GUIDELINE

Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update

by the Southern African HIV Clinicians Society

N P Govender, **G Meintjes** (Chairpersons)**, T Bicanic**, **H Dawood**, **T S Harrison**, **J N Jarvis**, **A S Karstaedt**, **G Maartens**, **K M McCarthy**, **H Rabie**, **E Variava**, **W D F Venter** (Expert panel members), **D R Boulware**, **T Chiller**, **D B Meya**, **J Scriven** (Reviewers)

Corresponding author: *N P Govender (neleshg@nicd.ac.za)*

Disclaimer: Specific recommendations provided here are intended only as a guide to clinical therapy, based on expert consensus and best current evidence. Treatment decisions for patients should be made by their responsible clinicians, with due consideration for individual circumstances. The most current version of this document should always be consulted.

Six years after the first Society guidelines were published, cryptococcal meningitis (CM) remains an important cause of morbidity and mortality among HIV-infected adults in South Africa. Several important developments have spurred the publication of updated guidelines to manage this common fungal opportunistic infection. Recommendations described here include: (1) screening and pre-emptive treatment; (2) laboratory diagnosis and monitoring; (3) management of a first episode of CM; (4) amphotericin B deoxycholate toxicity prevention, monitoring and management; (5) timing of antiretroviral therapy among patients with CM; (6) management of raised intracranial pressure; (7) management of relapse episodes of CM.

S Afr J HIV Med 2013;14(2):76-86. DOI:10.7196/SAJHIVMED.930

List of recommendations

1. Screening and pre-emptive treatment
2. Laboratory diagnosis and monitoring
3. Management of a first episode of CM
4. Amphotericin B deoxycholate toxicity prevention, monitoring and management
5. Timing of ART among patients with CM
6. Management of raised intracranial pressure
7. Management of relapse episodes of CM.

Six years after the first Society guidelines were published,[1] cryptococcal meningitis (CM) remains an important cause of morbidity and mortality among HIV-infected adults in South Africa (SA).[2] Several important developments have spurred the publication of updated guidelines to manage this common opportunistic fungal infection. First, for the first time in December 2011, the World Health Organization (WHO) published a Rapid Advice guideline focused on the management of HIV-associated CM in resource-limited settings.[3] Second, cryptococcal screening, an old strategy that has been revisited to detect cryptococcal disease earlier and pre-emptively reduce mortality, is being implemented in a phased manner in SA[4] and is being considered in other African countries. Third, the diagnostic landscape for CM has changed with the introduction of a United States Food and Drug Administration (FDA)-approved cryptococcal antigen (CrAg) lateral flow assay (LFA), which is simple, accurate and useful as a point-of-care test.[5] Finally, several clinical trials, many undertaken in Southern Africa, have improved our understanding of issues such as which first-line antifungal regimens are best suited to a resource-limited setting,[6-9] when to start antiretroviral therapy (ART),[10,11] and how to safely administer amphotericin B deoxycholate,[12] which has been used by many more SA clinicians as first-line induction-phase treatment for CM in the last 5 years.[13]

1. Screening and pre-emptive treatment

Refer to Table 1 for a summary of this recommendation.

1.1 Background

Early diagnosis of HIV infection and early initiation of ART before immunosuppression is the most important strategy to reduce the incidence of CM and associated mortality. In SA, patients should initiate ART according to the current national guidelines.[14,15] However, screening for early cryptococcal disease and pre-emptive antifungal treatment may be a useful adjunctive strategy, because the median CD4$^+$ T-lymphocyte

Table 1. Summary of recommendation 1: Screening and pre-emptive treatment

Scenario	Recommendations
HIV-infected adults with CD4⁺ T-lymphocyte count <100 cells/µl	• Screen for cryptococcal antigenaemia on serum or plasma by reflex laboratory or clinician-initiated testing • If clinician-initiated testing is performed, screening should be restricted to ART-naive adults with no prior CM • Either the LA or LFA may be used as a screening test
HIV-infected children or adolescents	• There are insufficient data to recommend screening in this population
Patients with a **positive** CrAg test result	• Refer to Fig. 1 and recommendations 1, 3 and 5 regarding further investigations, antifungal treatment and timing of ART • If ART was started *before* the CrAg-positive result was received, follow the algorithm in Fig. 1, continue ART and monitor the patient very carefully for symptoms and signs of cryptococcal IRIS
Patients with a **negative** CrAg test result	• Evaluate for other opportunistic infections and start ART as soon as possible

ART = antiretroviral therapy; LA = cryptococcal latex agglutination test; LFA = cryptococcal lateral flow assay (dipstick); CrAg = cryptococcal antigen; IRIS = immune reconstitution inflammatory syndrome.

count among patients at the time of ART initiation remains low in SA.[16] The WHO, in their recently issued Rapid Advice guideline, indicated that routine screening for cryptococcal disease in ART-naive adults with a CD4⁺ T-lymphocyte count <100 cells/µl may be considered prior to ART initiation in populations with a high prevalence of cryptococcal antigenaemia.[3] In two ART cohorts in SA, the prevalence of newly-diagnosed antigenaemia among patients with a CD4⁺ T-lymphocyte count <100 cells/µl was 4% and 7%, respectively.[17] This is greater than the threshold above which screening was found to be potentially cost-saving in a Ugandan study.[18,19] To reduce disability and deaths associated with HIV infection, screening and pre-emptive antifungal treatment of cryptococcal disease has been suggested for routine implementation as part of the South African National Strategic Plan for HIV, STIs and TB, 2012 - 2016.[4] Primary azole prophylaxis for cryptococcal disease, in the absence of a screening programme, is not routinely recommended by the WHO.[3]

