Cryptococcal Disease Guideline Update

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23 July 2020

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

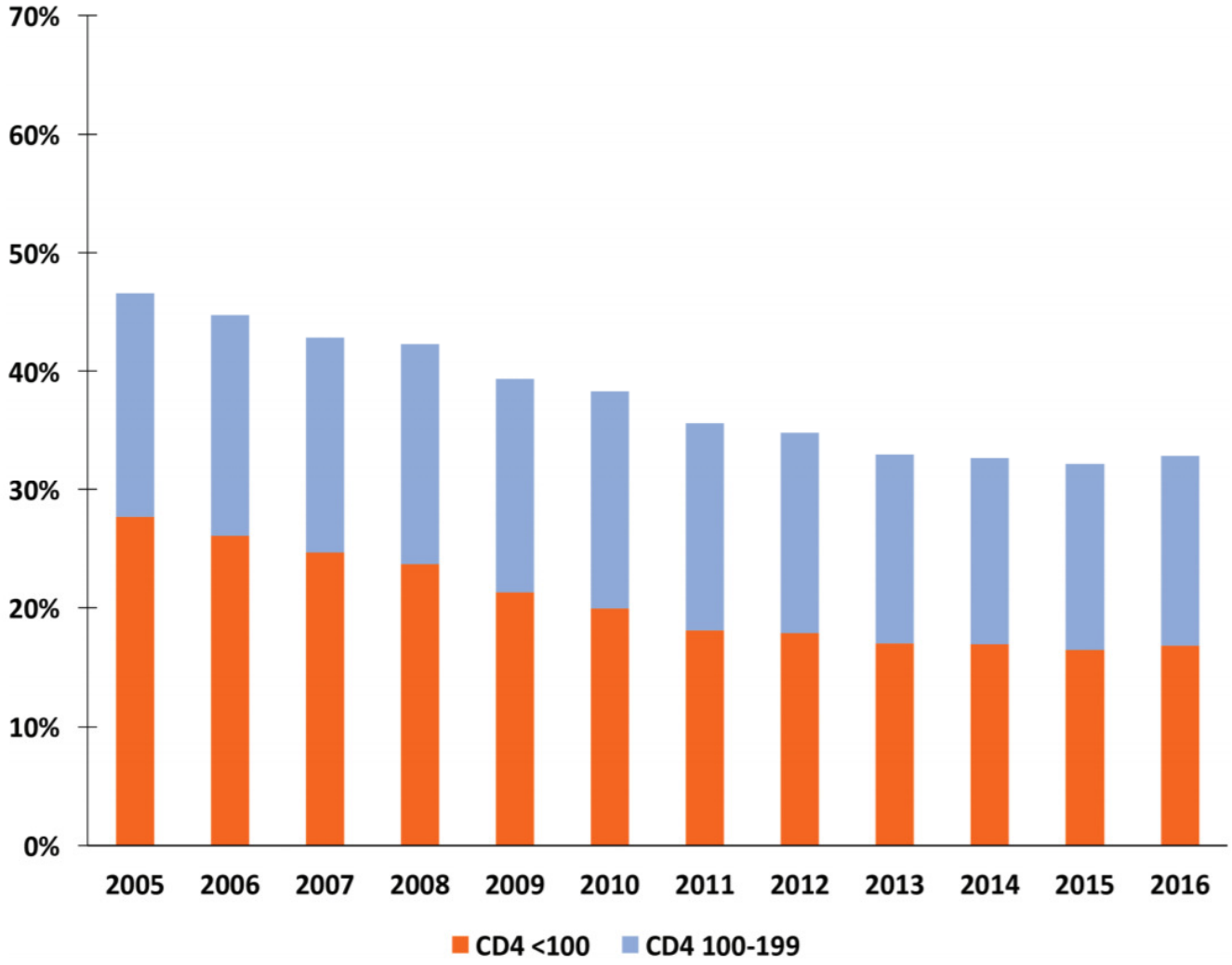
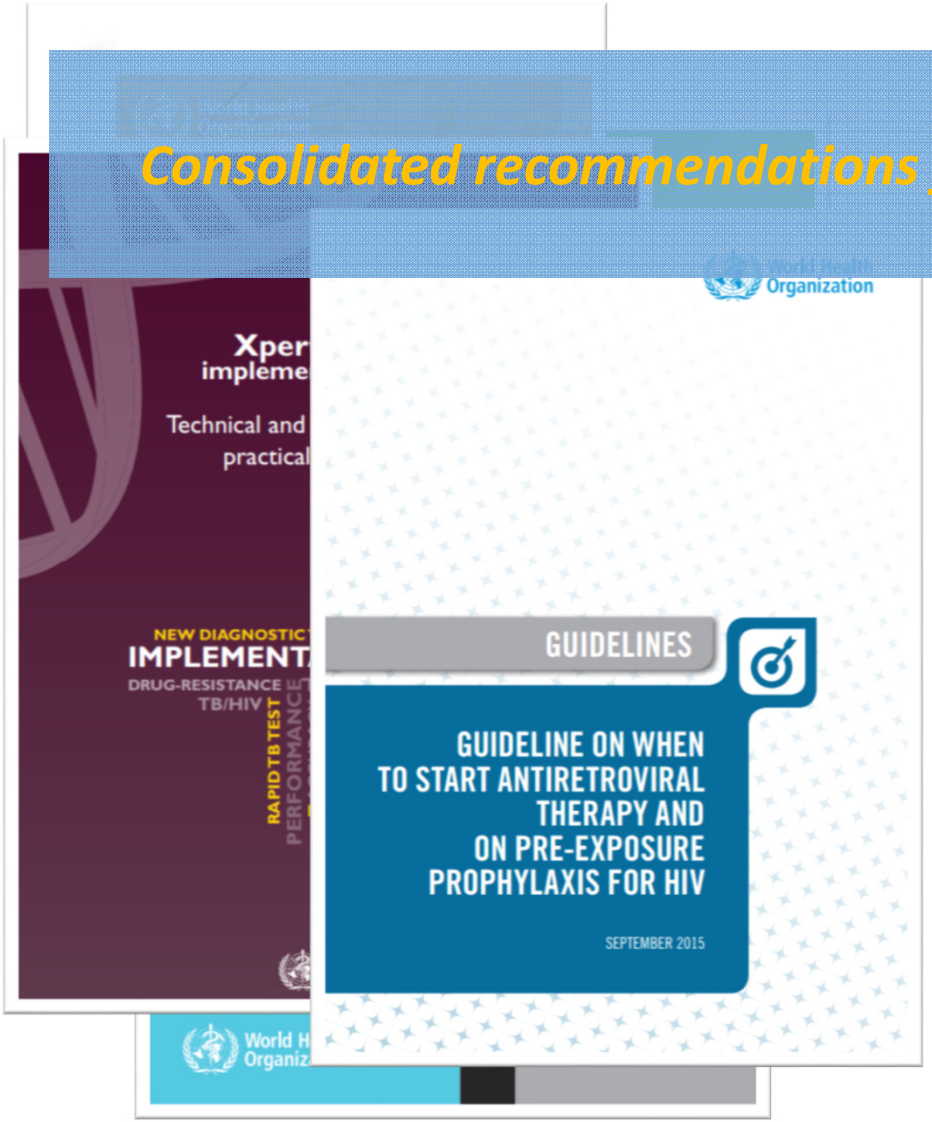
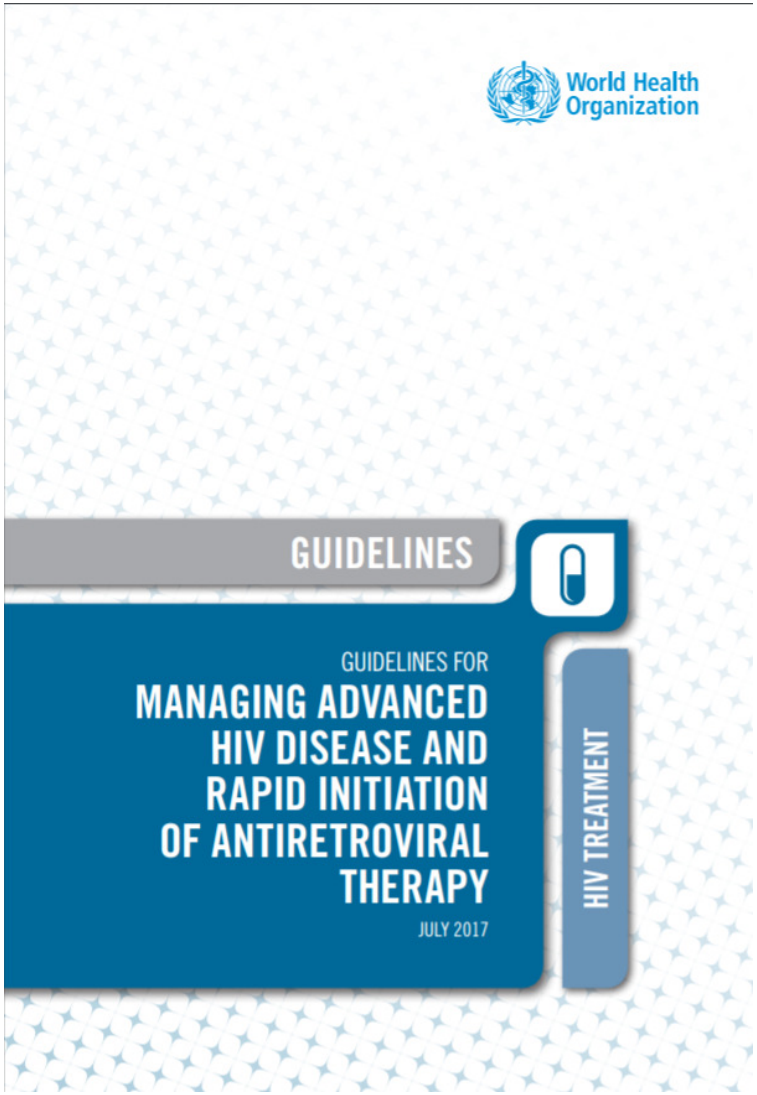


