Cryptococcal meningitis management

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SSISA / Newlands / Cape Town
8th February 2020
Optimize diagnosis and management of cryptococcal meningitis
Burden of Cryptococcal Meningitis (CM)

- Globally, CM responsible for 15% of AIDS-related deaths
- Annual global deaths estimated at 181,100
- 135,900 deaths in sub-Saharan Africa.
- 6,636 cases of se detected by GERMS in 2017 in SA
- (60%) of those were on ART at Dx or at some time in past

Indications for CM treatment

- CrAg+ with symptoms of meningitis
- Detection in CSF, regardless of symptoms
  - CSF India ink+ or
  - CSF CrAg+ or
  - CSF culture+
- Recurrent symptomatic episode with CSF culture+
- Culture + ve from any specimen (disseminated cryptococcosis)
## Previous recommended treatment regimen

<table>
<thead>
<tr>
<th>INDUCTION</th>
<th>CONSOLIDATION</th>
<th>MAINTENANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks Fluconazole (<strong>800mg daily</strong>) + Amphotericin B (1mg/kg/day)</td>
<td>8 weeks Fluconazole (800mg daily) 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily</td>
<td>Fluconazole (200 mg/day). For at least 12 months and until a single CD4 count is &gt;200 cells/µl and the HIV viral load is suppressed</td>
</tr>
<tr>
<td>Slow infusion, In dextrose 5% over 4 hours for 14 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Standard Treatment Guidelines and EML for South Africa: Hospital level, Adults. 2015
### Previous SA HIV Clinician’s Society & Current Public sector recommended treatment regimen

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>2 weeks Fluconazole (1200mg daily) + Amphotericin B (1mg/kg/day)</td>
<td>8 weeks Fluconazole (800mg daily) 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily</td>
<td>Fluconazole (200 mg/day). For at least 12 months and until a single CD4 count is &gt;200 cells/µl and the HIV viral load is suppressed</td>
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</table>

Southern African HIV Clinicians’ Society Guideline for the Prevention, Diagnosis and Management of Cryptococcal Disease among HIV-infected Persons: prior to 2019
Previously unavailable therapeutic options

<table>
<thead>
<tr>
<th>Flucytosine (5FC) Ancotil (Mylan)</th>
<th>Liposomal Amphotericin B Ambisome (Gilead)</th>
</tr>
</thead>
<tbody>
<tr>
<td>More effective partner drug that flucytosine</td>
<td>Compared to amphotericin B deoxycholate:</td>
</tr>
<tr>
<td>Half-life prolonged in patients with impaired renal function.</td>
<td>Similar efficacy and Less nephrotoxic</td>
</tr>
<tr>
<td>category C drug in pregnancy no data in breastfeeding</td>
<td>Registered in South Africa but expensive</td>
</tr>
<tr>
<td>Not yet registered but available on Section 21</td>
<td></td>
</tr>
</tbody>
</table>
5-FC superior to fluconazole as a partner to Amp B: 38% reduced hazards of death at 10 weeks

1-week AmB+5-FC associated with lowest 10-week mortality

New Southern African clinicians society guidelines recommend flucytosine as companion drug in regimen of choice

Guidance also includes use of Liposomal Amphotericin B in renal impairment

New guidelines have been released end of 2019
Best available treatment – using flucytosine

<table>
<thead>
<tr>
<th>INDUCTION</th>
<th>CONSOLIDATION</th>
<th>MAINTENANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week flucytosine (100 mg/kg/day in 4 divided doses + Amphotericin B (1mg/kg/day). followed by 1 week of fluconazole (1200 mg daily for adults; 12 mg/kg/day for children and adolescents to a maximum of 800 mg daily</td>
<td>8 weeks Fluconazole (800mg daily) 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily</td>
<td>Fluconazole (200 mg/day). For at least 12 months and until a single CD4 count is &gt;200 cells/µl and the HIV viral load is suppressed</td>
</tr>
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</table>

Southern African HIV Clinicians’ Society Guideline for the Prevention, Diagnosis and Management of Cryptococcal Disease among HIV-infected Persons: 2019 update
## Alternative induction regimen options