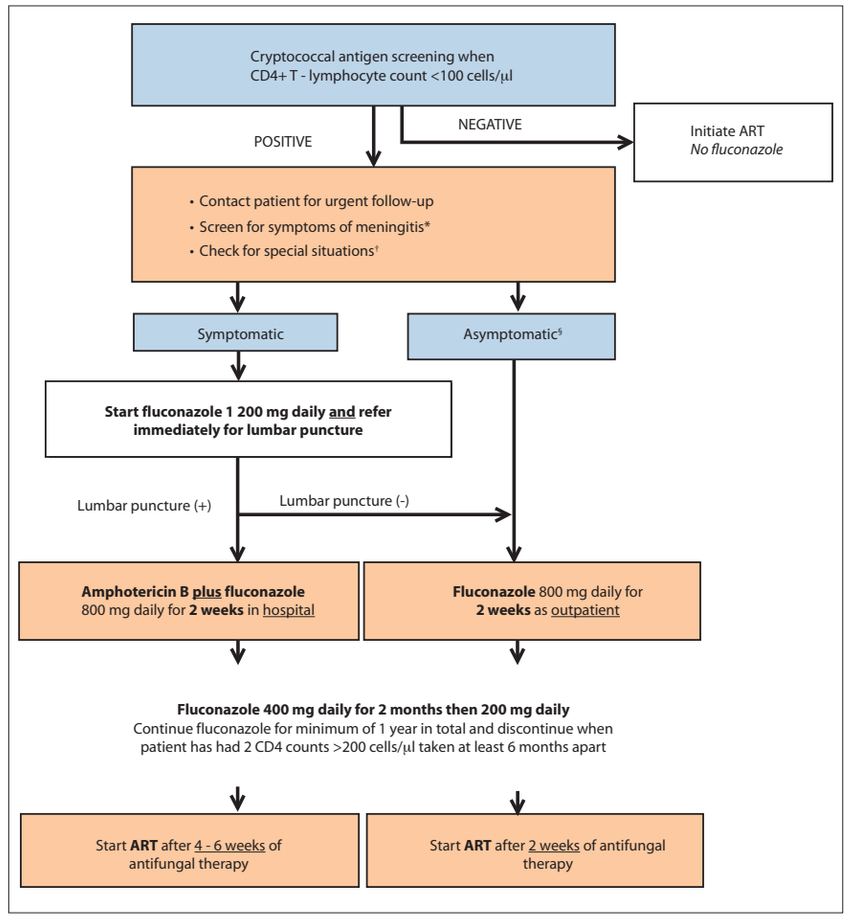

Fig. 1 Screen-and-treat algorithm for ART-naive adult patients with a CD4⁺ T-lymphocyte count <100 cells/µl.

** Symptomatic for meningitis if either of the following is present: headache; confusion.*

† Special situations include: prior cryptococcal meningitis; pregnancy or breastfeeding mothers; clinical liver disease.

§ A lumbar puncture may be considered if available.

1.2 Detailed recommendations

1.2.1 Who to screen

HIV-infected adults with a CD4⁺ T-lymphocyte count <100 cells/µl are recommended to be screened for cryptococcal antigenaemia. If screening is initiated by a clinician (medical practitioner or nurse trained in nurse-initiated management of ART (NIMART)) and not performed reflexively in the laboratory, then the expert panel recommends that screening be restricted to: ART-naive adults with CD4⁺ T-lymphocyte count <100 cells/µl **and** no prior CM. Although ART-experienced patients with a CD4⁺ T-lymphocyte count that remains <100 cells/µl may also be at risk for cryptococcal disease,[20] there is insufficient current evidence to routinely recommend screening ART-experienced adults. There are also insufficient data to recommend routine cryptococcal screening of HIV-infected children and adolescents, among whom the incidence of CM is much lower.[3, 21]

1.2.2 Screening strategies

The most cost-effective screening strategy has not yet been defined. Reflex laboratory screening, where blood samples with a $CD4^+$ T-lymphocyte count <100 cells/µl are automatically tested for CrAg, is being conducted at healthcare facilities in the Gauteng and Free State provinces in 2012/2013.[4] Screening initiated by clinicians is being conducted in other provinces such as the Western Cape.[4] Although the latex agglutination (LA) test has been more extensively evaluated for diagnosis of cryptococcal disease, the rapid LFA is equally valid as a screening test. The laboratory turnaround time is short for the CrAg screening test; however, initiation of ART should not be delayed unnecessarily while waiting for CrAg test results.

1.2.3 Management of CrAg-positive patients

The clinician should urgently evaluate CrAg-positive patients for symptoms and signs of meningitis, including headache and confusion (Fig. 1). For the management of symptomatic CrAg-positive patients, refer to recommendations 3, 4, 5 and 6. Patients *without* symptoms of meningitis may be offered a lumbar puncture (LP), if this is immediately accessible, to exclude early asymptomatic CM. For patients without suspected meningitis, oral fluconazole (800 mg for 2 weeks) followed by standard consolidation and maintenance treatment (refer to recommendation 3) is recommended; the same applies to patients with an LP that is cryptococcal test-negative. Among patients without signs or evidence of meningitis, ART is recommended to be started two weeks after antifungal therapy is initiated.

As part of the screen-and-treat algorithm (Fig. 1), CrAg-positive patients also need to be evaluated for the following clinical situations:

1.2.3.1 Prior CM

Patients with a history of CM do not need to be screened routinely as cerebrospinal fluid (CSF) and blood specimens may remain CrAg-positive for months to years. However, if a patient with prior CM is screened and found to be CrAg-positive and has new symptoms or signs of meningitis, a full evaluation should be undertaken for relapse disease (refer to recommendations 2 and 7). If the patient does not have new symptoms or signs of meningitis, the clinician should ensure that the patient has received or is receiving adequate fluconazole maintenance therapy (refer to recommendation 3). The serum/plasma (and CSF) CrAg test can remain positive for a prolonged period after successful treatment; therefore, if these tests are positive in the absence of symptoms and signs, this is not an indication of relapse.

1.2.3.2 Pregnant/breastfeeding women

Fluconazole is teratogenic (category D).[22] Women of child-bearing age who screen CrAg-positive should have a pregnancy test prior to starting fluconazole; those who are not pregnant and are started on fluconazole should be advised to avoid becoming pregnant during treatment. CrAg-positive patients who are pregnant should be offered an LP before a decision is made regarding management. If the patient has laboratory evidence of CM, then she should be treated for CM with amphotericin B. The risks, benefits and alternative to fluconazole treatment (i.e. ART and close clinical monitoring) should be discussed with the pregnant CrAg-positive patient *without* laboratory-confirmed CM and consultation with a medical practitioner who is experienced in the care of HIV-infected patients is recommended; in this context, consideration of factors such as the trimester and CrAg titre may be useful. For mothers who are breastfeeding, consultation with an experienced medical practitioner is also recommended as fluconazole can be transmitted in large amounts through breast milk to the infant.[22]

1.2.3.3 Clinical liver disease

Patients with a history of liver disease or with evidence of clinical liver disease deserve careful monitoring because fluconazole may cause liver injury. Consultation with a medical practitioner who is experienced in the care of HIV-infected patients is recommended.

2. Laboratory diagnosis and monitoring

Refer to Table 2 for a summary of this recommendation.

2.1 Background

Cryptococcus neoformans is the most commonly detected meningitis-causing pathogen in SA.[23] All adults with suspected meningitis should be investigated for CM. Patients with CM may present with fever as well as symptoms and signs related to inflamed meninges (including neck stiffness), raised intracranial pressure (including headache, confusion, altered level of consciousness, sixth cranial nerve palsies with diplopia and visual impairment, and papilloedema) and encephalitis (including memory loss and new-onset psychiatric symptoms).[24] Cutaneous lesions and pulmonary involvement (including cavitation, nodular infiltrates and consolidation) may also occur. Symptomatic relapses are common and are most often a result of inadequate or premature cessation of maintenance fluconazole treatment.[25] The incidence of CM is much lower among children;[21] African children with CM may present with an acute onset of illness and focal neurological signs may be less common.[26]

2.2 Detailed recommendations

2.2.1 Diagnosis of first CM episode

LP is required to establish an aetiological diagnosis of suspected meningitis. LP may also alleviate symptoms – such as headache, altered level of consciousness, and sixth cranial nerve palsies – that are a direct result of raised intracranial pressure. For a suspected first episode of CM, CSF should be submitted to the laboratory for a rapid test (either India ink or CrAg test) and fungal culture. If the India ink test is performed as the only rapid test and is negative, the laboratory should then perform a CrAg test (either LA or LFA). The sensitivity and specificity of CrAg tests (LA and LFA) are higher than of India ink.[3] *C. neoformans* can be cultured within 72 hours from the CSF of patients with a first episode. There is no need to routinely order a baseline CSF CrAg titre; most patients are diagnosed when the CSF fungal burden is high and antifungal treatment for a first episode is standardised and not influenced by the CrAg titre (refer to recommendation 3). If laboratory facilities are unavailable, a point-of-care LFA may be performed on CSF at the bedside.[5,27]

Antifungal susceptibility testing should not be requested for a first episode because antifungal drug minimum inhibitory concentrations (MICs) are invariably very low at first diagnosis[28] and, even if elevated, the relevance is difficult to interpret in this setting. If opening pressure was not measured at the time of the diagnostic LP, the LP should be repeated to measure the pressure once a diagnosis of CM is confirmed (refer to recommendation 6 for diagnosis and management of raised intracranial pressure).