Figure 1. Proportion of patients entering care with advanced and very advanced HIV disease (first CD4 count test <100 and 100–199 cells/μL).

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 <200cells/mm^3 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.

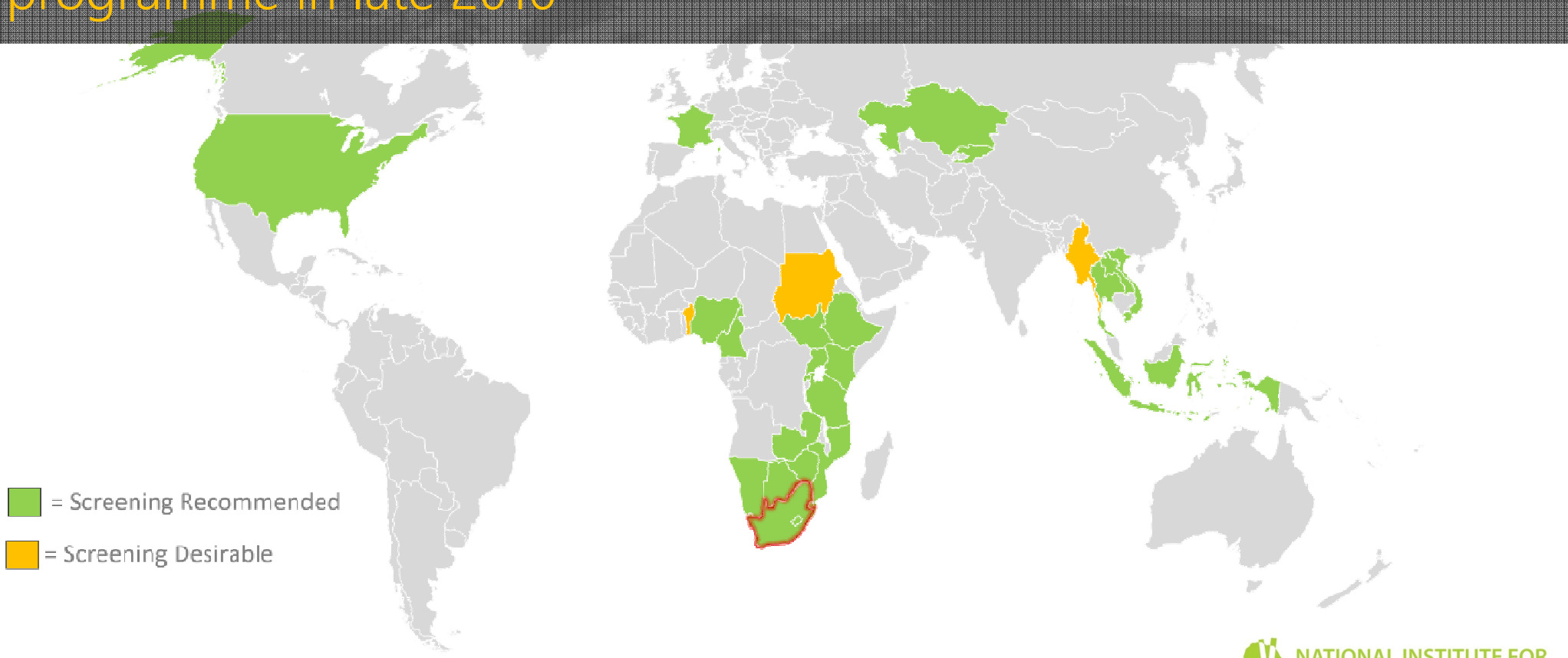
(Strong recommendation, moderate-quality evidence)