<table>
<thead>
<tr>
<th>Alternative Regimen Options</th>
<th>Induction Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Amp B unavailable, all oral regimen</td>
<td>2 weeks of fluconazole (1200 mg daily for adults; 12 mg/kg/day for children and adolescents) and flucytosine (100 mg/kg/day divided into four doses per day)</td>
</tr>
<tr>
<td>Flucytosine unavailable. (Current standard of care)</td>
<td>2 weeks of amphotericin B deoxycholate (1 mg/kg/day) and fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents)</td>
</tr>
<tr>
<td>Renal dysfunction &amp; Liposomal Amphotericin B available</td>
<td>1 week of liposomal amphotericin B (3-4 mg/kg/day) and flucytosine (100 mg/kg/day divided into four doses per day), followed by 1 week of fluconazole (both fluconazole and flucytosine doses adjusted for renal impairment)</td>
</tr>
</tbody>
</table>

*Southern African HIV Clinicians’ Society Guideline for the Prevention, Diagnosis and Management of Cryptococcal Disease among HIV-infected Persons: 2019 update*
1. Consider special situations: prior cryptococcal meningitis; pregnancy or breastfeeding mothers; clinical liver disease; initiation of ART prior to obtaining blood CrAg+ result
2. If symptoms of meningitis are present but CSF CrAg test is negative/LP declined, consider alternative diagnoses (such as TB meningitis) and/or treat as cryptococcal meningitis
3. A blood CrAg titre > 160 may indicate a high risk of CM and mortality in asymptomatic CrAg-positive patients. Monitor carefully for signs/symptoms of CM and consider empirical CM treatment
4. There is no evidence for appropriate ART timing in these groups

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

Blood CrAg-positive

- Lumbar puncture

- CSF positive for any cryptococcal test for 1st episode/culture for relapse
  - 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

Blood CrAg-negative

- Lumbar puncture

- CSF negative for CrAg\(^\text{1,4}\)
  - No consent for lumbar puncture
  - Asymptomatic\(^\text{1,4}\)
  - Symptoms of meningitis (headache and confusion)
  - Treat for CSF+ cryptococcal meningitis

- Initiate ART
  - No antifungal treatment screen for other OIs

Timing of ART

• The guideline recommends commencing ART 4 to 6 weeks after the diagnosis of CM. The guideline strongly advises that ART not be delayed beyond 6 weeks after diagnosis, and most experts advise that clinicians should aim to start exactly 4 weeks after diagnosis of CM.

• Among ART-naïve patients who are blood CrAg-positive on screening and have an LP that excludes CM, commence ART immediately.

• Among ART-naïve patients who are CrAg positive, symptom negative, but LP not possible, commence ART after 2 weeks of fluconazole.
For patients already on ART by time of CrAg result

• Immediate referral for LP and CSF analysis of anyone CrAg +ve initiating ART in last 4 weeks (or 6?)
  – If CSF negative continue ART and give fluconazole pre-emptive Tx.
  – No evidence on whether to stop ART if CSF positive – seek expert advice
# Laboratory Monitoring

<table>
<thead>
<tr>
<th>Test</th>
<th>Amp B + Fluconazole</th>
<th>Amp B &amp; 5FC</th>
<th>Amp B &amp; fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>Baseline &amp; weekly Hb</td>
<td>Baseline &amp; weekly Hb</td>
<td>Baseline &amp; weekly Hb</td>
</tr>
<tr>
<td>Creatinine &amp; Potassium</td>
<td>Baseline and twice weekly</td>
<td>Baseline and twice weekly</td>
<td>Baseline and twice weekly</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid balance</td>
<td>Monitor carefully throughout</td>
<td>Monitor carefully throughout</td>
<td>Monitor carefully throughout</td>
</tr>
<tr>
<td>Full blood count</td>
<td></td>
<td>Baseline FBC and differential count. Weekly FBC</td>
<td>Check levels if symptoms of hepatitis or jaundice develop</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Southern African HIV Clinicians’ Society Guideline for the Prevention, Diagnosis and Management of Cryptococcal Disease among HIV-infected Persons: 2019 update*
Safe administration of Amphotericin B

- Administer over 4 hrs to avoid arrythmias
- Renal toxicity more likely in 2nd week of Tx. (if using 2 week regimen). Monitor fluid input and output carefully
- Inject AmB dose into 1000ml bag of 5% Dextrose or 10% Dextrose (never N.Saline as drug will precipitate).
- Supplement potassium and magnesium
Fluid and electrolyte management helps avoid hypokalemia and renal failure when using Amp B

**Before treatment rehydrate**

- 1L N. Saline with KCl (20mmol) infused over 2 hrs, prior to AmB infusion.

