Cryptococcal Disease Guideline Update

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23 July 2020

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service
The 2019 SA HIV CS guideline can be accessed at https://sahivsoc.org/SubHeader?slug=sahcs-guidelines
Case

- 43-year-old man
- Seen at an urban hospital’s HIV outpatient clinic
- Diagnosed with advanced HIV in late 2019 and started first-line ART then...
- Interrupted treatment in March 2020 during lockdown
- Now – looks clinically well and is keen to restart ART

What would you do?

1. Restart ART on the same day
2. Examine him, order some blood tests and ask the patient to return in a week
3. Berate him for interrupting treatment
4. Refer him for adherence counselling
5. Something else
Ongoing high burden of advanced HIV disease in SA
Consolidated recommendations for AHD
What is an advanced disease package?

Definition of advanced HIV disease
For adults and adolescents, and children older than five years, advanced HIV disease is defined as CD4 cell count <200 cells/mm³ or WHO stage 3 or 4 event.
All children younger than five years old with HIV are considered as having advanced HIV disease.

Recommendation
A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease.
(Strong recommendation, moderate-quality evidence)
Table 1: Components of package of care interventions for advanced HIV disease

<table>
<thead>
<tr>
<th>Areas for the package</th>
<th>Intervention</th>
<th>CD4 cell count</th>
<th>Adults and adolescents</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening and diagnosis</td>
<td>Sputum Xpert MTB/RIF as first test for TB diagnosis in symptomatic patients</td>
<td>any</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Urine LF-LAM for TB diagnosis in patients with symptoms and signs of TB</td>
<td>≤100 cells/mm³ or at any CD4 cell count value if seriously ill</td>
<td>yes</td>
<td>yes*</td>
</tr>
<tr>
<td></td>
<td>Cryptococcal antigen (CrAg) screening</td>
<td>≤ 100 cells/mm³ *</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Prophylaxis and pre-emptive treatment</td>
<td>Co-trimoxazole prophylaxis&lt;sup&gt;1&lt;/sup&gt;</td>
<td>≤350 cells/mm³ or WHO clinical stage 3 or 4 event. Any CD4 cell count value in settings with high prevalence of malaria and/or severe bacterial infections</td>
<td>yes</td>
<td>yes**</td>
</tr>
<tr>
<td></td>
<td>TB preventive treatment&lt;sup&gt;2&lt;/sup&gt;</td>
<td>any</td>
<td>yes</td>
<td>yes*</td>
</tr>
<tr>
<td></td>
<td>Fluconazole pre-emptive therapy for CrAg-positive patients without evidence of meningitis</td>
<td>&lt; 100 cells/mm³</td>
<td>yes</td>
<td>Not applicable (Screening not advised)</td>
</tr>
<tr>
<td></td>
<td>Rapid ART initiation</td>
<td>any</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>ART initiation</td>
<td>Defer ART initiation if clinical signs and symptoms are suggestive of TB or cryptococcal meningitis</td>
<td>any</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Adapted adherence support</td>
<td>Tailored counselling to ensure optimal adherence to advance disease care package, including home visits if feasible</td>
<td>&lt; 200 cells/mm³</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

*updated to <200 in 2018 WHO guideline
South Africa was first to implement a national CrAg screening programme in late 2016.
South Africa uses a laboratory-based reflex screening model

**STEP 1**
- Initial blood draw

**STEP 2**
- Baseline CD4
- CrAg RDT
- If CD4 < 100

**STEP 3**
- Pre-emptive treatment

**Initial Visit**
- Lab CD4 + CrAg Testing

**First Follow-up Visit**
Careful initial assessment of patient

• No TB or meningitis symptoms
• Mild oral candidiasis (angular cheilitis)
• Assessed as clinical stage 2

• Referred for adherence counselling and restarted ART on the same day: TDF + 3TC + DTG (TLD)
• Ordered baseline bloods including a CD4 count
The Enduring Challenge of Advanced HIV Infection

- In the REALITY trial, almost half the patients with a CD4+ count of <100 cells/mm³ (the cut-off value for trial participation) had mild or no symptoms (i.e. WHO clinical stage 1 or 2 disease)
- Highlights the limits of relying on clinical assessment alone to identify HIV-positive patients at high risk for severe disease and death
- Reinforces the importance of maintaining the capacity to measure CD4+ cells
- If VL testing is available, CD4+ count is no longer required to determine eligibility for ART or to track the response to treatment...
- Yet a baseline CD4+ count is essential for assessing the risk of severe disease
  - both in patients who newly present for care and
  - in those who return for care after a period of treatment interruption

Ford N and Doherty M. N Engl J Med 2017
Follow-up assessment of patient

• 1 week later:
  – CD4 count 89 cells/µl*
  – Reflex blood CrAg test positive

*Note – you have to specifically order a CrAg screening test if the patient’s CD4 count is 100-200

CrAg screening is not specifically recommended among children aged <10 years
What are your next steps?
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+ 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

What’s new in the SAHCS guideline?