Table 1: Components of package of care interventions for advanced HIV disease

Areas for the package	Intervention	CD4 cell count	Adults and adolescents	Children
Screening and diagnosis	Sputum Xpert MTB/RIF as first test for TB diagnosis in symptomatic patients	any	yes	yes
	Urine LF-LAM for TB diagnosis in patients with symptoms and signs of TB	≤100 cells/mm³ Or at any CD4 cell count value if seriously ill	yes	yes*
	Cryptococcal antigen (CrAg) screening	≤ 100 cells/mm³ *	yes	no
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis§	≤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	yes	yes**
	TB preventive treatment§	any	yes	yes#
	Fluconazole pre-emptive therapy for CrAg-positive patients without evidence of meningitis	< 100 cells/mm³	yes	Not applicable (Screening not advised)
	Rapid ART initiation	any	yes	yes
ART initiation	Defer ART initiation if clinical signs and symptoms are suggestive of TB or cryptococcal meningitis	any	yes	yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to advance disease care package, including home visits if feasible	< 200 cells/mm³	yes	yes

*updated to <200 in 2018 WHO guideline

South Africa was first to implement a national CrAg screening programme in late 2016



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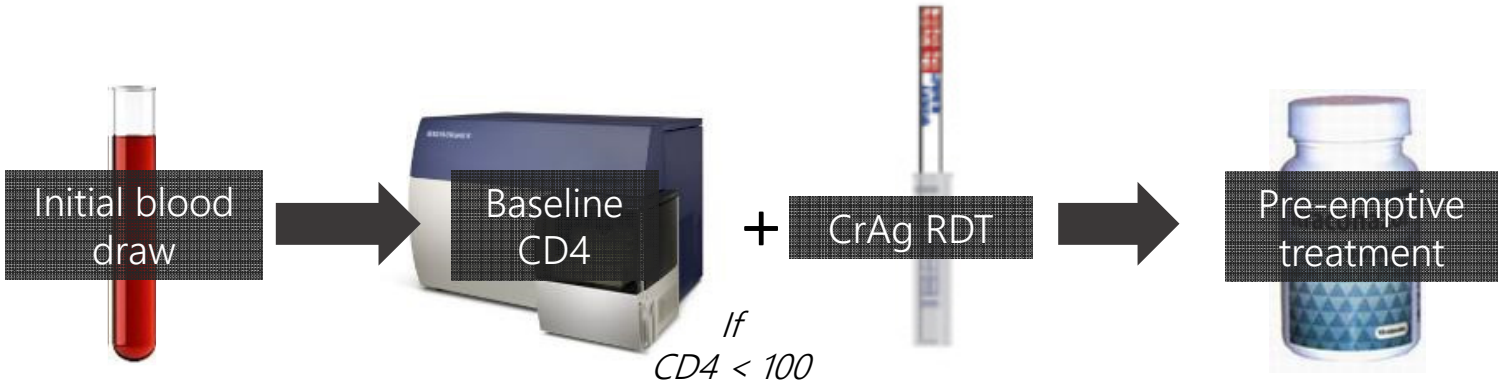
Division of the National Health Laboratory Service

South Africa uses a laboratory-based reflex screening model



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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/mm^3 (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

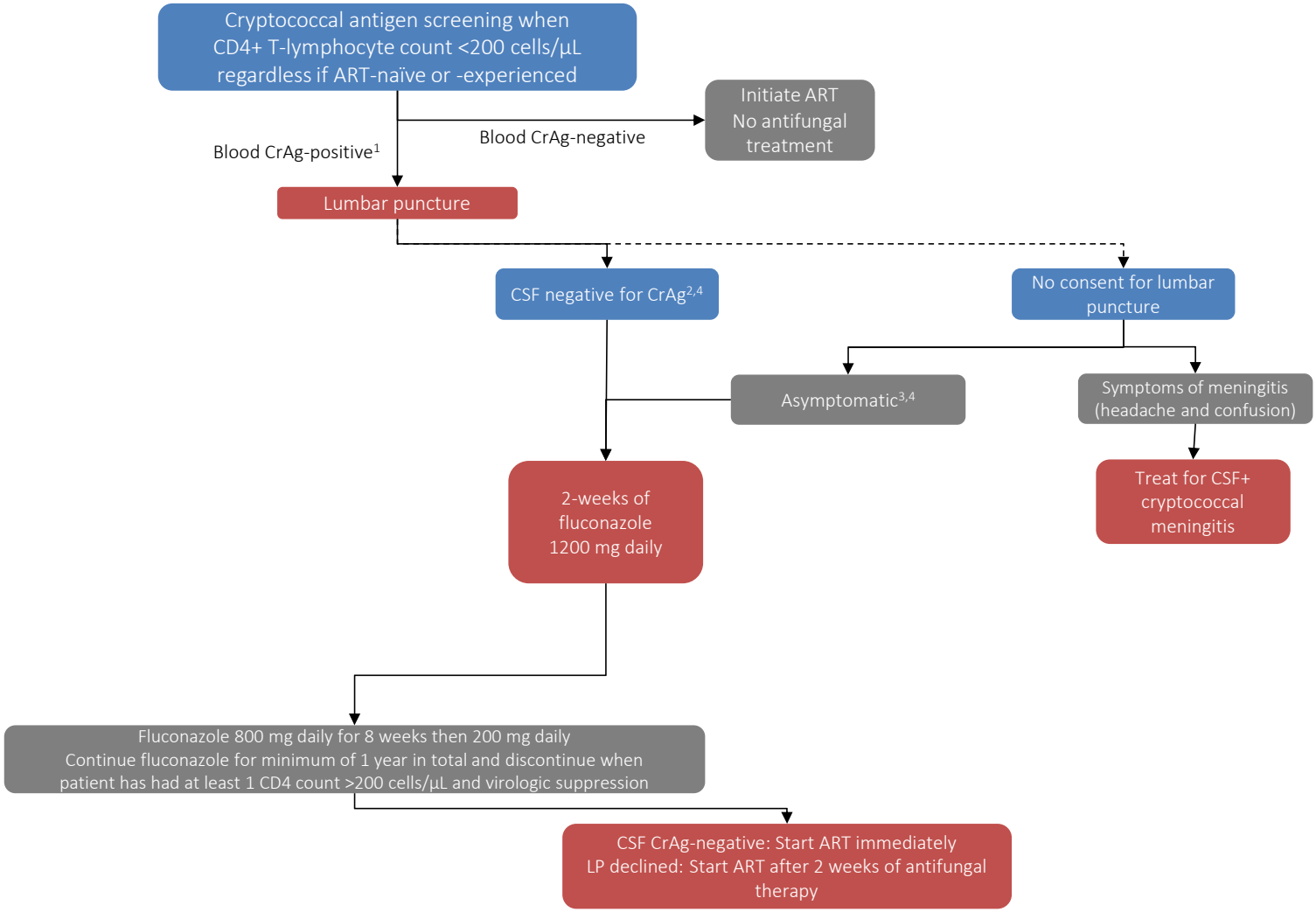
*Note – you have to specifically order a CrAg screening test if the patient's CD4 count is 100-200

