Cryptococcal Disease: Proposed Algorithm for Screening

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Acknowledgements

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# Proposed Algorithm for Screening

## Overview of screening
- Screening principles
- Implementation in South Africa

## Review of the screening algorithm
- Cryptococcal meningitis
- Asymptomatic cryptococcal antigenaemia
1. OVERVIEW OF SCREENING
High burden of cryptococcal meningitis in South Africa

Incidence of lab-confirmed cryptococcal meningitis (n=18,925) vs. number of persons on antiretroviral treatment (n=1,291,026), Gauteng province, South Africa, 2002-2011

<table>
<thead>
<tr>
<th>Year</th>
<th>ART Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>1194</td>
</tr>
<tr>
<td>2003</td>
<td>1511</td>
</tr>
<tr>
<td>2004</td>
<td>1539</td>
</tr>
<tr>
<td>2005</td>
<td>2000</td>
</tr>
<tr>
<td>2006</td>
<td>2253</td>
</tr>
<tr>
<td>2007</td>
<td>2109</td>
</tr>
<tr>
<td>2008</td>
<td>2141</td>
</tr>
<tr>
<td>2009</td>
<td>2141</td>
</tr>
<tr>
<td>2010</td>
<td>2099</td>
</tr>
<tr>
<td>2011</td>
<td>1938</td>
</tr>
</tbody>
</table>
High in-hospital mortality in South Africa

Induction treatment with amphotericin B and in-hospital case-fatality ratio for cases of incident lab-confirmed cryptococcal meningitis diagnosed at GERMS-SA enhanced surveillance sites, South Africa, 2005-2011
Pathogenesis of disease


Latent infection

HIV-infected with low CD4 count

Meningitis

Bloodstream
How cryptococcal screening works

- Identify HIV-infected patients with CD4<100
- Test for cryptococcal antigenaemia before symptom onset
- Treat with oral fluconazole
- Prevent cryptococcal meningitis and deaths
(Conditional) WHO Recommendation

The use of routine serum or plasma CrAg screening in ART-naïve adults, followed by pre-emptive anti-fungal therapy if CrAg-positive, to reduce the development of cryptococcal disease, may be considered prior to ART initiation in:

a. patients with a CD4 count less than 100 cells/mm$^3$, and
b. where this population also has a high prevalence of cryptococcal antigenaemia$^{13}$.

[Conditional recommendation, low quality of evidence]
A comprehensive screening programme

• Who should be screened and where?
• Develop clinical algorithm
• Integrate screening into ART and TB programmes
• Train healthcare personnel
• Educate patients
• Perform monitoring and evaluation to determine effectiveness
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Reflex screening</th>
<th>Clinician-initiated screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Provinces</strong></td>
<td>▪ Gauteng &amp; Free State (Phase 1)</td>
<td>▪ Western Cape</td>
</tr>
<tr>
<td><strong>Coverage of screening</strong></td>
<td>▪ Potentially broader</td>
<td>▪ Restricted (depends on clinicians ordering/performing test on a selected group)</td>
</tr>
<tr>
<td><strong>Location of laboratory testing</strong></td>
<td>▪ CD4 laboratory</td>
<td>▪ Microbiology laboratory</td>
</tr>
<tr>
<td><strong>Required specimen</strong></td>
<td>▪ CD4 EDTA-blood sample</td>
<td>▪ Separate serum sample submitted by clinician</td>
</tr>
<tr>
<td><strong>Test format</strong></td>
<td>▪ Lateral flow assay</td>
<td>▪ Latex agglutination test</td>
</tr>
<tr>
<td><strong>Test request</strong></td>
<td>▪ Reflex</td>
<td>▪ Depends on clinician awareness</td>
</tr>
<tr>
<td><strong>Clinician training</strong></td>
<td>▪ Augmented clinician training required because test not specifically requested</td>
<td>▪ No clinician training</td>
</tr>
<tr>
<td><strong>Selection of patients</strong></td>
<td>▪ All samples screened regardless of clinical background – including repeat CD4 samples from the same patient</td>
<td>▪ Clinicians select patients, e.g. ART-naïve vs. ART-experienced, no prior CM, adult, asymptomatic, no prior screening test</td>
</tr>
</tbody>
</table>
Figure 1: Number of blood specimens screened for CrAg at NHLS laboratories by month, Western Cape, 1 June to 8 Oct 2012
Reflex laboratory screening