2.2.2 Diagnosis of CM if focal neurological signs are present or if LP is not immediately available

Focal neurological signs are relatively uncommon in CM, except for sixth cranial nerve palsy. Where focal neurological signs are

Table 2. Summary of recommendation 2: Laboratory diagnosis and monitoring

Scenario	Recommendations
Diagnosis of first episode of suspected CM	• All adults with suspected meningitis should be investigated for CM • An LP should be performed to obtain CSF • CSF should be submitted to a laboratory for a rapid test (either India ink or CrAg test) and fungal culture • If opening pressure was not measured at the time of diagnostic LP, LP should be *repeated* to measure the pressure once a diagnosis of CM is confirmed (refer to recommendation 6 for the management of raised intracranial pressure) • The laboratory should routinely perform a CrAg test (either LA or LFA) when an India ink test is negative • If laboratory facilities are unavailable, a cryptococcal LFA may be performed at the bedside on drawing CSF • There is no need to routinely request a baseline CSF CrAg titre or antifungal susceptibility testing
Diagnosis of CM if LP is not immediately available or focal neurological signs are present	• Serum/plasma may be tested for CrAg to determine if the patient has disseminated cryptococcal disease • Patients with a positive serum/plasma CrAg test **and** symptoms and signs of meningitis should be empirically started on antifungal treatment (refer to recommendation 3) and referred to a centre where an LP and/or a CT brain scan can be performed
Diagnosis of subsequent episode of suspected CM	• A careful history should be taken and the patient should be assessed clinically for signs and symptoms of meningitis • An LP should be performed to obtain CSF • Opening pressure should be measured (refer to recommendation 6 for the management of raised intracranial pressure) • CSF should be submitted to a laboratory for prolonged fungal culture (minimum 14 days) (note: India ink and CrAg tests are not useful for the diagnosis of subsequent episodes of CM as they can stay positive for a prolonged period despite successful treatment) • Antifungal susceptibility testing may be considered in selected circumstances (see below and refer to recommendation 7)
Monitoring response to antifungal treatment	• Resolution of symptoms and signs can be used to monitor response to treatment • Unless there is a specific indication (e.g. persistent symptoms or signs suggesting late-onset raised intracranial pressure), LP should not be routinely performed after 14 days of antifungal treatment to document conversion of CSF from culture-positive to culture-negative* • CSF and serum/plasma CrAg titres should not be routinely monitored
Suspected antifungal drug-resistant isolate	• Consider antifungal susceptibility testing if a patient has had more than one relapse and the causes listed in Table 7 have been excluded (also refer to recommendation 7) • Fluconazole MICs should be determined at an academic or reference laboratory and interpreted by an experienced clinical microbiologist in conjunction with clinical findings
Screening for cryptococcal antigenaemia	• Refer to recommendation 1

CM = cryptococcal meningitis; LP = lumbar puncture; CSF = cerebrospinal fluid; CrAg = cryptococcal antigen; LA = latex agglutination test; LFA = lateral flow assay; MIC = minimum inhibitory concentration.

*If symptoms persist at or beyond 14 days, LP should be repeated to re-measure opening pressure, which may increase despite successful CSF sterilisation – refer to recommendation 6.

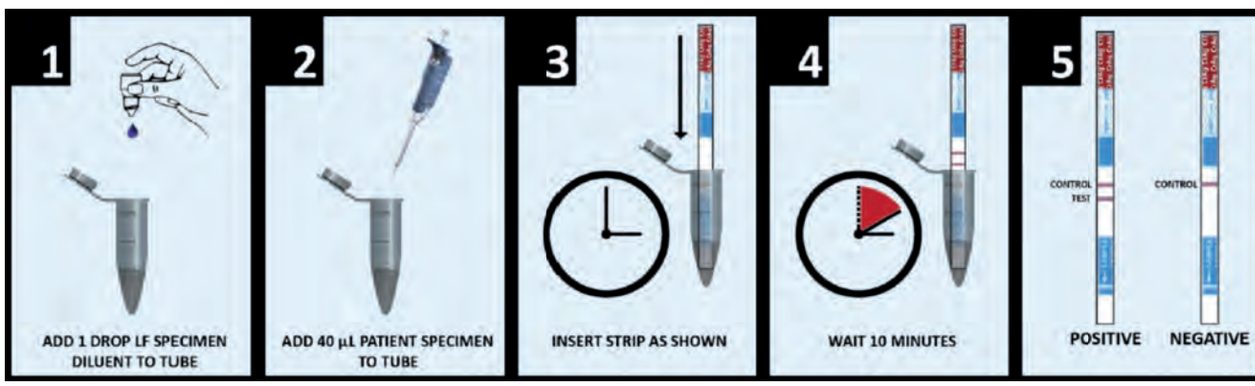

Fig. 2. Laboratory procedure to set up and read the cryptococcal antigen lateral flow assay (Immuno-Mycologics, Norman, OK) (source: Immy CrAg LFA package insert; reprinted with permission).

present, a CT brain scan should be performed first to exclude the presence of space-occupying lesions. If a CT brain scan cannot be performed immediately in the case of focal neurological signs, or if LP is not immediately available to make a diagnosis of meningitis, then serum/plasma may be tested for CrAg to determine if the patient has disseminated cryptococcal disease. Patients with a positive serum/plasma CrAg test **and** symptoms and signs of meningitis are very likely to have CM and should be started empirically on antifungal treatment (refer to recommendation 3). Patients without focal neurological signs should then be referred to a centre where LP can be performed, while patients with focal neurological signs first need to have a computed tomography (CT) brain scan, followed by an LP (if this is not contra-indicated by CT brain findings). Although aware that it may be difficult to access a CT brain scan in rural settings, the panel cannot recommend that an LP be performed in a patient with focal neurological signs without a scan.

2.2.3 Diagnosis of a subsequent episode of CM

A careful history should be taken including dates of previous episodes of CM and the patient should be assessed clinically for signs and symptoms of meningitis. An LP is indicated if the patient has signs and symptoms of meningitis. CSF should be submitted for fungal culture with plates incubated for at least 14 days to detect slow fungal growth. Rapid tests are not useful for diagnosis of subsequent episodes because both India ink and CrAg tests may remain positive for months to years even if treatment has been successful. Antifungal susceptibility testing may be considered in certain circumstances (see below and refer to recommendation 7).