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

CrAg screen-and-treat algorithm



Govender NP, et al. S Afr J HIV Med 2019

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

CD4	CrAg prevalence
≤ 100	6.5% (95% CI, 5.7%-7.3%)
101-200	2.0% (95% CI, 1.2-2.7%)

Ford N et al. CID. 2018;66(S2):S152-9

CD4	Mortality rate ratio
≤ 100	0.75 (95% CI, 0.58-0.95)
101-200	0.56 (95% CI, 0.32-0.97)

Mfinanga S et al. Lancet. 2015;385(9983):2173-82

- However, the NDOH recommendation has <u>not</u> changed as yet → screening threshold of <100 cells/µL

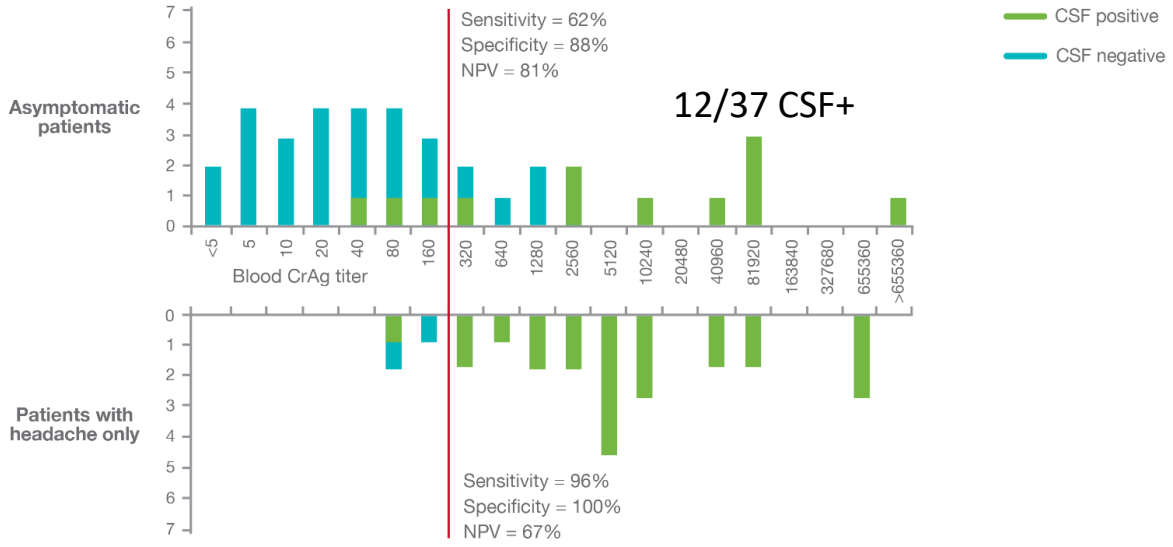
What's new in the SAHCS guideline?

- 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)

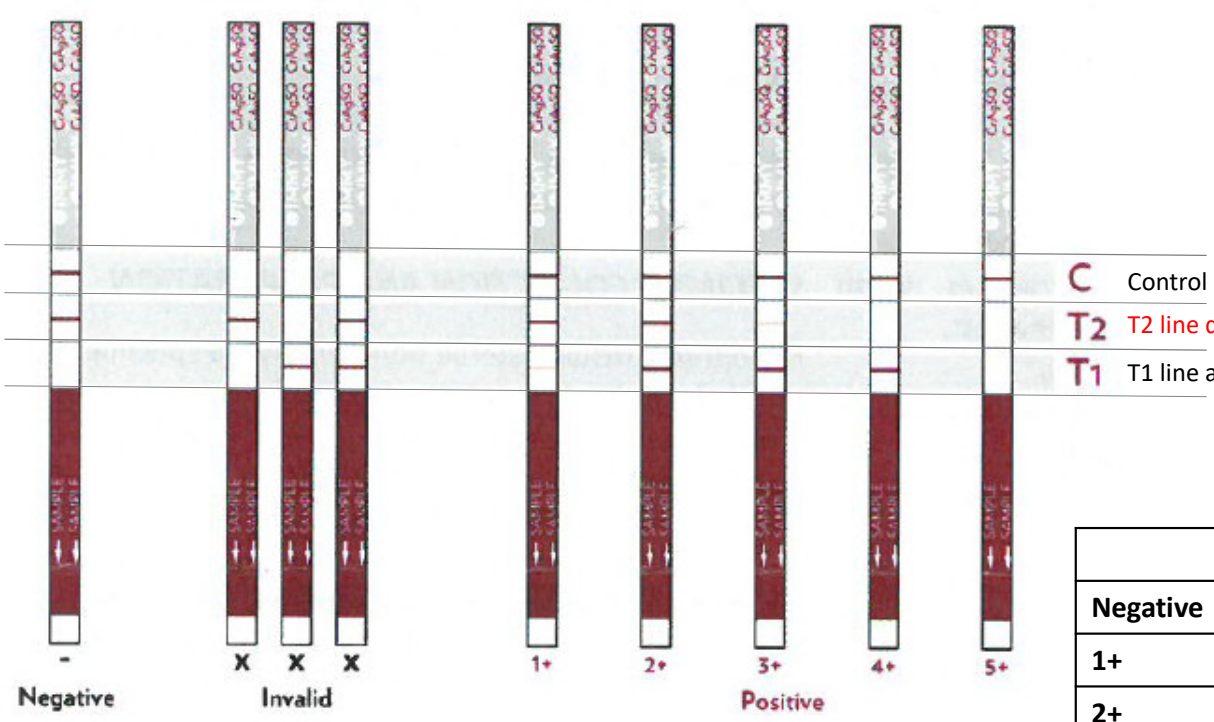
Why? 1 in 3 patients with a blood CrAg+ test have subclinical cryptococcal meningitis



Wake RM, et al. Clin Infect Dis 2017

Figure 3.
Blood cryptococcal antigen (CrAg) titers in asymptomatic CrAg-positive patients (n = 37) (Upper), CrAg-positive patients with headache only (n = 25) (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