• CrAg screening threshold is now <200 cells/µL (not <100 cells/µL), regardless of ART-naïve or -experienced

<table>
<thead>
<tr>
<th>CD4</th>
<th>CrAg prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 100</td>
<td>6.5% (95% CI. 5.7%-7.3%)</td>
</tr>
<tr>
<td>101-200</td>
<td>2.0% (95% CI. 1.2-2.7%)</td>
</tr>
</tbody>
</table>

Ford N et al. CID. 2018;66(52):5152-9

<table>
<thead>
<tr>
<th>CD4</th>
<th>Mortality rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 100</td>
<td>0.75 (95% CI. 0.58-0.95)</td>
</tr>
<tr>
<td>101-200</td>
<td>0.56 (95% CI. 0.32-0.97)</td>
</tr>
</tbody>
</table>


• However, the NDOH recommendation has **not** changed as yet → screening threshold of <100 cells/µL
What’s new in the SAHCS guideline?

• Recommended approach is by reflex (automated) lab screening and not clinician-initiated screening
What’s new in the SAHCS guideline?

• An LP is recommended for ALL patients with a new positive blood CrAg test regardless of symptoms (provided that there is no contraindication to doing a LP)

Why? 1 in 3 patients with a blood CrAg+ test have subclinical cryptococcal meningitis


Figure 3. Blood cryptococcal antigen (CrAg) titers in asymptomatic CrAg positive patients (n = 37) (Upper), CrAg positive patients with headache only (n = 29) (lower), with or without concurrent cryptococcal meningitis. CSF, cerebrospinal fluid; NPV, negative predictive value. Adapted from Figure 2A and 2B in Wake et al (Wake et al. 2018).
Semi-quantitative CrAg assay

Control line should always be present

- **T2** line disappears with a “stronger” reaction
- **T1** line appears with a “stronger” reaction, then disappears at 5+

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>1+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>2+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>4+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
A blood CrAg titre >160 may indicate a high risk of CM and mortality in asymptomatic CrAg+ patients. Particularly among those who decline LP, monitor carefully for signs/symptoms of CM.

CrAg+ patients, esp. those with high blood titres, may need “enhanced antifungal treatment” – this research question is under investigation by the ACACIA and EFFECT trials.
How to manage a blood CrAg+ result after recent ART initiation
Risk of CM IRIS

Risk of HIV disease progression and drug resistance*

*MORTALITY

Clinical equipoise

*Though lower risk with dolutegravir
How to manage a blood CrAg+ result after recent ART initiation

Initiation of ART in the 4 weeks prior to a CrAg+ result

Blood CrAg+ result obtained

Refer for immediate LP

CSF CrAg-

Safely continue ART
Start fluconazole pre-emptive treatment

CSF CrAg+ (new CM diagnosis)

Treat CM

Continue or stop ART?

What to do when LP is contraindicated?

• If focal neurological features are present, perform CT of the brain first
  – CT findings: features of gross generalised brain swelling or significant hemispherical shift related to a mass lesion → LP should not be performed
  – If these features are not present, and there are no NON-neurological contraindications for performing LP → LP can be performed (use clinical judgement)
  – Note: normal CT brain does not exclude presence of raised ICP so clinical discretion is needed

• If blood CrAg test is positive with signs of meningitis, treat for cryptococcal meningitis

• Standard blood cultures should be performed
  – Antibiotics should be given to the patient while the patient waits for a CT scan, or until causative organism is found
  – Note: consider other causes of meningitis such as TB
Cryptococcus is the most common cause of meningitis

Britz E, et al. PLOS One 2016
Test CSF to confirm diagnosis

• Perform a lumbar puncture and submit CSF to the laboratory for investigation

• Which diagnostic tests should be requested?
Measure opening pressure

- CSF opening pressure = 30 cm H$_2$O
- *How should pressure be measured? What is normal?*
Raised intracranial pressure (ICP)

• Up to 75% of patients with CM
• Due to CSF outflow obstruction
• May be present at diagnosis or develop on treatment
• Symptoms and signs:
  – Headache
  – Vomiting
  – Reduced level of consciousness
  – Ophthalmoplegia
  – Visual loss or disturbance
  – New-onset hypertension (as part of Cushing’s triad)
How should raised ICP be managed?

