (0.04-0.30, $p=0.01$)

Combination Antifungal Therapy for Cryptococcal Meningitis

Combination therapy for Cryptococcal Meningitis

• Open label, randomized controlled trial
• Primary objective to compare Amphotericin plus flucytosine, Amphotericin plus fluconazole to amphotericin monotherapy.
• Primary Outcomes
• All cause mortality at 14 and 70 days after randomization
• Secondary Outcomes
• 6 month mortality
• Study Groups notably longer Amphotericin B only therapy, and higher fluconazole dose in combination with amphotericin B
• Group 1: Amphotericin B (1mg/kg/day) x 4 weeks followed by oral fluconazole 400mg/day x 6 weeks
• Group 2: Amphotericin B (1mg/kg/day) plus flucytosine (100mg/kg/day) x 2 weeks followed by oral fluconazole 400mg/day x 8 weeks
• Group 3: Amphotericin B and fluconazole (400mg twice daily) x 2 weeks followed by oral fluconazole 400mg/day x 8 weeks
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amp/flucyt vs Amp only</th>
<th>p value</th>
<th>Amp/Flzole vs. Amp only</th>
<th>p value</th>
<th>Amp/Flcyt vs Amp/Flzole</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death by day 14</td>
<td>0.57 (0.3-1.08)</td>
<td>0.08</td>
<td>0.78 (0.44-1.41)</td>
<td>0.42</td>
<td>0.72 (0.47-1.41)</td>
<td>0.34</td>
</tr>
<tr>
<td>Death by day 70</td>
<td>0.61 (0.39-0.97)</td>
<td>0.04</td>
<td>0.71 (0.45-1.11)</td>
<td>0.13</td>
<td>0.87 (0.53-1.42)</td>
<td>0.57</td>
</tr>
<tr>
<td>Death by day 70 in per protocol</td>
<td>0.60 (0.36-0.99)</td>
<td>0.04</td>
<td>0.68 (0.41-1.11)</td>
<td>0.12</td>
<td>0.88 (0.52-1.51)</td>
<td>0.65</td>
</tr>
<tr>
<td>Death by day 182</td>
<td>0.56 (0.36-0.86)</td>
<td>0.01</td>
<td>0.78 (0.53-1.16)</td>
<td>0.23</td>
<td>0.72 (0.46-1.12)</td>
<td>0.14</td>
</tr>
<tr>
<td>Estimated change in CSF fungal count in first 14 days</td>
<td>-0.10 (-0.14 to -0.07)</td>
<td>&lt;0.001</td>
<td>0.00 (-0.04 to 0.03)</td>
<td>0.83</td>
<td>-0.10 (-0.14 to -0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No of patients with fungal clearance</td>
<td>3.18 (2.17-4.66)</td>
<td>&lt;0.001</td>
<td>1.39 (0.94-2.07)</td>
<td>0.10</td>
<td>2.29 (1.59-3.29)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Summary of Study Outcomes

- Unadjusted 14 day mortality was higher in the Amphotericin B only group (25%) as compared with Groups 2 (15%) and 3 (20%).
- Unadjusted 70 day mortality was also higher in the Amphotericin B only (44%) group as compared with Groups 2 (30%) and 3 (33%).
- Higher proportions of patients with fungal clearance in the Ampho/flucytosine group than in the other two groups.
- Time to fungal clearance was shorter in patients receiving Ampho/flucytosine than in the other two groups. Rates of colony count decline:
  - Ampho/flucyt vs Ampho only: -0.42 log10 CFU/day vs -0.31 log10 CFU/day
  - Ampho/fluc vs Ampho only: -0.31 log10 CFU/day vs -0.32 log10 CFU/day. P<0.001
## Treatment of Cryptococcal Meningitis in Resource Limited Settings

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<th>Target Population</th>
<th>Drugs available</th>
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<th>Maintenance/secondary prophylaxis options</th>
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</table>
| **Adults**        | Amphotericin B<sup>15</sup> ± 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<sup>15</sup> not available | 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
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
<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}) (2 weeks)</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  
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WHO, 2011
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.
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.

Complications of Amphotericin B

- TC was started on fluconazole 600mg po bd. 2 days later an uncle was able to obtain amphotericin B. She received Amphotericin B with fluconazole 600mg po bd. On day 10 her creatinine increased and her eGFR went from a baseline of 89 to 45, despite receiving adequate pre and post hydration with normal saline, and amphotericin B infusion over 4-6 hours.
- Amphotericin was stopped for 2 days, received continuous hydration with improvement of her creatinine. Amphotericin B was reinfused at 0.7mg/kg. Repeat LP at 2 weeks was culture negative for organisms and she was place on consolidation phase therapy with Fluconazole 600mg po bd x 8 weeks, then on Fluconazole 200mg po od for maintenance therapy.
- She was initiated on a PI based second-line ART regimen after having received antifungal therapy for a total of 4 weeks.
Amphotericin B toxicity

Minimizing Amphotericin B toxicity

• Pre-hydration with 1L normal saline with potassium supplementation (20mEq). If available magnesium supplementation should be added.
• Infuse amphotericin B slowly over 4-6 hours
• Check serum K+ and creatinine at baseline and twice weekly
• Check hemoglobin at baseline and once weekly

Managing toxicities

• If Cr increases by ≥2x, then discontinue amphotericin, increase prehydration to 1L NS q8 hours, recheck and if normalized then restart at a lower dose of Amphotericin B (0.7mg/kg). If renal impairment does not resolve then start on Fluconazole 600mg po twice daily.
When to Start ART?

- **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.
- 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 in Cryptococcal disease

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

Makadzange, AT CID (2010) 50:1532
Early ART in Cryptococcal Disease treated with Amphotericin B

- In COAT Trial, deferred ART initiation at 5 weeks had superior survival vs. early ART at 1-2 weeks.

Boulware et al, CROI, 2013
Summary

• Cryptococcal disease remains one of the leading causes of morbidity and mortality among people with HIV/AIDS in sub-Saharan Africa

• Screening of individuals with low CD4 counts may improve mortality

• Effective therapy with Amphotericin B based regimens improves clinical outcomes

• ART should be initiated a few weeks after successful antifungal therapy.
Further Research questions

- Among individuals who screen positive by a cryptococcal antigen test and are asymptomatic which individuals are at risk of disseminated disease and require a LP?
- What is the optimal therapy for individuals with asymptomatic cryptococcal antigenemia?
- When should ART be initiated in individuals with asymptomatic cryptococcal antigenemia?
- Are short courses of liposomal amphotericin B therapy a good alternative?
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