2.2.4 Monitoring response to treatment

Resolution of symptoms and signs should be used to monitor response to treatment. LP should not be routinely performed after 14 days of antifungal treatment to document conversion of CSF from culture-positive to culture-negative, because the expert panel advises routinely changing from induction to consolidation phase treatment at 14 days. Given that the culture result takes several days (up to 14 days) to become available, the culture result will not affect the timing of this change. If symptoms persist at day 14, LP should be repeated to re-measure opening pressure, which may increase despite successful CSF sterilisation. Patients with raised intracranial pressure should be managed according to recommendation 6. CSF CrAg may remain positive for months to years and CrAg titres are not recommended to be routinely measured to monitor response to treatment. Serum/plasma CrAg titres are also not useful to monitor response to treatment.[29]

2.2.5 Suspected antifungal drug-resistant isolate

Antifungal susceptibility testing may be considered if the patient has had more than one relapse episode and the causes listed in Table 7 have been excluded. Isolates with elevated fluconazole MICs have been described occasionally from relapse episodes – especially where fluconazole monotherapy is initially given – and are unusual if amphotericin B-based induction treatment was administered during the first episode. As there are no established clinical breakpoints for *C. neoformans* and fluconazole, it is useful to test isolates from the initial and subsequent episodes in parallel at an academic or reference laboratory and document a four-fold (double-dilution) change in MIC,[14,16] which may suggest resistance. This requires storage of the initial isolate, which may not always be possible at a diagnostic laboratory. MICs should be interpreted by an experienced clinical microbiologist, in conjunction with the clinical history. Refer to recommendation 7 for the management of patients with fluconazole-resistant isolates. Non-susceptibility to amphotericin B is very unusual and susceptibility testing to this drug should not be requested.

3. Management of first episode of CM

Refer to Table 3 for a summary of this recommendation.

3.1 Detailed recommendations

The antifungal treatment of CM is divided into 3 phases: induction, consolidation and maintenance.

3.1.1 Induction phase (2 weeks)

Guidelines of the Infectious Disease Society of America (IDSA) and the WHO recommend the first choice for induction-phase treatment as: amphotericin B (0.7 - 1.0 mg/kg/dose) **and** flucytosine (100 mg/kg/day).[3,30] Unfortunately, flucytosine is not currently available in Southern Africa. The panel supports international advocacy efforts to provide greater access to flucytosine in resource-limited settings, particularly in light of the findings of a recently-published clinical trial in Vietnam showing improved survival among patients with CM treated with amphotericin B plus flucytosine v. amphotericin B alone.[9]

In the absence of flucytosine, the expert panel advocates that Southern African patients should be treated with the following induction therapy for the first two weeks: amphotericin B deoxycholate (1 mg/kg/day intravenous (IV) administration) plus fluconazole (800 mg *per os* (PO) daily). Among SA adults, the 1 mg/kg/day dose of amphotericin B is well tolerated.[31] The panel advises adding fluconazole (800 mg/day) during the induction phase in line with the WHO guideline; this is supported by evidence from a clinical trial that this combination is associated with a marginally superior rate of CSF clearance compared with amphotericin B alone, and evidence from two trials showing a non-significant decrease in mortality and neurological morbidity.[3,6,9,32]

Table 3. Summary of recommendation 3: Management of first episode of CM

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

IV = intravenous; PO = *per os*.

Where amphotericin B is unavailable or cannot be given safely, the patient should be transferred to a hospital where amphotericin B is available. It is reasonable to give a fluconazole dose of 1 200 mg PO daily while transfer is awaited.

In countries where amphotericin B is unavailable, the panel would advise clinicians to follow the WHO guideline with respect to high-dose fluconazole options.[3] However, in SA, all patients diagnosed with CM should have access to amphotericin B-based induction-phase treatment.

3.1.2 Consolidation phase (further 8 weeks)

The panel recommends 400 mg fluconazole PO daily for 8 weeks.

3.1.3 Maintenance phase

This is also termed secondary prophylaxis. The panel recommends 200 mg fluconazole PO daily for at least a further 10 months (i.e. until at least 12 months after treatment for CM was started). Maintenance fluconazole should only be stopped when the $CD4^+$ T-lymphocyte count is >200 cells/µl for at least 6 months and the most recent HIV-1 viral load is suppressed. Patients with CM should have 6-monthly $CD4^+$ T-lymphocyte measurements until fluconazole can be stopped.

3.1.4 Adolescents and children

A dose of 1 mg/kg/day amphotericin B should be prescribed during the induction phase. Fluconazole doses should also be calculated according to body weight. Induction phase: 12 mg/kg/day (up to 800 mg daily); consolidation phase: 6 - 12 mg/kg/day (up to 400 mg daily); maintenance phase: 6 mg/kg/day (up to 200 mg daily).

3.1.5 Baseline renal impairment

If patients have renal impairment at the time of diagnosis, this is not a contraindication to receiving amphotericin B deoxycholate at the standard dose (i.e. 1 mg/kg/day); however, creatinine should be monitored frequently and if it deteriorates significantly, then amphotericin B may need to be stopped and treatment continued with fluconazole monotherapy. When used as monotherapy during induction, the fluconazole dose would be 1 200 mg daily with normal renal function. With a creatinine clearance of 10 - 50 ml/min, the dose of fluconazole used as monotherapy should be reduced by 50% to 600 mg daily, and if creatinine clearance is <10 ml/min, fluconazole should be reduced to 400 mg daily. If the baseline renal impairment is thought to be due to dehydration, then intensive IV rehydration efforts should occur while starting amphotericin B. For the prevention, monitoring and management of renal impairment that develops during amphotericin B deoxycholate administration, refer to recommendation 4.

3.1.6 Patients receiving TB treatment

In contrast to previous guidelines, the panel does not recommend a fluconazole dose increase in patients receiving rifampicin, as the induction of fluconazole metabolism by rifampicin causes only moderate reductions in fluconazole exposure,[33] and because of the high doses of fluconazole that are initially being used.

3.1.7 Adjunctive corticosteroid therapy

The panel does not currently recommend adjunctive corticosteroid therapy in the initial management of CM. There is an ongoing international clinical trial that aims to address this question.[34] Refer to recommendation 7 for the use of corticosteroids in patients with immune inflammatory reconstitution syndrome (IRIS).

3.1.8 Immunological failure on ART

In patients who develop immunological failure while receiving ART and where the $CD4^+$ T-lymphocyte count drops <200 cells/µl after secondary prophylaxis has been stopped, the panel advises restarting fluconazole at 200 mg daily. Refer to the above section on maintenance-phase treatment for the duration of treatment.

3.1.9 Non-adherence to maintenance treatment

In patients who stop taking fluconazole maintenance prematurely and then return for care but are asymptomatic, the panel advises simply restarting fluconazole (200 mg daily) and monitoring closely for the recurrence of meningitis. Refer to the above section on maintenance-phase treatment for the duration of treatment.

3.1.10 Analgesia

Therapeutic LP is the best form of 'analgesia' for headaches associated with raised intracranial pressure. Paracetamol can be used, but not non-steroidal anti-inflammatory drugs (NSAIDs), due to the nephrotoxicity concern with amphotericin B deoxycholate. Morphine may also be appropriate and is not contraindicated in the presence of raised intracranial pressure.