• If opening pressure is >25 cm H₂O, remove 10-30 ml CSF to reduce pressure by at least 50% or to <20 cm H₂O

• Repeat LP whenever there are symptoms or signs of RICP

• **Daily therapeutic LPs** may be required
Therapeutic LP

• If no manometer:
  – Drop counting: ≥40 drops in 1 min using a 22-gauge spinal needle
  – Makeshift manometers from IV line sets (underestimates pressures)
  – “Eyeball test”: powerful squirt of CSF

• Where a manometer is not available and there are clinical symptoms or signs of raised intracranial pressure, advise 20-30 ml of CSF is removed
Case

• How should the patient be treated?
  – Which antifungal agents?
  – For how long?
Antifungal treatment

CrAg screen-and-treat algorithm

Cryptococcal antigen screening when CD4+ T-lymphocyte count <200 cells/μL regardless if ART-naive or -experienced

Blood CrAg-negative

Blood CrAg-positive

Lumbar puncture

CSF positive for any cryptococcal test regardless of symptoms

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

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

Initiate ART
No antifungal treatment

Previously-unavailable therapeutic options

<table>
<thead>
<tr>
<th>Anti-yeast drugs</th>
<th>Liposomal Amphotericin B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flucytosine (5-FC)</strong>&lt;br&gt; <em>Ancotil (Mylan)</em></td>
<td><strong>Liposomal amphotericin B</strong>&lt;br&gt; <em>Ambisome (Gilead)</em></td>
</tr>
<tr>
<td>More effective partner drug than fluconazole</td>
<td>Compared to AmB deoxycholate: similar efficacy and less nephrotoxic</td>
</tr>
<tr>
<td>Half-life prolonged in patients with impaired renal function.</td>
<td>Registered in South Africa but expensive ($16.25 per 50 mg vial)</td>
</tr>
<tr>
<td>Category C drug in pregnancy; no data in breastfeeding</td>
<td><strong>NOTE - DIFFERENT DAILY DOSE TO AMPHOTERICIN B DEOXYCHOLATE</strong></td>
</tr>
<tr>
<td>Not yet registered but available through Section 21 application</td>
<td></td>
</tr>
</tbody>
</table>
Regulatory Status

Mylan has conducted the following regulatory activities in a few short months:

- December 2019 – Filed 250mg and 500mg strengths with SAHPRA, South Africa
- January 2020 – Filed 250mg and 500mg strengths with WHO Pre-Qualification
- February 2020 – Received approval for the 500mg strength by FHI360. This review makes Mylan’s 5FC eligible for Global Fund and USAID procurement

Pricing

An ex-works price of $75/pack (100 tablets) is being offered to all low-income and lower middle-income countries, as defined by the World Bank. This pricing is contingent on MoQs and minimum lead times being met.

Example: A 60 kg adult needs 12 pills a day for 7 days = 84 pills @ $0.75/pill = $63 = R1043

Source: Mylan 5-FC fact sheet
The South African CM access programme

• Established in 2018 by SAHCS and MSF at 15 facilities with approval from NDOH
  – Section 21 approval
  – Procurement and distribution of 5-FC (and limited liposomal AmB) stock by MSF
  – >400 patients treated with very good clinical outcomes

• In 2020, the national AHD task team decided to expand the access programme to 50 facilities
  – National Section 21 approval obtained
  – High-burden facilities prioritized
  – Virtual training and mentoring planned for expansion facilities

UNITAID CHAI AHD Newsletter July 2020
Case

• But
  – Baseline serum creatinine = 250 µmol/l

• Are these antifungal drugs contraindicated or should dose adjustments be made?
Dose adjustments

Example – age 43 years, weight 50 kg, serum creatinine 250 µmol/l

MDRD GFR equation (https://www.mdcalc.com/mdrd-gfr-equation) = 31.7 ml/min/1.73 m²

Note - no dose adjustments with fluconazole and rifampicin co-administration
# Recommended regimens with baseline renal impairment

Calculate creatinine clearance (GFR)