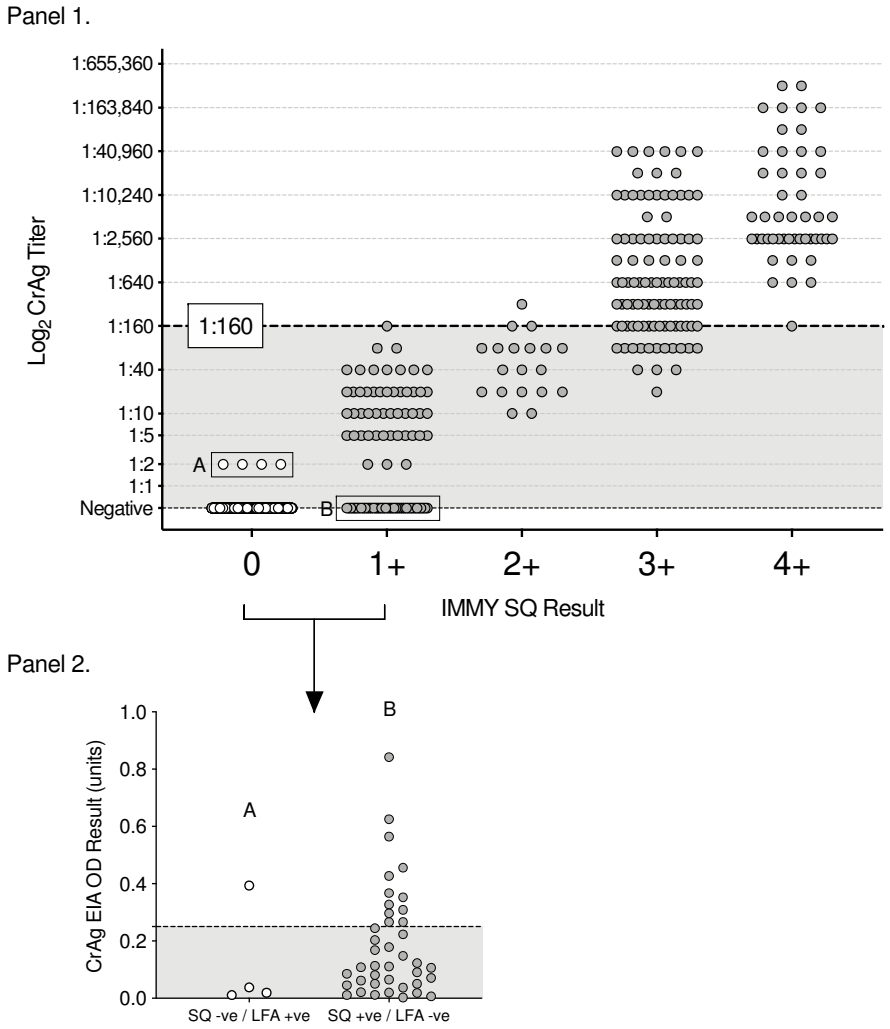
C Control line should always be present

T2 T2 line disappears with a “stronger” reaction

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

	C	T1	T2
Negative	+	-	+
1+	+	+/-	+
2+	+	+	+
3+	+	+	+/-
4+	+	+	-
5+	+	-	-

www.immy.com



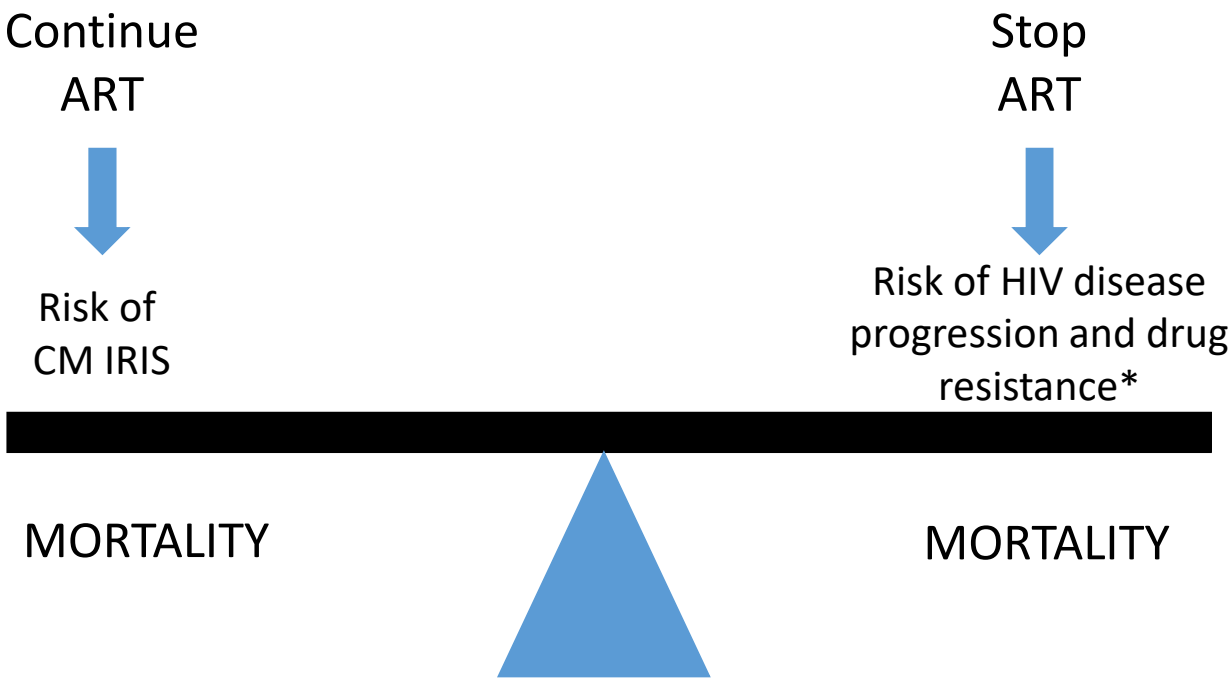
Jarvis JN, et al. J Clin Microbiol 2020

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

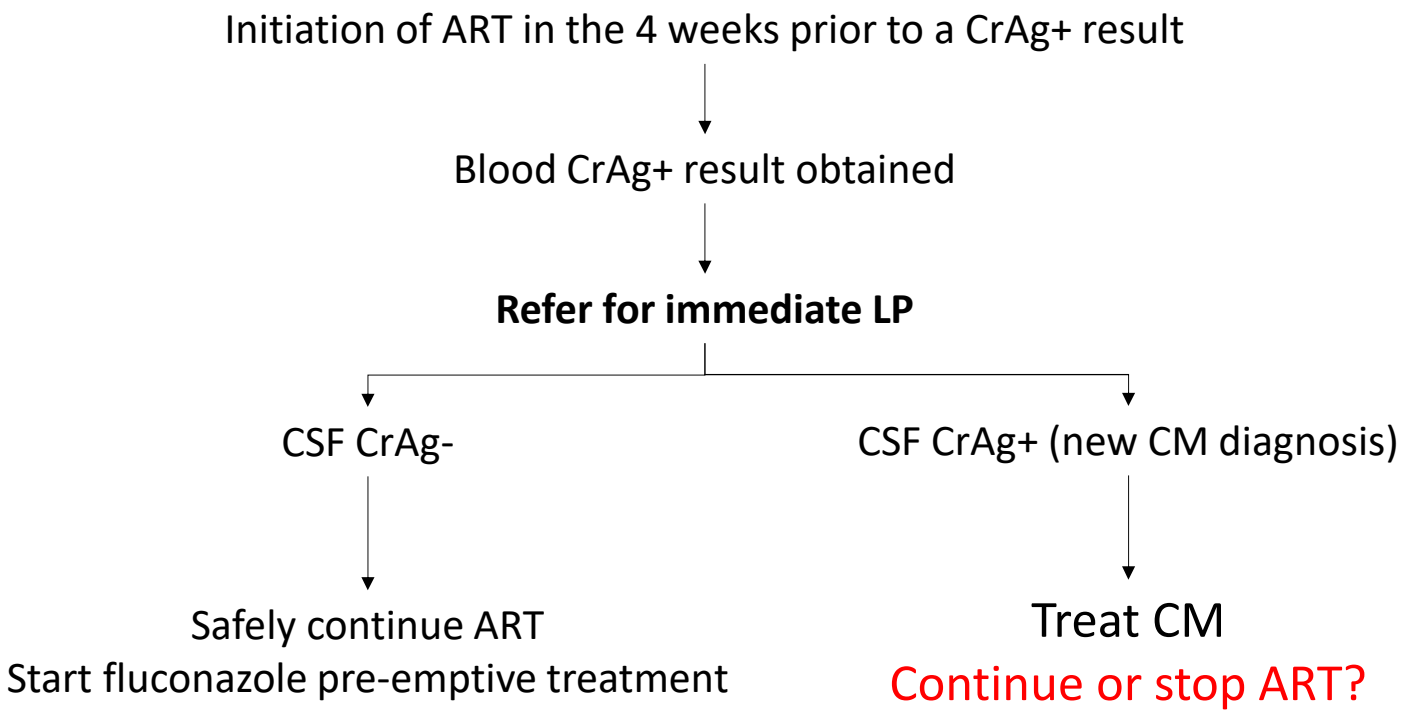
How to manage a blood CrAg+ result after recent ART initiation