4. Amphotericin B toxicity prevention, monitoring and management

Refer to Table 4 for a summary of this recommendation.

4.1 Background

Major adverse effects of amphotericin B deoxycholate include renal impairment due to renal tubular toxicity (usually in the second week of therapy), hypokalaemia, hypomagnesaemia, anaemia, febrile reactions and chemical phlebitis. Nephrotoxicity and electrolyte abnormalities may be prevented by pre-hydration, by avoiding concurrent use of other nephrotoxins (e.g. NSAIDs and aminoglycosides) and by routine administration of potassium and magnesium supplements. Phlebitis is very common in patients receiving amphotericin B and increases the risk of localised cellulitis as well as sepsis. Anaemia commonly occurs among patients receiving amphotericin B and can be clinically significant, particularly among those with a low baseline haemoglobin level. Haemoglobin decreases >2 g/dl occurred in 50 - 71% of patients over 2 weeks of treatment in an SA trial.[7] It is important also to exclude other treatable causes of anaemia and consider transfusion in symptomatic patients.

4.2 Detailed recommendations

4.2.1 Administration of amphotericin B deoxycholate

Amphotericin B deoxycholate powder (50 mg vials) should be refrigerated between 2°C and 8°C and protected from light.[35] The total daily dose of amphotericin B is calculated based on a dose of 1 mg/kg/day; amphotericin B deoxycholate powder from each 50 mg vial should be aseptically reconstituted in 10 ml of sterile water. The calculated volume of the concentrate (i.e. reconstituted drug in sterile water) should be injected into a 1 litre bag of 5% dextrose water and shaken to mix. Amphotericin B deoxycholate should **never** be mixed with normal saline or half-normal saline as it will precipitate. Once mixed, the solution (≤0.1 mg amphotericin B per 1 ml

Table 4. Summary of recommendation 4: Amphotericin B toxicity prevention, monitoring and management

Scenario	Recommendations
Administration of amphotericin B deoxycholate*	• Amphotericin B powder should be reconstituted in sterile water; inject the calculated volume of reconstituted drug in water into 1 litre of **5% dextrose water** and administer within 24 hours • Amphotericin B can be administered via peripheral IV line if the solution contains ≤0.1 mg amphotericin B in 1 ml of 5% dextrose water • A test dose is unnecessary • The solution should be infused over at least 4 hours
Prevention of amphotericin B deoxycholate-related toxicities	• Patients should be pre-hydrated with 1 litre of normal saline containing 1 ampoule of potassium chloride (20 mmol) infused over 2 hours **before** the amphotericin B infusion† • Twice-daily oral potassium and daily oral magnesium supplementation should be administered (adults) • To minimise the risk of phlebitis, lines should be flushed with normal saline after amphotericin B infusion is complete and the infusion bag should not be left attached to the IV administration set after infusion is complete
Monitoring	• Baseline and twice-weekly creatinine and potassium (and magnesium, if available) • Baseline and weekly haemoglobin • Fluid input and output monitoring
Management of toxicities	• If creatinine doubles, then 1 dose of amphotericin B may be omitted or pre-hydration can be increased to to 1 litre 8-hourly. If creatinine remains elevated or repeatedly rises, then amphotericin B should be stopped and fluconazole used as suggested in recommendation 3 (baseline renal impairment section). • Febrile reactions can be treated with paracetamol (1 g) 30 minutes before infusion (if severe, hydrocortisone (25 mg IV) can be given before subsequent infusions)

IV = intravenous.

* For adolescents and children, drugs should be calculated by body weight.

† For children and adolescents, normal saline, with 1 ampoule of potassium chloride (20 mmol) added per litre of fluid, should be infused at 10 - 15 ml/kg over 2 - 4 hours (not more than 1 litre) prior to amphotericin B administration. If saline is unavailable, then other parenteral rehydration solutions, e.g. Darrow's solution or Ringer's lactate that already contain potassium can be used.

5% dextrose water for infusion through a peripheral IV line[22]) must be infused within 24 hours of preparation or discarded. A test dose is not recommended.[3] Protection from light with a brown bag is unnecessary.[35] The line that is used for amphotericin B infusion should not be used to administer other drugs simultaneously. The solution should be infused over 4 hours or more (infusion over <4 hours can result in cardiac complications). Once the infusion is complete, the line should be flushed with normal saline.

4.2.2 Prevention of amphotericin B deoxycholate-related toxicities

Patients should be pre-hydrated with 1 litre of normal saline containing 1 ampoule of potassium chloride (20 mmol K^+ per 10 ml ampoule) infused over 2 hours before administration of amphotericin B deoxycholate. This reduces renal toxicity and hypokalaemia. Patients should be given 1 200 mg of potassium chloride twice daily (equivalent to 16 mmol of oral potassium, e.g. two Slow-K 600 mg tablets twice daily, 8 mmol K^+ per tablet) and up to one 500 mg magnesium chloride daily (e.g. two Slow-Mag 535 mg tablets daily, 5.33 mmol Mg^{2+} per tablet) for the duration of treatment with amphotericin B deoxycholate. Routine pre-emptive potassium supplementation should not be given to patients with pre-existing renal impairment or hyperkalaemia. To minimise the risk of phlebitis, lines should be flushed with normal saline after amphotericin B infusion is complete. The empty bag should not be left attached to the IV line. The IV line should be removed if the patient develops a fever after the infusion, or at the first sign of redness or discomfort at the insertion site. Febrile reactions may occur; to prevent recurrence, the infusion should be administered at a slow rate over the first half-hour while observing the patient closely, as treatment such as paracetamol may be required.

4.2.3 Clinical and laboratory monitoring

At minimum, for the duration of amphotericin B deoxycholate treatment, baseline and twice-weekly monitoring of serum creatinine and potassium, and baseline and weekly monitoring of haemoglobin are recommended. Renal toxicity is more likely to develop in the second week of treatment. Fluid input and output should be monitored carefully. Chemical phlebitis is often complicated by infection at the IV line insertion site, which can result in bacteraemia; the insertion site should be monitored by regular clinical examination, and febrile patients with a suspected insertion site infection should be appropriately investigated and managed.

4.2.4 Management of toxicities

For patients with significant hypokalaemia (serum K^+ <3.3 mmol/l), IV replacement is required: 2 ampoules of potassium chloride (20 mmol K^+ per 10 ml ampoule) in 1 litre of normal saline 8-hourly. Among those who develop hypokalaemia, serum potassium should be monitored daily until resolved. If hypokalaemia remains uncorrected, serum magnesium should be checked (if this test is available) and/or oral magnesium supplementation doubled. IV magnesium sulphate may be considered for persistent hypokalaemia and hypomagnesaemia. If serum creatinine doubles from baseline, one dose of amphotericin B deoxycholate may be omitted and/or pre-hydration may be increased to 1 litre of normal saline 8-hourly; serum creatinine should then be monitored daily. If serum creatinine improves, amphotericin B may be restarted at a dose of

0.7 mg/kg/day and alternate-day treatment could be considered. If creatinine remains elevated or repeatedly rises, amphotericin B should be stopped and fluconazole used as suggested in recommendation 3 (baseline renal impairment section). If febrile reactions occur, paracetamol (1 g) may be given 30 minutes before infusion, or for severe reactions, hydrocortisone (25 mg IV) can be administered before subsequent infusions.[22]

5. Timing of ART among patients with CM

Refer to Table 5 for a summary of this recommendation.