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50 mL/min</td>
<td><strong>LAmB available</strong></td>
<td><strong>LAmB available</strong></td>
</tr>
<tr>
<td></td>
<td>LAmB 3-4 mg/kg/day + 5FC</td>
<td>LAmB 3-4 mg/kg/day + 5FC</td>
</tr>
<tr>
<td></td>
<td><strong>LAmB unavailable</strong></td>
<td><strong>LAmB unavailable</strong></td>
</tr>
<tr>
<td></td>
<td>AmBd 1 mg/kg/day + 5FC</td>
<td>Fluconazole + 5FC</td>
</tr>
<tr>
<td>&lt;30 mL/min</td>
<td><strong>LAmB and 5FC unavailable</strong></td>
<td>AmBd 0.7 mg/kg stat and then on alternate days if CrCL static + fluconazole</td>
</tr>
</tbody>
</table>

Note - Fluconazole and 5FC should be dose adjusted as per previous slide
Liposomal AmB (AmBisome)

• Ensure no confusion between AmB deoxycholate (Fungizone) and liposomal AmB (AmBisome) because **different doses!!!**
Liposomal AmB (AmBisome)

• Recommended regimen for CM: **3-4 mg/kg/day IV**

• Reconstitution and preparation for infusion
  – Use sterile water for injection to reconstitute each 50 mg vial
  – 12 ml water per AmBisome 50 mg vial yields 4.16 mg/ml amphotericin B concentrate
  – Dilute 1 part amphotericin B concentrate in 19 parts 5% dextrose solution = 0.21 mg/ml
  – DO NOT use normal saline

• Administer by IV infusion over a 2-hour period

• The bag does not need to be covered
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Number of 50 mg vials</th>
<th>Total daily dose of AmBisome (mg)</th>
<th>Approximate daily dose/weight (mg/kg)</th>
<th>Volume of reconstituted AmBisome (ml) at 4 mg/ml</th>
<th>Additional dextrose (ml) to create a 1-litre total infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>3</td>
<td>150</td>
<td>3.8</td>
<td>37.5</td>
<td>962.5</td>
</tr>
<tr>
<td>41-45</td>
<td>3</td>
<td>150</td>
<td>3.3</td>
<td>37.5</td>
<td>962.5</td>
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<td>46-50</td>
<td>4</td>
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<td>4.0</td>
<td>50</td>
<td>950</td>
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<td>51-55</td>
<td>4</td>
<td>200</td>
<td>3.6</td>
<td>50</td>
<td>950</td>
</tr>
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<td>56-60</td>
<td>4</td>
<td>200</td>
<td>3.3</td>
<td>50</td>
<td>950</td>
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<td>61-65</td>
<td>5</td>
<td>250</td>
<td>3.8</td>
<td>62.5</td>
<td>937.5</td>
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<td>66-70</td>
<td>5</td>
<td>250</td>
<td>3.6</td>
<td>62.5</td>
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</tr>
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<td>71-75</td>
<td>6</td>
<td>300</td>
<td>4.0</td>
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<td>81-85</td>
<td>6</td>
<td>300</td>
<td>3.5</td>
<td>75</td>
<td>925</td>
</tr>
</tbody>
</table>
Case

• Induction-phase treatment *with renal adjustment*:
  – Wk. 1: amphotericin B 1 mg/kg per day + 5-FC 25 mg/kg BD
  – Wk. 2: fluconazole 600 mg per day

• How should 5-FC be administered?
How to administer 5-FC?

• Dosing for the induction stage is 100 mg/kg/day in 4 divided doses (i.e. every 6 hours) PO

• Nausea and vomiting may occur; this can be prevented by giving 5-FC pills individually during a 15-minute window

• 5-FC can cause bone marrow depression with neutropenia and thrombocytopenia
5-FC