Clinical equipoise

*Though lower risk with dolutegravir

How to manage a blood CrAg+ result after recent ART initiation

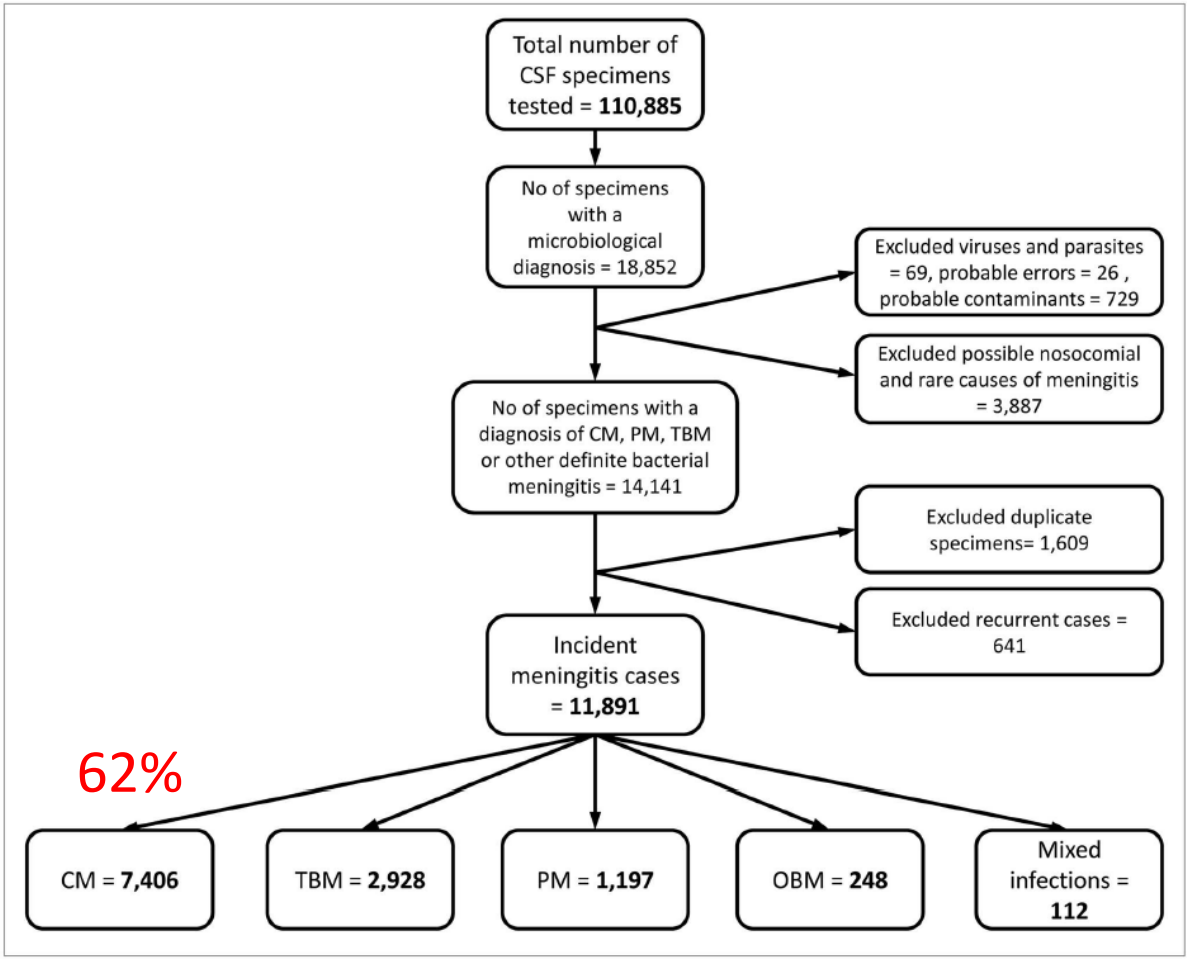


Govender NP, et al. S Afr J HIV Med 2019

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

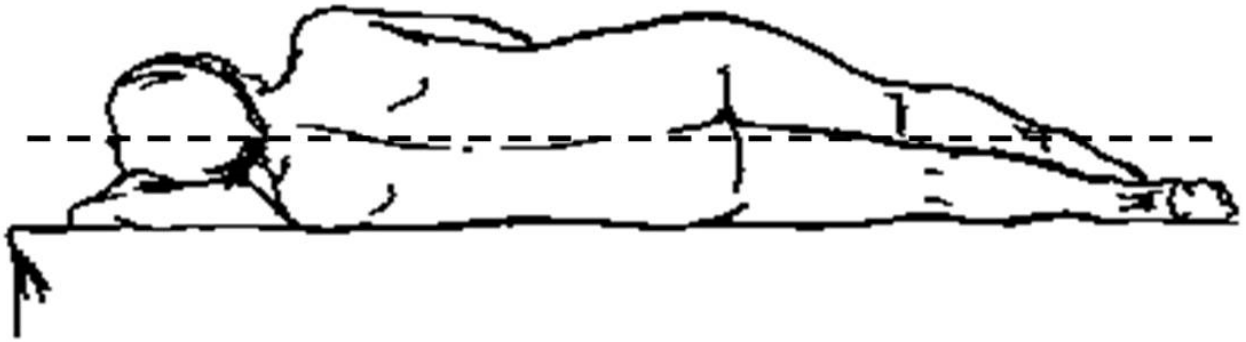
Test CSF to confirm diagnosis

- 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_2O
- *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 H_20, remove 10-30 ml CSF to reduce pressure by at least 50% or to <20 cm H_20
- 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