5.1 Detailed recommendations

All HIV-infected patients who are diagnosed with CM are eligible for co-trimoxazole preventative therapy and ART.

The panel recommends commencing ART 4 - 6 weeks after CM diagnosis, and strongly advises that ART not be delayed beyond 6 weeks after diagnosis; some panel members advise that clinicians should aim to start exactly 4 weeks after diagnosis of CM. Although most patients with CM have advanced immunosuppression with very low $CD4^+$ T-lymphocyte counts, two randomised clinical trials in sub-Saharan Africa have shown excess early mortality when ART was commenced while patients were still receiving induction-phase treatment for CM.[10,11] In the latter trial, conducted in Uganda and SA, patients who started ART 1 - 2 weeks after CM diagnosis had a 15% higher mortality rate than those who deferred ART until 5 - 6 weeks.[11] Another small trial showed possible excess IRIS in those patients who started early.[36]

The long in-hospital stay associated with amphotericin B therapy should be utilised for pre-ART counselling, identification of a treatment supporter and early referral to an ART clinic. Clinicians should aim to set up an ART clinic appointment within one week of discharge from hospital; this prevents delays in ART initiation beyond what is advised in this guideline. Patients initiated on ART should be counselled regarding the risk of developing IRIS. If a patient is referred to another facility for ART, then the need for fluconazole maintenance therapy should be communicated.

The panel recommends standard first-line ART regimens among patients with CM.[14,15] If nephrotoxicity occurred on amphotericin B, the renal function should be checked before starting ART to ensure that it has improved (creatinine clearance >60 ml/min) before commencing tenofovir. There are potential interactions between nevirapine and fluconazole, but studies have shown that these interactions do not affect the efficacy or toxicity of therapy.[37,38] The panel recommends checking ALT if symptoms of hepatitis or jaundice develop while patients are receiving fluconazole, but routine alanine transaminase (ALT) monitoring is not indicated.

The panel advises that, among patients who present with relapse of CM or a first CM episode after defaulting ART, ART is also restarted after 4 - 6 weeks.

One situation where ART may be delayed further is if a patient is still symptomatic with headaches at the visit when ART is due to be started. In such a situation, an LP should be repeated to measure pressure and fungal culture should be used to exclude persistent culture-positivity. ART should be deferred and such patients may require further LPs or amphotericin B therapy to ensure control of symptoms before starting ART.

Among patients who are serum/plasma CrAg-positive on screening, but do not have symptoms of meningitis and thus do not have an LP performed or have an LP that excludes CM, the panel advises starting ART 2 weeks after starting fluconazole (Fig. 1).

6. Management of raised intracranial pressure

Refer to Table 6 for a summary of this recommendation.

6.1 Background

Raised intracranial pressure occurs in ≤75% of patients with CM and is thought to result from obstruction of CSF outflow, resulting in build-up of CSF pressure.[39] It may be present at diagnosis of CM or develop while the patient is receiving treatment. It may cause severe headaches, vomiting, confusion or a depressed level of consciousness, ophthalmoplegia (particularly sixth cranial nerve palsies) and visual disturbance/loss. Clinicians need to consider raised intracranial pressure as part of the differential diagnosis and act appro-

Table 5. Summary of recommendation 5: Timing of ART among patients with CM

Recommendations
• Start ART 4 - 6 weeks after diagnosis of CM. The panel strongly advises that ART not be delayed beyond 6 weeks after diagnosis; some members of the panel advise that clinicians should aim to initiate ART exactly 4 weeks after diagnosis of CM.
• No adjustment in first-line ART regimen is required for patients who are ART-naive (unless renal dysfunction precludes the use of tenofovir).

Table 6. Summary of recommendation 6: Management of raised intracranial pressure

Recommendations
• Measure baseline opening pressure
• If opening pressure >25 cm H_2O, remove 10 - 30 ml of CSF
• Repeat LP whenever there are symptoms or signs of raised intracranial pressure (headache, vomiting, drowsiness, confusion, sixth cranial nerve palsy, visual disturbance)
• Daily therapeutic LPs may be required

CSF = cerebrospinal fluid; LP = lumbar puncture.

priately if a patient exhibits these symptoms or signs at any stage of CM management. To alleviate raised pressure, therapeutic LPs are indicated. New-onset hypertension may be a sign of increased intracranial pressure (i.e. Cushing's triad) and should prompt an LP to measure opening pressure instead of anti-hypertensive medications.

6.2 Detailed recommendations

It is good practice to measure the CSF opening pressure whenever a diagnostic LP is done. However, in practice the opening pressure will not have been measured at the initial diagnostic LP in CM. Thus, once the diagnosis of CM is made, an LP should be repeated to measure CSF opening pressure, particularly if the patient still has a headache (which is usually the case). The pressure should be measured with the patient lying down and without excessive spinal flexion. If the opening pressure is raised (>25 cm H_2O), then 10 - 30 ml of CSF should be drained (to normalise pressure to <20 cm H_2O or decrease the pressure by at least 50% – based on repeat measurements of closing pressure). Thereafter, the need for pressure relief should be dictated by the recurrence of symptoms of raised intracranial pressure. Patients may require daily LPs. Patients with raised intracranial pressure experience considerable relief of symptoms following therapeutic LPs. Approximately 15% of patients with initially normal intracranial pressure will develop raised intracranial pressure during treatment; therefore, all patients should be monitored daily for headache or signs of raised pressure that should prompt an LP.

Patients with persistent pressure symptoms and who fail to respond to serial lumbar punctures may require lumbar drain insertion or shunting procedures. Neurosurgical consultation should be sought.

In situations where manometers are not available, the panel suggests using a central venous pressure set manometer and attaching this to the LP needle using aseptic technique. In situations where this is also unavailable, if there are symptoms or signs of raised intracranial pressure due to CM (severe headache, drowsiness, sixth cranial nerve palsies), then the panel recommends performing an LP and removing 20 ml of CSF and repeating daily, if necessary.

Manometers can be ordered from Rocket Medical PLC (Tyne and Wear, UK) through Summit Surgical (Gauteng) (email: phil@acroteq.co.za or jim@wycliffe.edu; fax: +27 (0)86 565 6347).

7. Management of relapse episodes of CM

There are several possible reasons for the recurrence of symptoms of meningitis in patients treated for CM. In certain cases, recurrence is due to microbiological relapse, but situations exist where there is symptom recurrence but CSF fungal cultures are negative. The causes are summarised in Table 7.

When a patient presents with a recurrence, it is not always possible immediately to be sure of the aetiology. Assessment should include:

- Assessment of adherence to fluconazole consolidation and maintenance-phase treatment (self-reported and pharmacy refill data)
- To support an IRIS diagnosis, an enquiry as to whether the patient recently started ART
- An LP to measure opening pressure, assess CSF inflammation and for a prolonged fungal culture (14 days) – there is no role for India ink staining or CSF/serum/plasma CrAg assays in establishing the cause of recurrence, as these may remain positive for months (years even) in patients after successful treatment (refer to recommendation 2)
- If the CSF is culture-positive and non-adherence does not appear to be the cause, then fluconazole susceptibility testing should be considered (refer to recommendation 2) and should be performed in a reference laboratory; the panel recommends this especially when there has been more than one relapse, despite reported good adherence.