**TABLE 5: Flucytosine dosing in children and adults with normal renal function.**

<table>
<thead>
<tr>
<th>Lower weight limit (kg)</th>
<th>Upper weight limit (kg)</th>
<th>Number of pills</th>
<th>Total dose (mg)</th>
<th>Daily dose for lower weight limit (mg/kg)</th>
<th>Daily dose for upper weight limit (mg/kg)</th>
<th>Dose 1†</th>
<th>Dose 2†</th>
<th>Dose 3†</th>
<th>Dose 4†</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>24</td>
<td>4</td>
<td>2000</td>
<td>100.00</td>
<td>83.33</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>25</td>
<td>29</td>
<td>5</td>
<td>2500</td>
<td>100.00</td>
<td>86.21</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>34</td>
<td>6</td>
<td>3000</td>
<td>100.00</td>
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<td>8</td>
<td>4000</td>
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<td>45</td>
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<td>5000</td>
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<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>55</td>
<td>59</td>
<td>11</td>
<td>5500</td>
<td>100.00</td>
<td>93.22</td>
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<td>3</td>
<td>3</td>
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<td>64</td>
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<td>6000</td>
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<td>93.75</td>
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</tr>
<tr>
<td>65</td>
<td>69</td>
<td>13</td>
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<td>100.00</td>
<td>94.20</td>
<td>4</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>70</td>
<td>74</td>
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<td>7000</td>
<td>100.00</td>
<td>94.59</td>
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<td>79</td>
<td>15</td>
<td>7500</td>
<td>100.00</td>
<td>94.94</td>
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<td>4</td>
<td>3</td>
</tr>
<tr>
<td>80</td>
<td>84</td>
<td>16</td>
<td>8000</td>
<td>100.00</td>
<td>95.24</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

†, Number of 500 mg pills per dose.
Case

• Induction-phase treatment with renal adjustment:
  – Wk. 1: amphotericin B 1 mg/kg per day + 5-FC 25 mg/kg BD
  – Wk. 2: fluconazole 600 mg per day

• How should amphotericin B deoxycholate be administered?
## 10-step checklist for AmBd

<table>
<thead>
<tr>
<th>Item</th>
<th>Check if done</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has correct daily dose been prescribed based on body weight (1 mg/kg/day)?</td>
<td>✔</td>
<td>If yes, proceed</td>
</tr>
<tr>
<td>Have lab tests been checked?</td>
<td>✔</td>
<td>If yes, proceed</td>
</tr>
<tr>
<td>Is peripheral IV line correctly inserted?</td>
<td>✔</td>
<td>If yes, proceed</td>
</tr>
<tr>
<td>Is there any sign of phlebitis?</td>
<td>✔</td>
<td>If yes, stop and replace line</td>
</tr>
<tr>
<td>Are other meds being administered?</td>
<td>✔</td>
<td>If yes, stop until finished</td>
</tr>
<tr>
<td>Has 1 litre normal saline with 20 mmol KCl been infused over 2 hours?</td>
<td>✔</td>
<td>If yes, proceed</td>
</tr>
<tr>
<td>Has AmB powder been reconstituted in 50 mg vial in 10 ml sterile water, has the correct dose been injected into 1 litre 5% dextrose water and has the bag been shaken to mix?</td>
<td>✔</td>
<td>If yes, proceed</td>
</tr>
<tr>
<td>Has AmB been infused over 4 hours minimum?</td>
<td>✔</td>
<td>If no, watch for arrhythmias</td>
</tr>
<tr>
<td>Has line been flushed with normal saline once infusion completed?</td>
<td>✔</td>
<td>If yes, proceed</td>
</tr>
<tr>
<td>Has bag containing AmB been removed?</td>
<td>✔</td>
<td>If yes, end of procedure</td>
</tr>
</tbody>
</table>
Amphotericin B deoxycholate is toxic
Monitoring lab tests for AmBd and 5-FC

<table>
<thead>
<tr>
<th>Induction regimen</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Laboratory monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>Amphotericin B deoxycholate + 5-FC</td>
<td>Fluconazole</td>
<td>Day 0: Full blood count and differential, creatinine clearance, potassium, magnesium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 3: Full blood count (only if low baseline haemoglobin), creatinine clearance, potassium, magnesium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 7: Full blood count and differential, creatinine clearance, potassium, magnesium</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Fluconazole + 5-FC</td>
<td>Fluconazole + 5-FC</td>
<td>Day 0: Full blood count and differential, creatinine clearance</td>
</tr>
<tr>
<td>unavailable</td>
<td></td>
<td></td>
<td>Day 3: Full blood count (if low baseline haemoglobin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 7: Full blood count and differential</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 10: Full blood count and differential (if any abnormalities previously)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 14: Full blood count and differential, creatinine clearance can be done more frequently if baseline is abnormal</td>
</tr>
<tr>
<td>S-FC is unavailable</td>
<td>Amphotericin B deoxycholate + fluconazole</td>
<td>Amphotericin B deoxycholate + fluconazole</td>
<td>Day 0: Creatinine clearance, potassium, magnesium, full blood count</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 3: Creatinine clearance, potassium, magnesium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 7: Creatinine clearance, potassium, magnesium, full blood count</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 10: Creatinine clearance, potassium, magnesium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 14: Creatinine clearance, potassium, magnesium, full blood count</td>
</tr>
</tbody>
</table>

Case

• Resolution of symptoms and signs
  – No need for CSF analysis at the end of induction treatment for a first episode*
• Discharged after 14 days of treatment

• When should ART ideally be started after a CM diagnosis?