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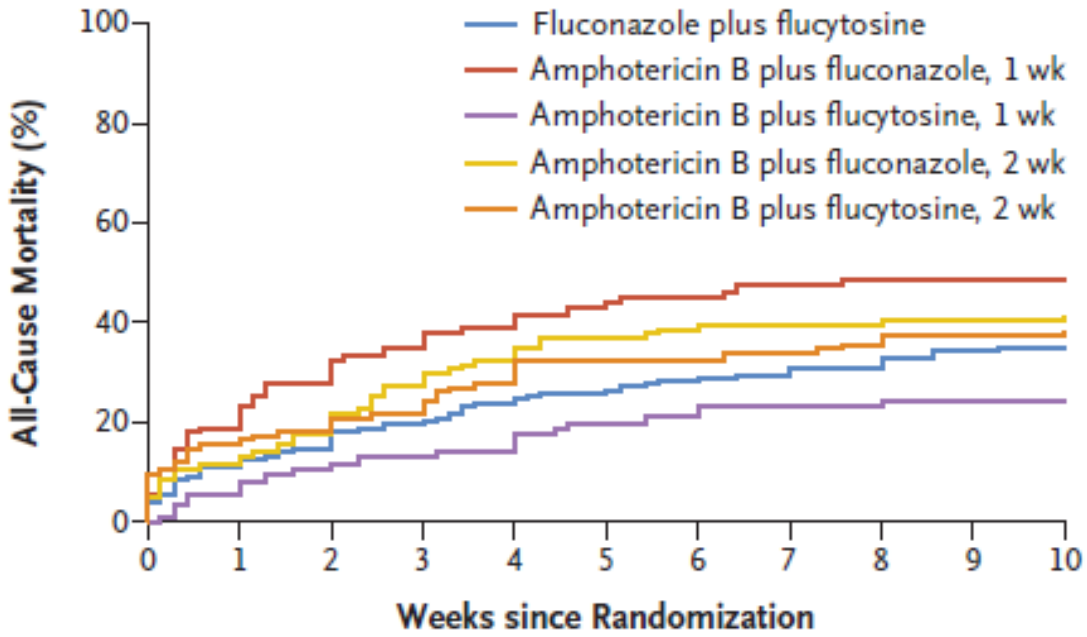
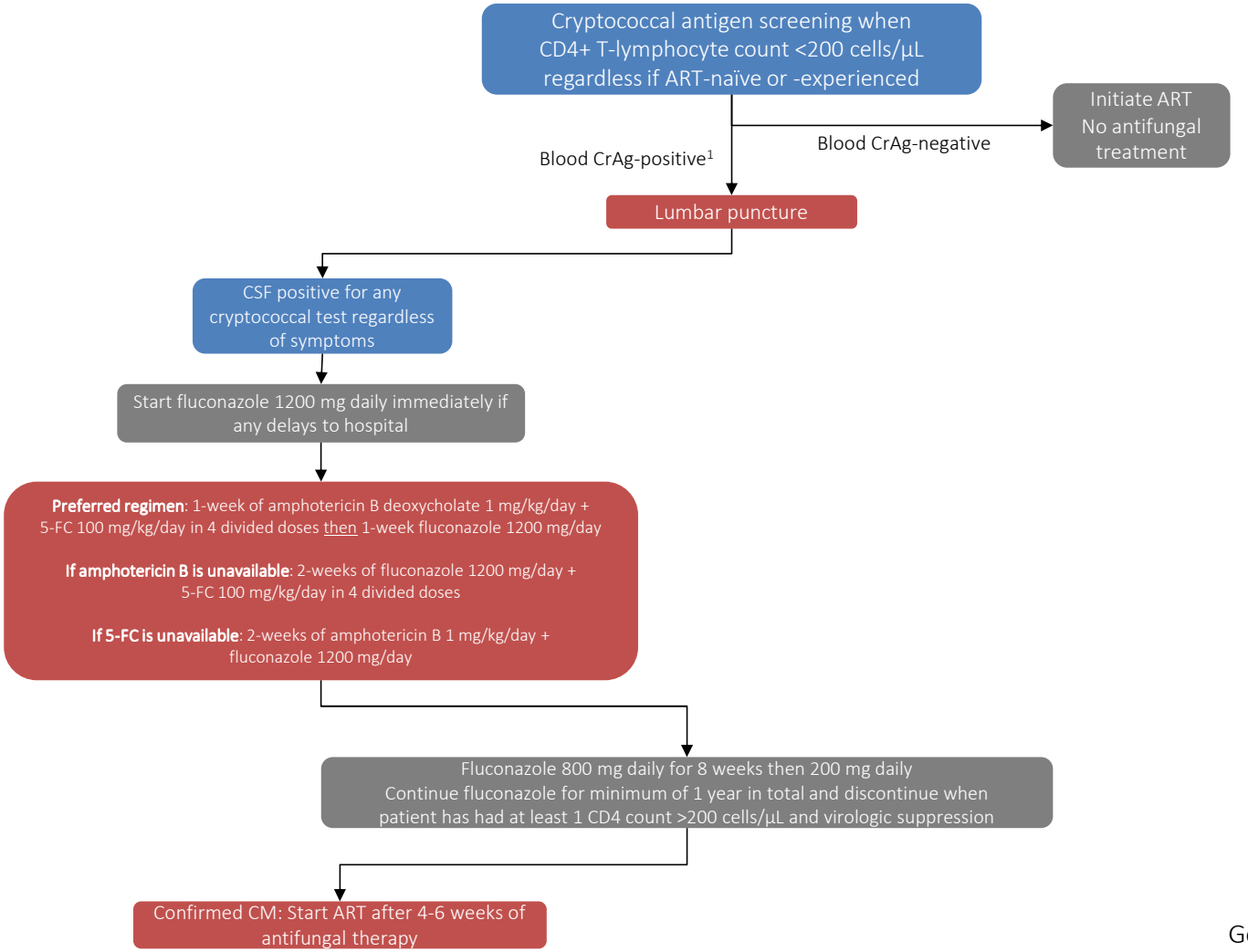


Molloy S, et al. N Engl J Med 2018

CrAg screen-and-treat algorithm



Govender NP, et al. S Afr J HIV Med 2019

Previously-unavailable therapeutic options

Flucytosine (5-FC)
Ancotil (Mylan)

More effective partner drug than fluconazole

Half-life prolonged in patients with impaired renal function.