**During treatment supplement potassium**

- 1200 mg potassium chloride orally twice daily equivalent to 16 mmol of oral potassium, e.g. 2 Slow-K 600 mg tablets twice daily, 8 mmol K⁺ per tablet

**During treatment supplement Magnesium**

- Up to 1500 mg magnesium chloride orally daily e.g. 2 Slow-Mag 535 mg tablets daily, 5.33 mmol Mg²⁺ per tablet or 2 Ultimag tablets daily, 660 mg Mg²⁺ with zinc oxide 6 mg

Southern African HIV Clinicians’ Society Guideline for the Prevention, Diagnosis and Management of Cryptococcal Disease among HIV-infected Persons: 2019 update
Safe Amp-B administration: administration

- Inject AmB dose into 1000ml bag of 5% Dextrose or 10% Dextrose (never N.Saline as drug will precipitate).
- Administer over 4 hours to avoid arrhythmias.
- Supplements: 1-2 8mEq KCL tablets twice daily, 2x 250mg
- Magnesium trisilicate twice daily.
- KCl can cause nausea in some patients
- Renal toxicity is more likely to develop in the second week of treatment in regimens where 2 weeks of amphotericin is used. Fluid input and output should be carefully monitored
Safe Amphotericin B (deoxycholate) administration: avoiding and managing infection at IV site

Chemical phlebitis is often complicated by infection at IV insertion site - can cause bacteraemia - Monitor daily for thrombophlebitis.

Flush IV lines with normal saline immediately after amphotericin B infusion is complete.

The empty bag should not be left attached to the intravenous line.

Remove IV if the patient develops a fever after the infusion or at the first sign of redness or discomfort at the insertion site.

If amphotericin B-induced rigors occur, the infusion length can be increased and/or acetaminophen / paracetamol (650-1000mg) PO/PR administered 30 minutes prior to AmB.

Febrile patients with a suspected insertion site infection should be appropriately investigated and managed.
Liposomal Amphotericin B (AmBisome) use

Indications
• If available consider if baseline creatinine clearance is <50 ml/min
• If creatinine clearance on Tx. drops on treatment to <50 ml/min

Dosage
• 1 week of liposomal amphotericin B (3-4 mg/kg/day) and flucytosine (100 mg/kg/day divided into four doses per day),
• Followed by 1 week of fluconazole
• Fluconazole and flucytosine dose-adjusted for creatinine clearance

Cautions
• Ensure no confusion between AmB deoxycholate (Fungizone) and liposomal AmB (AmBisome) because different doses!
• Other principles of safe Amp-B deoxycholate administration apply
Amphotericin B deoxycholate dose adjustment for renal failure

• Standard dose not contra-indicated with baseline renal function impairment.

• If creatinine doubles, omit 1 dose or increase pre-hydration to 1 litre 8 hourly.

• If creatinine remains elevated or rises, stop amphotericin B and use an alternative (see alternative regimens above)

• Amphotericin B is poorly dialysed; no dose adjustment or supplemental dose is necessary for those on dialysis
How to administer 5-FC

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

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

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

• 5-FC monitoring for HIV-associated CM is not routinely required
### Simplified 5-FC dosing schedule

<table>
<thead>
<tr>
<th>Weight of Patient</th>
<th>Quarterly 6 Hour Dosing (mg)</th>
<th>500mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 39 kg</td>
<td>500-1000-500-1000</td>
<td>1-2-1-2</td>
</tr>
<tr>
<td>40 - 49 kg</td>
<td>1000</td>
<td>2-2-2-2</td>
</tr>
<tr>
<td>50 - 59 kg</td>
<td>1000-1500-1000-1500</td>
<td>2-3-2-3</td>
</tr>
<tr>
<td>60 - 69 kg</td>
<td>1500</td>
<td>3-3-3-3</td>
</tr>
<tr>
<td>70 - 79 kg</td>
<td>1500-1200-1500-2000</td>
<td>3-4-3-4</td>
</tr>
</tbody>
</table>
Renal toxicity management for 5-FC

- Ensure adequate hydration

- If creatinine remains high or climbs despite increased hydration, then switch to a second-line induction regimen: 2 weeks of fluconazole + 5FC

- Avoid nephrotoxic drugs such as NSAIDs including ibuprofen and aminoglycosides

- Monitor electrolytes closely – acute renal failure can lead to life threatening hyperkalaemia
5-FC dose adjustment for renal impairment