If the cause of the recurrence is attributed to non-adherence, then the patient should be treated as for the first episode. The reasons for non-adherence should be explored and the patient should receive additional adherence counselling, preferably with a treatment supporter. If the patient also defaulted ART, this should be re-initiated 4 - 6 weeks after presentation. ART may need to be adjusted if there is concern that there has been virological failure on first-line ART.

Paradoxical cryptococcal IRIS occurs among patients treated for cryptococcal disease who start ART and develop a recurrence or worsening of the clinical manifestations of cryptococcal disease. IRIS is thought to be the result of an immunopathological reaction directed at residual cryptococcal antigen at sites of the disease.[40] IRIS occurs, on average, 6 weeks after ART is commenced, but delayed cases (even more than a year after ART initiation) are described.[41] IRIS affects approximately 20% of patients with cryptococcal disease who start ART, and mortality may be substantial.[42] The most frequent manifestation is a recurrence of the symptoms of meningitis, often with raised intracranial pressure. Typically, the CSF fungal culture is negative at the time of IRIS presentation; IRIS represents

Table 7. Possible causes of recurrent symptoms and signs of meningitis in CM

- Non-adherence to fluconazole consolidation or maintenance treatment
- Non-adherence to ART
- Paradoxical IRIS
- 'Breakthrough' of *C. neoformans* growth in CSF without laboratory evidence of resistance
- Ongoing raised intracranial pressure without one of the above (i.e. isolated mechanical problem)
- Virological failure on ART after having stopped fluconazole maintenance treatment
- Resistance to fluconazole (this is uncommon if amphotericin B induction therapy is used)
- Other diagnoses (e.g. TB meningitis)

ART = antiretroviral therapy; CSF = cerebrospinal fluid; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis.

an immunological reaction rather than a microbiological recurrence. However, in cases where induction therapy was recent (<2 months), the CSF fungal culture may still be positive. Other cryptococcal IRIS manifestations include lymphadenitis and cryptococcomas.[40]

In all patients with **suspected paradoxical CM IRIS**, an LP should be performed to measure pressure and obtain a fungal culture incubated for up to 14 days. It is not possible to make a diagnosis of IRIS with certainty prior to excluding microbiological relapse on CSF fungal culture. **If the symptoms are mild**, the panel recommends performing therapeutic LPs if there is raised intracranial pressure, providing analgesia and increasing the fluconazole dose to 1 200 mg daily with regular review and follow-up of the CSF fungal culture result. If the CSF fungal culture is negative, the dose of fluconazole can be reduced back to what it was (400 mg or 200 mg daily depending on the timing of the CM IRIS event). **If patients with suspected CM IRIS have severe symptoms** or deteriorate with the approach above, the panel recommends treating with amphotericin B (1 mg/kg/day IV) plus fluconazole (800 mg PO daily) until the CSF culture is confirmed as negative. If the CSF culture is still negative after 7 days of incubation, amphotericin B can be stopped. If the fungal culture is positive by 7 days, then amphotericin B should be continued for 14 days. Daily therapeutic LPs may be required if the opening pressure is raised. A CT head scan should be considered, as mass lesions and cerebral oedema can occur with IRIS. Analgesia should be provided. For patients with severe IRIS who do not respond to the above treatment, corticosteroids (e.g. prednisone 1mg/kg/day PO or dexamethasone IV) should be considered. The panel recommends that corticosteroids preferably be used among patients with IRIS who are documented to be CSF fungal culture-negative and when other aetiologies are excluded; however, if there is life-threatening neurological deterioration, corticosteroids should be started immediately.

In patients with CM due to fluconazole-resistant isolates, subsequent management should be discussed with a medical practitioner experienced in the treatment of CM. Such patients should receive induction therapy with amphotericin B again. Consolidation and maintenance options depend on the fluconazole MIC and include high-dose fluconazole with or without weekly amphotericin B infusions or voriconazole.

In patients with multiple relapses, it is important to document the conversion of CSF from culture-positive to culture-negative before stopping amphotericin B. Such cases should be discussed with an experienced medical practitioner and fluconazole susceptibility testing should be performed (refer to recommendation 2).

Conflict of interest. T Bicanic, J N Jarvis, G Maartens, K M McCarthy, T Chiller and J Scriven have declared no conflicts of interest. N P Govender has received speaking-engagement honoraria from Merck, and research support from Pfizer (investigator-initiated grant) and Immuno-Mycologics (provision of cryptococcal antigen tests for studies). G Meintjes is a Senior Clinical Consultant for Aid for AIDS. H Dawood has received honoraria from MSD-South Africa and Novartis-South Africa for speaking engagements and a travel grant from Novartis-South Africa. T S Harrison has received speaking-engagement honoraria from Gilead Sciences and research support from Immuno-Mycologics (provision of cryptococcal antigen tests for studies). H Rabie is a Consultant for Aid for AIDS and has received honoraria from Abbott Abvie for speaking engagements. W D F Venter has received conference travel support from Adcock Ingram and speaking-engagement honoraria from Merck, Jansen, Tibotech and Abbott. D R Boulware has received research support from GlaxoSmithKline (investigator-initiated grant) and Merck (medication for a clinical trial). D B Meya has received research support.