CD4 < 100
Health Facilities in South Africa

CMJAH NHLS CD4 lab node and 25 facilities
### Laboratory Statistics

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of NHLS CD4 laboratories enrolled in screening programme</td>
<td>1</td>
</tr>
<tr>
<td>Number of NHLS CD4 laboratories reporting data</td>
<td>1</td>
</tr>
<tr>
<td>Number of CrAg screening tests performed</td>
<td>1458</td>
</tr>
<tr>
<td>Number of CrAg-positive tests/number of specimens tested (%)</td>
<td>71/1458 (4.9%)</td>
</tr>
</tbody>
</table>

### Case Statistics

<table>
<thead>
<tr>
<th>Description</th>
<th>Sep 2012</th>
<th>Oct 2012</th>
<th>Nov 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients tested CrAg (month/YTD)</td>
<td>467/467</td>
<td>607/1074</td>
<td>324/1398</td>
</tr>
<tr>
<td>Number of CrAg-positive patients (month/YTD)</td>
<td>25/25</td>
<td>30/55</td>
<td>9/64</td>
</tr>
<tr>
<td>Number of CrAg-positive patients who had a lumbar puncture (month/YTD)</td>
<td>12/12</td>
<td>16/28</td>
<td>2/30</td>
</tr>
<tr>
<td>Number of CrAg-positive patients who had a lumbar puncture with laboratory-confirmed CM (month/YTD)</td>
<td>5/5</td>
<td>4/9</td>
<td>1/10</td>
</tr>
<tr>
<td>Number of CrAg-positive patients treated with fluconazole (month/YTD)</td>
<td>17/17</td>
<td>17/34</td>
<td>1/35</td>
</tr>
</tbody>
</table>

A comprehensive screening programme

• Who should be screened and where?

  • Develop clinical algorithm
  • Integrate screening into ART and TB programmes

• Train healthcare personnel

• Educate patients

• Perform monitoring and evaluation to determine effectiveness
2. REVIEW OF THE SCREENING ALGORITHM
CASE

• 35 year-old woman
• Newly-diagnosed HIV infection
• Seen at a rural facility in the Free State
• Screened for TB symptoms → cough and loss of weight
• Sputum submitted to the laboratory → Xpert MTB-positive/ RIF-negative
• Started on TB regimen 1
• Second sputum specimen submitted for microscopy
CASE

• Referred to another healthcare worker in the same clinic for ARV assessment
• Baseline blood tests submitted to the laboratory including CD4 count
• Patient was asked to return to the clinic in 1 week
**Lymphocyte Subset Analysis**

<table>
<thead>
<tr>
<th>Flag</th>
<th>Ref Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD45 +ve WBC</td>
<td>9.27 x 10^9/L</td>
</tr>
<tr>
<td>CD4 % of Lymphocytes</td>
<td>2.63 %</td>
</tr>
<tr>
<td>Absolute CD4</td>
<td>20 x 10^6/L</td>
</tr>
<tr>
<td></td>
<td>L-</td>
</tr>
<tr>
<td></td>
<td>500 - 2010</td>
</tr>
</tbody>
</table>

**Cryptococcal Antigen Test**

- **Cryptococcal antigen**: Positive

Reflex testing for cryptococcal antigen has been performed because the patient's CD4+ T-cell count is below 100 cells/μL. Cryptococcal antigen has been detected. If the patient has previously diagnosed with cryptococcal disease, please ensure that the patient continues antifungal treatment.

If this is a new diagnosis, the patient should be evaluated for signs and symptoms of disseminated disease, including meningitis. Symptomatic patients will need a lumbar puncture to exclude meningitis while asymptomatic patients should be started on fluconazole after evaluation for special conditions.