- 5-FC may accumulate in patients with renal impairment owing to poor excretion
- The half life of 5-FC is prolonged in patients with renal insufficiency; the average half-life is 85 hours (versus 2.4-4.8 hours in patients with normal renal function)
- If creatinine clearance reduces to <50 ml/min, give same initial dose but reduce subsequent doses by 50%
- Intermittent haemodialysis: 25 mg/kg every 58-72hrs (administer after dialysis)

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Individual dose (mg/kg)</th>
<th>Dose Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40</td>
<td>25</td>
<td>6 hourly</td>
</tr>
<tr>
<td>20-40</td>
<td>25</td>
<td>12 hourly</td>
</tr>
<tr>
<td>10-19</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>&lt;10</td>
<td>25</td>
<td>48 hourly</td>
</tr>
</tbody>
</table>

Est. creatinine clearance =
(140 – age) * (weight in kg) / (72 * Cr in mg/dL)
[Multiply result by 0.85 for women]
Flucytosine is associated with bone marrow toxicity and resultant anaemia, neutropenia, and thrombocytopenia. But less common with a 1-week regimen. If a patient has a sustained grade 3 neutropenia (confirmed the following day), halve the dose of 5-FC. If grade 4 neutropenia (<400 cells/mm$^3$), or neutropenia-related complications develop, stop 5-FC immediately. Consider re-introduction of 5-FC if the neutrophil count the following day is grade 3 or better. If grade 3, re-introduce at half dose.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
<th>Neutrophil count (cells/mm$^3$)</th>
<th>Neutrophil count (cells/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>800 to 1000</td>
<td>0.8 to 1.0</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>600 to 799</td>
<td>0.6 to 0.799</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>400 to 599</td>
<td>0.4 to 0.599</td>
</tr>
<tr>
<td>4</td>
<td>Potentially life-threatening</td>
<td>&lt;400</td>
<td>&lt;0.4</td>
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# Severity grades for neutropenia

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<th>Neutrophil count (cells/mm³)</th>
<th>Neutrophil count (cells/L)</th>
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<td>&lt;400</td>
<td>&lt;0.4</td>
</tr>
</tbody>
</table>

DAIDS Table for Grading Severity of Adult Adverse Events v2.1 2017
**Safe administration of Fluconazole**

- Oral antifungal available in 50, 100, 150, or **200 mg** tablets.
- Used for the maintenance and consolidation phases of CM Tx.
  - 200mg tablet preferred to avoid high pill burden.
- Can also be taken as an oral suspension.
- Taken with or without food and taken at any time of day.
- Also used for vaginal candidiasis (thrush) & oropharyngeal candidiasis.
- If Hx. liver disease / evidence clinical liver disease careful monitoring
  - fluconazole may cause liver injury.
  - Consultation with a medical practitioner experienced in the care of HIV-seropositive patients is recommended.
Fluconazole dose adjustments with renal dysfunction

Pre-existing renal dysfunction

Can start AmB 1 mg/kg/day BUT monitor creatinine regularly

Creatinine doubles from baseline

Omit a dose and increase pre-hydration

Creatinine improves

Creatinine worsens or repeatedly rises

Creatinine clearance  | Fluconazole
---|---
Normal renal function | 1200 mg/day
10-50 ml/min | 600 mg/day
<10 ml/min | 400 mg/day

AmB 0.7 mg/kg/day alternate days

No dose adjustments with rifampicin

SAHCS Guideline 2013
Intracranial pressure measurement and therapeutic LP

• Results achieved in ACTA trial were in the context of settings where therapeutic LP used.
• The pressure should be measured using a manometer with the patient lying down and without excessive spinal flexion.
• Approximately 15% of patients with initially normal intracranial pressure will develop raised intracranial pressure during treatment; thus all patients should be monitored daily for headache or signs of raised intracranial pressure that should prompt an LP.
When to measure the ICP?