References

1. McCarthy K, Meintjies G, Arthington-Skaggs B, et al. Guidelines for the Diagnosis, Management and Prevention of Cryptococcal Meningitis and Disseminated Cryptococcosis in HIV-infected patients. Southern African Journal of HIV Medicine 2007;8(3):25-35.
2. National Institute for Communicable Diseases. GERMS-SA Annual Report 2011. Johannesburg: National Institute for Communicable Diseases, 2012.
3. World Health Organization. Rapid Advice - Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-infected Adults, Adolescents and Children. Geneva: World Health Organization, 2011. http://www.who.int/hiv/pub/cryptococcal_disease2011/en/ (accessed 7 May 2013).
4. Govender NP, Chetty V, Roy M, et al. Phased implementation of screening for cryptococcal disease in South Africa. S Afr Med J 2012;102:914-917. [http://dx.doi.org/10.7196/samj.6228]
5. Jarvis JN, Percival A, Bauman S, et al. Evaluation of a Novel Point of Care Cryptococcal Antigen (CRAG) Test on Serum, Plasma and Urine from Patients with HIV-associated Cryptococcal Meningitis. Clin Infect Dis 2011;53:1019-1023. [http://dx.doi.org/10.1093/cid/cir613]
6. Pappas PG, Chetchotisakd P, Larsen RA, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. Clin Infect Dis 2009;48:1775-1783. [http://dx.doi.org/10.1086/599112]
7. Bicanic T, Wood R, Meintjes G, et al. High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: A randomized trial. Clin Infect Dis 2008;47:123-130. [http://dx.doi.org/10.1086/588792]
8. Loyse A, Wilson D, Meintjes G, et al. Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis. Clin Infect Dis 2012;54:121-128. [http://dx.doi.org/10.1093/cid/cir745]
9. Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med 2013;368:1291-1302. [http://dx.doi.org/10.1056/NEJMoa1110404].
10. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis 2010;50:1532-1538. [http://dx.doi.org/10.1086/652652]
11. Boulware DR, Meya D, Muzoora C, et al. ART Initiation within the First 2 Weeks of Cryptococcal Meningitis Is Associated with Higher Mortality: A Multisite Randomized Trial. 20th Conference on Retroviruses and Opportunistic Infections (Abstract number 144), 3 - 6 March 2013, Atlanta, GA, USA.
12. Kambugu A, Meya DB, Rhein J, et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. Clin Infect Dis 2008;46:1694-1701. [http://dx.doi.org/10.1086/533468]
13. Govender N, Cohen C, Meiring S, et al. Trends in Treatment of Adults with Incident Cryptococcosis, South Africa, 2005-2008. In Abstracts and Programme: 17th Conference on Retroviruses and Opportunistic Infections (Abstract number 800), 16 - 19 February 2010, San Francisco, CA, USA.
14. National Department of Health. The South African Antiretroviral Treatment Guidelines - 2013. Pretoria: National Department of Health, 2013. http://www.doh.gov.za/docs/policy/2013/ART_Treatment_Guidelines_Final_25March2013.pdf (accessed 9 May 2013).
15. Meintjes G, Maartens G, Boulle A, et al. Guidelines for Antiretroviral Treatment in Adults. Southern African Journal of HIV Medicine 2013;13(1):114-133.
16. Sanne IM, Westreich D, Macphail AP, Rubel D, Majuba P, Van RA. Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: A prospective cohort study. J Int AIDS Soc 2009;12:38. [http://dx.doi.org/10.1186/1758-2652-12-38]
17. Jarvis JN, Lawn S, Vogt M, Bangani N, Wood R, Harrison TS. Screening for Cryptococcal Antigenaemia Among Patients in an Antiretroviral Treatment Program in South Africa. Clin Infect Dis 2009;48:856-862. [http://dx.doi.org/10.1086/597262]
18. Meya DB, Manabe YC, Castelnuovo B, et al. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a $CD4^+$ cell count ≤ 100 cells/μL who start HIV therapy in resource-limited settings. Clin Infect Dis 2010;51:448-455. [http://dx.doi.org/10.1086/655143]
19. Rajasingham R, Meya DB, Boulware DR. Integrating cryptococcal antigen screening and pre-emptive treatment into routine HIV care. J Acquir Immune Defic Syndr 2012;59:e85-e91. [http://dx.doi.org/10.1097/QAI.0b013e31824c837e]
20. Jarvis JN, Lawn SD, Wood R, Harrison TS. Cryptococcal antigen screening for patients initiating antiretroviral therapy: Time for action.

Clin Infect Dis 2010;51:1463-1465. [http://dx.doi.org/10.1086/657405]
21. Meiring ST, Quan VC, Cohen C, et al. A comparison of cases of paediatric-onset and adult-onset cryptococcosis detected through population-based surveillance, 2005 - 2007. AIDS 2012;26:2307-2314. [http://dx.doi.org/10.1097/QAD.0b013e3283570567]
22. Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town. South African Medicines Formulary – Tenth Edition. Cape Town: Health and Medical Publishing Group, 2012.
23. Jarvis JN, Meintjes G, Williams A, Brown Y, Crede T, Harrison TS. Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases. BMC Infect Dis 2010;10:67. [http://dx.doi.org/10.1186/1471-2334-10-67]
24. McCarthy KM, Morgan J, Wannemuehler KA, et al. Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence. AIDS 2006;20:2199-2206.
25. Jarvis JN, Meintjes G, Williams Z, Rebe K, Harrison TS. Symptomatic relapse of HIV-associated cryptococcal meningitis in South Africa: the role of inadequate secondary prophylaxis. S Afr Med J 2010;100:378-382.
26. Gumbo T, Kadzirange G, Mielke J, Gangaidzo IT, Hakim JG. *Cryptococcus neoformans* meningoencephalitis in African children with acquired immunodeficiency syndrome. Pediatr Infect Dis J 2002;21:54-56.
27. McMullan BJ, Halliday C, Sorrell TC, et al. Clinical utility of the cryptococcal antigen lateral flow assay in a diagnostic mycology laboratory. PLOS ONE 2012;7:e49541. [http://dx.doi.org/10.1371/journal.pone.0049541]
28. Govender NP, Patel J, van Wyk M, Chiller TM, Lockhart SR. Trends in antifungal drug susceptibility of Cryptococcus neoformans isolates obtained through population-based surveillance in South Africa in 2002 - 2003 and 2007 - 2008. Antimicrob Agents Chemother 2011;55:2606-2611. [http://dx.doi.org/10.1128/AAC.00048-11]
29. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: Value in the management of AIDS-associated cryptococcal meningitis. Clin Infect Dis 1994;18:789-792.
30. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010;50:291-322. [http://dx.doi.org/10.1086/649858]
31. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with amphotericin B or fluconazole. Clin Infect Dis 2007;45:76-80.
32. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: A randomised trial. Lancet 2004;363:1764-1767.
33. Panomvana Na Ayudhya D, Thanompuangseree N, Tansuphaswadikul S. Effect of rifampicin on the pharmacokinetics of fluconazole in patients with AIDS. Clin Pharmacokinet 2004;43:725-732.
34. Day JN. A randomized, double blind, placebo-controlled phase III trial of adjunctive dexamethasone in HIV-infected adults with cryptococcal meningitis. Current Controlled Trials ISRCTN59144167. [http://dx.doi.org/10.1186/ISRCTN59144167]
35. Theron E. Development of a tool to ensure correct stock management and accurate administration of intravenous amphotericin B. S Afr Pharmaceut J 2009:40-42.
36. Bisson GP, Molefi M, Bellamy S, et al. Early Versus Delayed Antiretroviral Therapy and Cerebrospinal Fluid Fungal Clearance in Adults With HIV and Cryptococcal Meningitis. Clin Infect Dis 2013;56:1165-1173. [http://dx.doi.org/10.1093/cid/cit019]
37. Wakeham K, Parkes-Ratanshi R, Watson V, Ggayi AB, Khoo S, Lalloo DG. Co-administration of fluconazole increases nevirapine concentrations in HIV-infected Ugandans. J Antimicrob Chemother 2010;65:316-319. [http://dx.doi.org/10.1093/jac/dkp451]
38. Manosuthi W, Athichathanabadi C, Uttayamakul S, Phoorisri T, Sungkanuparph S. Plasma nevirapine levels, adverse events and efficacy of antiretroviral therapy among HIV-infected patients concurrently receiving nevirapine-based antiretroviral therapy and fluconazole. BMC Infect Dis 2007;7:14.
39. Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. Clin Infect Dis 2000;30:47-54.
40. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infect Dis 2010;10:791-802. [http://dx.doi.org/10.1016/S1473-3099(10)70170-5]
41. Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: A prospective study. J Acquir Immune Defic Syndr 2009;51:130-134. [http://dx.doi.org/10.1097/QAI.0b013e3181a56f2e]
42. Muller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: A systematic review and meta-analysis. Lancet Infect Dis 2010;10:251-261. [http://dx.doi.org/10.1016/S1473-3099(10)70026-8]