**Authorised by:**

- Test(s): CD4
- Test(s): Crypt

--- End of Laboratory Report ---
Reflex cryptococcal antigen screening of CD4 <100 specimens

**Positive**
- Contact patient for urgent follow-up
- Screen for symptoms of meningitis
- Check for other clinical conditions

**Symptomatic**
Start fluconazole 400 mg daily and refer immediately for lumbar puncture

Lumbar puncture (+) -> Amphotericin B-based regimen for 2 weeks in hospital

Lumbar puncture (-) -> Outpatient treatment with fluconazole 400 mg daily

Start ART after 2 weeks of antifungal therapy

**Asymptomatic**

Initiate ART
No fluconazole

*Patient is symptomatic for meningitis if they have any of the following:
1. Headache greater than 24 hours
2. Fever
3. Confusion or coma
4. Blurred vision

*Other clinical conditions include:
- Patients on tuberculosis medications
- Patients on nevirapine
- Patients with previous history of cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Liver disease
- Children.

*A lumbar puncture may be considered if available.

*Some clinicians prefer to use a higher dose.

Cryptococcal antigen screening when CD4 <100

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

**Symptomatic**

- Start Fluconazole 800 mg daily and refer immediately for lumbar puncture

**Asymptomatic**

- Lumbar puncture (+) → Amphotericin B plus Fluconazole 800 mg daily for 2 weeks in hospital
- Lumbar puncture (-) → Fluconazole 800 mg daily for 2 weeks as outpatient

**POSITIVE**

- Start ART after 4 weeks of antifungal therapy

**NEGATIVE**

- Start ART after 2 weeks of antifungal therapy

*Patient is symptomatic for meningitis if they have any of the following:
1. Headache
2. Confusion

**Other special situations include:**
- Patients on tuberculosis medications
- Patients with previous history of cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease

* A lumbar puncture may be considered if available.

Outpatient treatment with Fluconazole 400 mg daily for 2 months, then 200 mg daily until CD4+ T-lymphocyte count >200 cells/µl for at least 6 months on ART (total – at least 1 year)

Initiate ART

No fluconazole
Cryptococcal antigen screening when CD4 <100

**Initiate ART**
*No fluconazole*

**Cryptococcal antigen screening when CD4 <100**

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

**Symptomatic**

- Start Fluconazole 800 mg daily and refer immediately for lumbar puncture

**Asymptomatic§**

- Lumbar puncture (+)
- Lumbar puncture (-)

**Positive**

- Amphotericin B plus Fluconazole 800 mg daily for 2 weeks in hospital
- Fluconazole 800 mg daily for 2 weeks as outpatient

**Negative**

- Start ART after 2 weeks of antifungal therapy
- Start ART after 4 weeks of antifungal therapy

**Outpatient treatment**

- Fluconazole 400 mg daily for 2 months, then 200 mg daily until CD4+ T-lymphocyte count >200 cells/µl for at least 6 months on ART (total – at least 1 year)

**Patient is symptomatic for meningitis if they have **any** of the following:**

1. Headache
2. Confusion

**Other special situations include:**

- Patients on tuberculosis medications
- Patients with previous history of cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease

§ A lumbar puncture may be considered if available.

† Other special situations include:

- Patients on tuberculosis medications
- Patients with previous history of cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease
TB Symptom Screening and IPT

Person living with HIV *

Screen for TB with any one of the following: **
- Current cough
- Fever
- Night sweats
- Weight loss

LATENT TB INFECTION

TB excluded; potentially eligible for IPT ***

SUSPECTED ACTIVE TB DISEASE

Investigate for TB and other diseases****

Other diagnosis
- Not TB
- TB

Give appropriate treatment; potentially eligible for IPT

Follow up; potentially eligible for IPT

Treat for TB

Screen regularly for TB

Cryptococcal antigen screening when CD4 <100

**Initiate ART**
No fluconazole

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

**Symptomatic**
Start Fluconazole 800 mg daily and refer immediately for lumbar puncture

Lumbar puncture (+)
**Amphotericin B plus Fluconazole**
800 mg daily for 2 weeks in hospital

Start ART after 4 weeks of antifungal therapy

Lumbar puncture (-)
**Fluconazole**
800 mg daily for 2 weeks as outpatient

Start ART after 2 weeks of antifungal therapy

All HIV+ patients with a CrAg+ screening test have disseminated cryptococcal disease

Outpatient treatment with Fluconazole 400 mg daily for 2 months, then 200 mg daily until CD4+ T-lymphocyte count >200 cells/µl for at least 6 months on ART (total – at least 1 year)

**Asymptomatic**

† Other special situations include:
- Patients on tuberculosis medications
- Patients with previous history of cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease

§§

* Patient is symptomatic for meningitis if they have any of the following:
  1. Headache
  2. Confusion

§§§

‡‡‡

§§ §§

A lumbar puncture may be considered if available.
CASE

• Printed laboratory report with CrAg-positive result was not noticed by busy clinic personnel
• Fortunately, the laboratory also phoned the clinic with CrAg-positive result
• NIMART-trained nurse contacted the patient and asked that she return to clinic the next day
HIV-infected patients with CrAg+ test = DISSEMINATED DISEASE

- PRIOR cryptococcal meningitis
- No prior cryptococcal meningitis

- CrAg may persist in body fluids for weeks to months after an episode of cryptococcal meningitis → may be detected by screening

- Ensure that this patient is receiving adequate maintenance therapy for prior episode
- If new symptoms, need evaluation for relapse and/or IRIS
CASE

• Patient returned to clinic a few days earlier than her appointment
  – No history of cryptococcal meningitis
  – Complained of a mild headache with prompting
HIV-infected patients with CrAg+ test = DISSEMINATED DISEASE

PRIOR cryptococcal meningitis

No prior cryptococcal meningitis

HOW CAN THESE PATIENTS BE SEPARATED?

Cryptococcal meningitis

Asymptomatic antigenaemia

HOSPITAL-based treatment

OUTPATIENT treatment
HIV-infected patients with CrAg+ test = DISSEMINATED DISEASE

PRIOR cryptococcal meningitis

No prior cryptococcal meningitis

LUMBAR PUNCTURE

Cryptococcal meningitis

HOSPITAL-based treatment

Asymptomatic antigenaemia

OUTPATIENT treatment
HIV-infected patients without symptoms $n=131$

Cryptococcal meningitis $n=3$ (25%)

No cryptococcal meningitis $n=9$ (75%)


HIV-infected patients with and without symptoms

Cryptococcal meningitis 62% to 66%

No cryptococcal meningitis

HIV-infected patients with CrAg+ test = DISSEMINATED DISEASE

PRIOR cryptococcal meningitis

No prior cryptococcal meningitis

SYMPTOM SCREEN

Positive
Refer for LP in all cases

Negative
Offer LP if logistically feasible

But which symptoms & signs predict meningitis...
TB Symptom Screening

Person living with HIV *

Screen for TB with any one of the following: **
- Current cough
- Fever
- Night sweats
- Weight loss

None present

TB excluded; potentially eligible for IPT ***

At least 1 present

Investigate for TB and other diseases****

Other diagnosis

Give appropriate treatment; potentially eligible for IPT

Not TB

Follow up; potentially eligible for IPT

TB

Treat for TB

Screen regularly for TB

Symptoms and signs of cryptococcal meningitis

Table 2. Symptoms, signs and concurrent illnesses present on admission in cases of cryptococcosis observed during population-based surveillance in Gauteng, 2002–2004.

<table>
<thead>
<tr>
<th>Symptom, sign or concurrent illness</th>
<th>Percentage of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2147 (78%)</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>1900 (69%)</td>
</tr>
<tr>
<td>Fever</td>
<td>1514 (55%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1129 (41%)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>853 (31%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>248 (9%)</td>
</tr>
<tr>
<td>Coma</td>
<td>83 (3%)</td>
</tr>
<tr>
<td>6th cranial nerve palsy</td>
<td>28 (1%)</td>
</tr>
</tbody>
</table>

Cryptococcal antigen screening when CD4 <100

**Initiate ART**
No fluconazole

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

- **Symptomatic**
  - Start Fluconazole 800 mg daily and refer immediately for lumbar puncture

  - Lumbar puncture (+)
    - Amphotericin B plus Fluconazole 800 mg daily for 2 weeks in hospital
    - Start ART after 4 weeks of antifungal therapy
    - Outpatient treatment with Fluconazole 400 mg daily for 2 months, then 200 mg daily until CD4+ T-lymphocyte count >200 cells/µl for at least 6 months on ART (total – at least 1 year)

  - Lumbar puncture (-)
    - Fluconazole 800 mg daily for 2 weeks as outpatient
    - Start ART after 2 weeks of antifungal therapy

- **Asymptomatic**

  - Patient is symptomatic for meningitis if they have any of the following:
    1. Headache
    2. Confusion