• At the time of the initial LP
• Repeat LP and measurement of ICP: persistent symptoms during induction therapy, especially if severe or worsening: especially if the baseline ICP was elevated
• If recurrent symptoms after initial improvement (suspect treatment failure)
Therapeutic LP

• If the opening pressure is raised (>25 cm H$_2$O), then 10-30 ml CSF should be drained (to normalise pressure to <20 cm H$_2$O or decrease the pressure by at least 50% - based on repeat measurement of closing pressure)

• Thereafter need dictated by recurrence of symptoms of raised ICP intracranial pressure

• Patients may require daily LPs. Where a manometer is not available and there are clinical symptoms or signs advise ≥ 20 ml of CSF is removed

• Therapeutic LP typically relieves symptoms if they were due to increased ICP
Therapeutic LP

• reduce the opening pressure to <20 cm CSF; in symptomatic patients with extremely high CSF pressures (eg, ≥30 cm CSF),
• goal is to reduce the ICP by 50 percent of the initial value.
• daily LPs until the patient is asymptomatic and the CSF pressure: normal and/or stable.
• recommendations are based on large data sets, smaller observational studies and anecdotal experience
Reference slides
LAmB has similar efficacy to AmBd

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. (%) of patients, by regimen</th>
<th>Treatment difference, % (95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L-AmB 3</td>
<td>L-AmB 6</td>
</tr>
<tr>
<td>Mycological success(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>35 (58.3)</td>
<td>36 (48)</td>
</tr>
<tr>
<td>Week 10</td>
<td>36 (60)</td>
<td>53 (70.7)</td>
</tr>
<tr>
<td>Therapeutic success: c, week 10</td>
<td>27 (67.5)</td>
<td>42 (73.7)</td>
</tr>
<tr>
<td>Clinical success</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2(^d)</td>
<td>48 (65.8)</td>
<td>64 (75.3)</td>
</tr>
<tr>
<td>Week 10(^e)</td>
<td>31 (70.5)</td>
<td>43 (72.9)</td>
</tr>
<tr>
<td>Survival: f, week 10</td>
<td>74 (86)</td>
<td>85 (90.4)</td>
</tr>
</tbody>
</table>

Table 4. Adverse Events among Recipients of Liposomal Amphotericin B and Conventional Amphotericin B Deoxycholate (AmB)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. (%) of patients, by regimen</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L-AmB 3</td>
<td>L-AmB 6</td>
<td>AmB</td>
<td></td>
</tr>
<tr>
<td>Creatinine level of 2.0 times baseline and &gt;1.2 mg/dL</td>
<td>12 (14.9)</td>
<td>20 (21.3)</td>
<td>29 (33.3)</td>
<td>.004</td>
</tr>
<tr>
<td>Serum potassium level, &lt;3.0 mmol/L</td>
<td>8 (9.3)</td>
<td>33 (35.1)</td>
<td>26 (29.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Hemoglobin concentration, ≤8 g/dL</td>
<td>20 (23.3)</td>
<td>39 (41.5)</td>
<td>38 (43.7)</td>
<td>.006</td>
</tr>
</tbody>
</table>

**NOTE.** L-AmB 3, liposomal amphotericin at 3.0 mg/kg/day; L-AmB 6, liposomal amphotericin at 6.0 mg/kg/day.
IDSA 2010 recommendations

HIV-Infected Individuals

Primary therapy: induction and consolidation

1. Amphotericin B (AmB) deoxycholate (AmBd; 0.7–1.0 mg/kg per day intravenously [IV]) plus flucytosine (100 mg/kg per day orally in 4 divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least 2 weeks, followed by fluconazole (400 mg [6 mg/kg] per day orally) for a minimum of 8 weeks (A-I). Lipid formulations of AmB (LFAmB), including liposomal AmB (3–4 mg/kg per day IV) and AmB lipid complex (ABLC; 5 mg/kg per day IV) for at least 2 weeks, could be substituted for AmBd among patients with or predisposed to renal dysfunction (B-II).

Liposomal AmB (AmBisome)

- Recommended regimen for CM: 3-4 mg/kg/day
  - Example: 50 kg = 150-200 mg per day; need 3-4 x 50 mg vials per day

- Reconstitution
  - Use sterile water for injection with no bacteriostatic agent to reconstitute each 50 mg vial
  - 12 ml water per AmBisome 50 mg vial yields 4.16 mg/ml amphotericin B concentrate

- Preparation for infusion
  - Dilute 1 part amphotericin B concentrate in 19 parts 5% dextrose solution = 0.21 mg/ml
  - DO NOT use normal saline

- Administered by IV infusion over a 2-hour period
Acknowledgements

• Dr Amir Shroufi
• South African NDoH
• SA HIV Clinicians’ Society
• CDC foundation for support to training development and delivery
• MSF for support to access programme
• DREAMM trial investigators for sharing teaching aids
• *Ambition trial investigators for sharing teaching aids*