*Though this is recommended for patients with multiple CSF culture+ relapse episodes
When to start ART after a diagnosis of CM?
Case

• Readmitted to hospital several months later with severe headache

• How should a subsequent episode of CM be diagnosed and managed?
Careful clinical assessment

• Assess patient clinically for symptoms and signs of meningitis

• Adherence to fluconazole and ART regimens
  – Self-reported
  – Pharmacy refill records

• Is intracranial pressure raised?

• Timing of ART (could this be IRIS?)
Diagnosis of a subsequent episode

- Perform LP (with opening pressure) and submit CSF for culture
  - Laboratory should be asked to incubate plates for at least **14 days** to detect slow growth
  - Rapid tests (CrAg and India ink stains) are *not* useful for diagnosis

- Also exclude TBM (CSF Xpert Ultra)
Dead or alive?
Is this IRIS?

• Affects 20% of patients with CM who start ART
• Occurs six weeks after ART initiation, on average, but delayed cases have occurred >1 year after ART initiation
• Usually recurrence of meningitis with raised ICP
  – Typically CSF culture is negative but may still be positive if recent induction treatment
  – Higher CSF white cell counts (compared to initial culture+ episode)
• Less commonly, lymphadenitis and cryptococcomas
Algorithm for suspected paradoxical IRIS

Perform LP to exclude culture-positive relapse

Mild symptoms
- Perform therapeutic LP if RICP
- Analgesia
- Increase fluconazole to 1200 mg daily

CSF culture negative after 14 days
- Decrease dose back to 800 mg or 200 mg daily

Severe symptoms
- Perform therapeutic LP if RICP
- Analgesia
- CT head
- AmB + 5-FC (or AmB + fluconazole 1200 mg daily)
- Corticosteroids* if life-threatening or no response

CSF culture negative after 7 days
- Change back to fluconazole 800 mg or 200 mg daily

*Preferred if CSF culture is known NEGATIVE and other aetiologies excluded (TB, viral)
When should fluconazole resistance be considered?

- At least 1 relapse episode and other causes excluded

- If fluconazole MICs are elevated, consider an alternative maintenance regimen:
  - Higher-dose fluconazole
  - Other triazole agents
  - Weekly amphotericin B
How to manage a blood CrAg+ result in a pregnant woman

Blood CrAg+ result obtained in pregnancy (2% in a Ugandan screening cohort)

Refer for immediate LP

CSF CrAg- or declines LP

Counsel that benefits of fluconazole outweigh risks

If in first trimester, treat with fluconazole 200 mg daily and then high-resolution ultrasound scan <20 wks. gestation to look for abnormalities

CSF CrAg+ (new CM diagnosis)

Treat CM using standard treatment

Key differences between SAHCS and NDOH guidelines

<table>
<thead>
<tr>
<th></th>
<th>SAHCS 2019</th>
<th>NDOH 2019 (ART and STG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 threshold for CrAg screening (cells/µl)</td>
<td>• &lt;200 • Reflex preferred where possible</td>
<td>• &lt;100 by reflex testing</td>
</tr>
<tr>
<td>ART initiation timing if blood CrAg+</td>
<td>• Immediate if CSF CrAg- • Defer until completed 2 weeks of fluconazole treatment if LP declined</td>
<td>• Defer until completed 2 weeks of fluconazole treatment</td>
</tr>
<tr>
<td>First-line CM induction regimen</td>
<td>• 1 wk. AmB + 5-FC, then 1 wk. fluconazole</td>
<td>• 2 wks. AmB + fluconazole</td>
</tr>
<tr>
<td>Alternative CM induction regimens</td>
<td>• 2 wks. fluconazole + 5-FC • 2 wks. AmB + fluconazole • Consider liposomal AmB as an option for renal dysfunction</td>
<td>• No alternative regimens except at 5-FC access sites</td>
</tr>
</tbody>
</table>

Acknowledgements

- National AHD task team
- SA HIV Clinicians Society
- DREAMM trial consortium for sharing some teaching aids
- Ambition-CM trial consortium for sharing some teaching aids