- **Other special situations include**:
  - Patients on tuberculosis medications
  - Patients with previous history of cryptococcal meningitis
  - Pregnancy or breastfeeding mothers
  - Clinical liver disease

**NEGATIVE**

- Screen for symptoms of meningitis
- Check for other special situations

† A lumbar puncture may be considered if available.
HIV-infected patients with CrAg+ test = DISSEMINATED DISEASE

PRIOR cryptococcal meningitis

No prior cryptococcal meningitis

SYMPTOM SCREEN

Positive

Refer for LP

Positive

Cryptococcal meningitis

Negative

Asymptomatic antigenaemia
# Cryptococcal Meningitis: Antifungal treatment

<table>
<thead>
<tr>
<th>Drugs available</th>
<th>Toxicity prevention package</th>
<th>Induction (2 weeks)</th>
<th>Consolidation (8 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmB ± Flucytosine</td>
<td>Available</td>
<td>AmB + Flucytosine [Strong/High]</td>
<td>Fluconazole 400 mg to 800 mg [Strong/Low]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AmB + Fluconazole [Strong/Moderate]</td>
<td></td>
</tr>
<tr>
<td>AmB</td>
<td>Not Available</td>
<td>AmB + Fluconazole (short course) [Conditional/Low]</td>
<td>Fluconazole 800 mg</td>
</tr>
<tr>
<td>No AmB</td>
<td>Not Available</td>
<td>Fluconazole ± Flucytosine</td>
<td>Fluconazole 800 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole 1200mg [Conditional/Low]</td>
<td></td>
</tr>
</tbody>
</table>

WHO Rapid Advice Guidelines 2011.
Cryptococcal Meningitis: Timing of ART

- Immediate ART initiation is not recommended in patients with meningitis due to high risk of IRIS, which may be life-threatening. (Conditional recommendation, low quality of evidence)
- Defer ART initiation until evidence of a sustained clinical response to anti-fungal therapy AND after...

<table>
<thead>
<tr>
<th>Induction regimen</th>
<th>Meningitis</th>
<th>Non-meningeal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>2-4 weeks</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>4-6 weeks</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

(Conditional recommendation, low quality of evidence)

WHO Rapid Advice Guidelines 2011.
Cryptococcal antigen screening when CD4 <100

Initiate ART
No fluconazole

**Cryptococcal antigen screening when CD4 <100**

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

**Symptomatic**

- Start Fluconazole 800 mg daily and refer immediately for lumbar puncture

**Asymptomatic**

- Lumbar puncture (+)
- Lumbar puncture (-)
- Amphotericin B plus Fluconazole 800 mg daily for 2 weeks in hospital
- Fluconazole 800 mg daily for 2 weeks as outpatient

**Outpatient treatment with Fluconazole 400 mg daily for 2 months, then 200 mg daily until CD4+ T-lymphocyte count >200 cells/µl for at least 6 months on ART (total – at least 1 year)**

*Patient is symptomatic for meningitis if they have any of the following:
1. Headache
2. Confusion

†Other special situations include:
- Patients on tuberculosis medications
- Patients with previous history of cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease

§A lumbar puncture may be considered if available.
CASE

• Despite careful counselling, patient refused to be referred to the nearest hospital 100 km away for a lumbar puncture
HIV-infected patients with CrAg+ test = DISSEMINATED DISEASE

PRIOR cryptococcal meningitis

No prior cryptococcal meningitis

SYMPTOM SCREEN

Negative

Asymptomatic antigenaemia

Cryptococcal meningitis

Offer LP if logistically feasible

Positive

Asymptomatic antigenaemia
Asymptomatic antigenaemia predicts death during early ART

<table>
<thead>
<tr>
<th>Relative risk(\dagger)</th>
<th>95% Confidence interval</th>
<th>(P)</th>
<th>Relative risk(\dagger)</th>
<th>95% Confidence interval</th>
<th>(P)</th>
<th>Population attributable risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.20</td>
<td>1.73–15.61</td>
<td>0.0033</td>
<td>6.62</td>
<td>1.86–23.61</td>
<td>0.0036</td>
<td>0.18 (0.02–0.33)</td>
</tr>
</tbody>
</table>

ART is not enough to treat asymptomatic antigenaemia

ART-eligible patients n=707

CrAg-negative n=661

CrAg-positive* n=46

No prior CM n=25

Prior CM n=21

Patients ONLY received ART

No patients developed subsequent CM

Developed subsequent CM n=7 (28%)

*All CrAg-positive patients were asymptomatic

Fluconazole is associated with improved survival

Survival in Persons with Asymptomatic Cryptococcal Antigenemia (CRAG+)

Fluconazole
200 mg to 400 mg daily for 2-4 weeks

Fluconazole use P=.002
CD4 count P=.029

High-dose fluconazole decreases time to CSF sterilisation

Cryptococcal antigen screening when CD4 <100

Initiate ART
No fluconazole

POSITIVE

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

Symptomatic
Start Fluconazole 800 mg daily and refer immediately for lumbar puncture

Asymptomatic§

Lumbar puncture (+) → Amphotericin B plus Fluconazole 800 mg daily for 2 weeks in hospital

Lumbar puncture (-) → Fluconazole 800 mg daily for 2 weeks as outpatient

Start ART after 2 weeks of antifungal therapy

Start ART after 4 weeks of antifungal therapy

Outpatient treatment with Fluconazole 400 mg daily for 2 months, then 200 mg daily until CD4+ T-lymphocyte count >200 cells/µl for at least 6 months on ART (total – at least 1 year)

NEGATIVE

*Patient is symptomatic for meningitis if they have any of the following:
1. Headache
2. Confusion

†Other special situations include:
- Patients on tuberculosis medications
- Patients with previous history of cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease

§A lumbar puncture may be considered if available.
CASE

- Patient started on fluconazole 800 mg daily for 2 weeks
- What about drug interactions?

But no need for dose adjustment
CASE

• Patient called the clinic two days later complaining of nausea and vomiting after taking the fluconazole and TB medications together

• Patient asked to return to clinic
  – No clinical symptoms or signs of hepatotoxicity so ALT not checked
  – Advised to divide the dose of fluconazole to 400 mg two times per day and to take the fluconazole separately from the TB medications

• Tolerated the medications better
Case discussion points

• Many patients with CD4 counts less than 100 will have TB and cryptococcal disease

• Both fluconazole and TB medications are potentially hepatotoxic →
  – check for symptoms and signs of liver toxicity (abdominal pain, nausea/vomiting or jaundice) and measure ALT if concerned
  – Preferably start an efavirenz-based ART regimen

• Fluconazole can cause nausea/gastrointestinal problems as can TB medications → split the fluconazole dose to two times per day and if severe nausea occurs, give an anti-emetic 30 minutes before
Cryptococcal antigen screening when CD4 <100

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

Initiate ART
No fluconazole

*Patient is symptomatic for meningitis if they have any of the following:
1. Headache
2. Confusion

†Other special situations include:
- Patients on tuberculosis medications
- Patients with previous history of cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease

§§ A lumbar puncture may be considered if available.

Symptomatic
- Start Fluconazole 800 mg daily and refer immediately for lumbar puncture

Asymptomatic§

Lumbar puncture (+)  
Lumbar puncture (-)

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

Fluconazole 800 mg daily for 2 weeks as outpatient

Start ART after 4 weeks of antifungal therapy

Start ART after 2 weeks of antifungal therapy

Outpatient treatment with Fluconazole 400 mg daily for 2 months, then 200 mg daily until CD4+ T-lymphocyte count >200 cells/µl for at least 6 months on ART (total – at least 1 year)
CASE

- Started on first-line ART approximately 3 weeks after fluconazole started
  - Tenofovir
  - Lamivudine
  - Efavirenz

- Issues to consider
  - Three co-morbid infections
  - Pill burden
  - Child-bearing age

Good counselling
Integration with routine HIV and TB care
Summary

- Cryptococcal screening is currently being implemented in at least two provinces
  - Potential to shift diagnosis to PHC rather than hospital setting
  - This algorithm will be used in Phase 1 sites (GA/FS)
  - Updated Society guidelines for cryptococcal meningitis and asymptomatic antigenaemia will be published in mid-2013

- Challenges
  - Tracing CrAg-positive patients
  - Managing multiple conditions simultaneously
  - Integration of screening into TB and ART programmes

- More studies are required to answer several key questions around the management of patients with asymptomatic antigenaemia
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