Category C drug in pregnancy; no data in breastfeeding

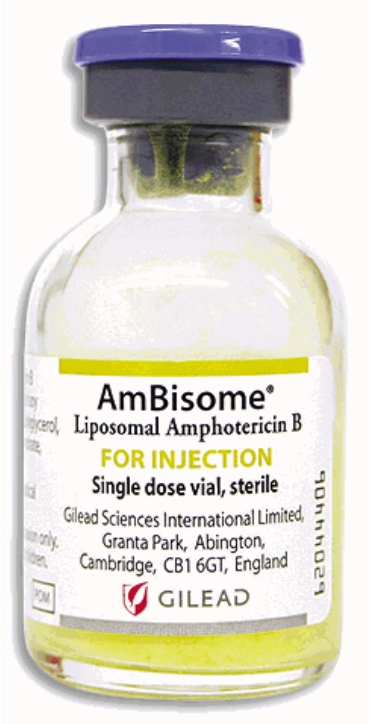
Not yet registered but available through Section 21 application

Liposomal amphotericin B
Ambisome (Gilead)

Compared to AmB deoxycholate: similar efficacy and less nephrotoxic

Registered in South Africa but expensive ($16.25 per 50 mg vial)

NOTE - DIFFERENT DAILY DOSE TO AMPHOTERICIN B DEOXYCHOLATE



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

Shroufi A, et al. Int J Infect Dis 2019
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

TABLE 6: Induction therapy doses of flucytosine, fluconazole and amphotericin B adjusted according to estimated glomerular filtration rates for adults.

Antifungal agent	eGFR > 50	eGFR 10–50	eGFR < 10	Haemodialysis
Amphotericin B deoxycholate	1 mg/kg	1 mg/kg	1 mg/kg	1 mg/kg (can administer during dialysis)
Fluconazole	1200 mg daily	600 mg daily	600 mg daily	600 mg daily; dose after dialysis
Flucytosine	25 mg/kg 6 hourly	25 mg/kg 12 hourly	25 mg/kg daily	25 mg/kg daily; dose after dialysis

Source: The Sanford guide to antimicrobial therapy 2019 / editors, David N. Gilbert, M.D., George M. Eliopoulos, M.D., Henry F. Chambers, M.D., Michael S. Saag, M.D., Andrew T. Pavia, M.D. Sperryville, VA, USA: Antimicrobial Therapy, Inc., [2019]

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 m^2

Note - no dose adjustments with fluconazole and rifampicin co-administration

Recommended regimens with baseline renal impairment

Calculate creatinine clearance (GFR)

30-50 mL/min

	Week 1	**Week 2**
LAmB available	LAmB 3-4 mg/kg/day + 5FC	Fluconazole
LAmB unavailable	AmBd 1 mg/kg/day + 5FC	Fluconazole

<30 mL/min

	Week 1	**Week 2**
LAmB available	LAmB 3-4 mg/kg/day + 5FC	Fluconazole
LAmB unavailable	Fluconazole + 5FC	Fluconazole
LAmB and 5FC unavailable	AmBd 0.7 mg/kg stat and then on alternate days if CrCL static + fluconazole	As for week 1

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

Weight (kg)	Number of 50 mg vials	Total daily dose of AmBisome (mg)	Approximate daily dose/ weight (mg/kg)	Volume of reconstituted AmBisome (ml) at 4 mg/ml	Additional dextrose (ml) to create a 1-litre total infusion
40	3	150	3.8	37.5	962.5
41-45	3	150	3.3	37.5	962.5
46-50	4	200	4.0	50	950
51-55	4	200	3.6	50	950
56-60	4	200	3.3	50	950
61-65	5	250	3.8	62.5	937.5
66-70	5	250	3.6	62.5	937.5
71-75	6	300	4.0	75	925
76-80	6	300	3.8	75	925
81-85	6	300	3.5	75	925

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.

Lower weight limit (kg)	Upper weight limit (kg)	Number of pills	Total dose (mg)	Daily dose for lower weight limit (mg/kg)	Daily dose for upper weight limit (mg/kg)	Dose 1†	Dose 2†	Dose 3†	Dose 4†
20	24	4	2000	100.00	83.33	1	1	1	1
25	29	5	2500	100.00	86.21	2	1	1	1
30	34	6	3000	100.00	88.24	2	1	2	1
35	39	7	3500	100.00	89.74	2	2	2	1
40	44	8	4000	100.00	90.91	2	2	2	2
45	49	9	4500	100.00	91.84	3	2	2	2
50	54	10	5000	100.00	92.59	3	2	3	2
55	59	11	5500	100.00	93.22	3	3	3	2
60	64	12	6000	100.00	93.75	3	3	3	3
65	69	13	6500	100.00	94.20	4	3	3	3
70	74	14	7000	100.00	94.59	4	3	4	3
75	79	15	7500	100.00	94.94	4	4	4	3
80	84	16	8000	100.00	95.24	4	4	4	4

†, Number of 500 mg pills per dose.

Case

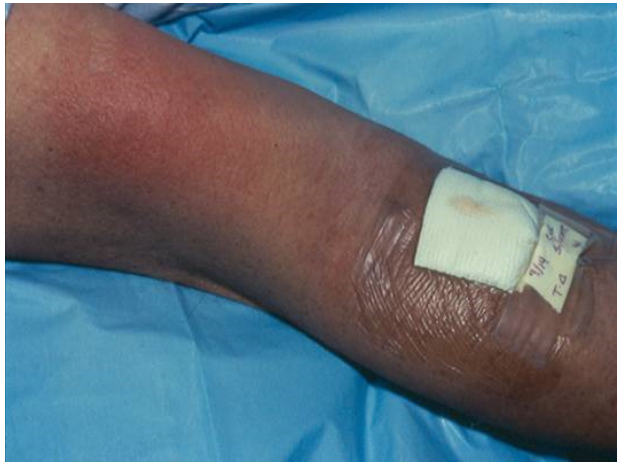
- Induction-phase treatment *with renal adjustment*:
  - Wk. 1: amphotericin B 1 mg/kg per day + 5-FC 25 mg/kg BD
  - Wk. 2: fluconazole 600 mg per day

- *How should amphotericin B deoxycholate be administered?*

10-step checklist for AmBd

	Item	Check if done	Response
1	Has correct daily dose been prescribed based on body weight (1 mg/kg/day)?	✓	If yes, proceed
2	Have lab tests been checked?	✓	If yes, proceed
3	Is peripheral IV line correctly inserted?	✓	If yes, proceed
4	Is there any sign of phebitis?	✓	If yes, stop and replace line
5	Are other meds being administered?	✓	If yes, stop until finished
6	Has 1 litre normal saline with 20 mmol KCl been infused over 2 hours?	✓	If yes, proceed
7	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?	✓	If yes, proceed
8	Has AmB been infused over 4 hours minimum?	✓	If no, watch for arrhythmias
9	Has line been flushed with normal saline once infusion completed?	✓	If yes, proceed
10	Has bag containing AmB been removed?	✓	If yes, end of procedure

Amphotericin B deoxycholate is toxic



Monitoring lab tests for AmBd and 5-FC

TABLE 8: Laboratory monitoring according to induction regimen used.

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

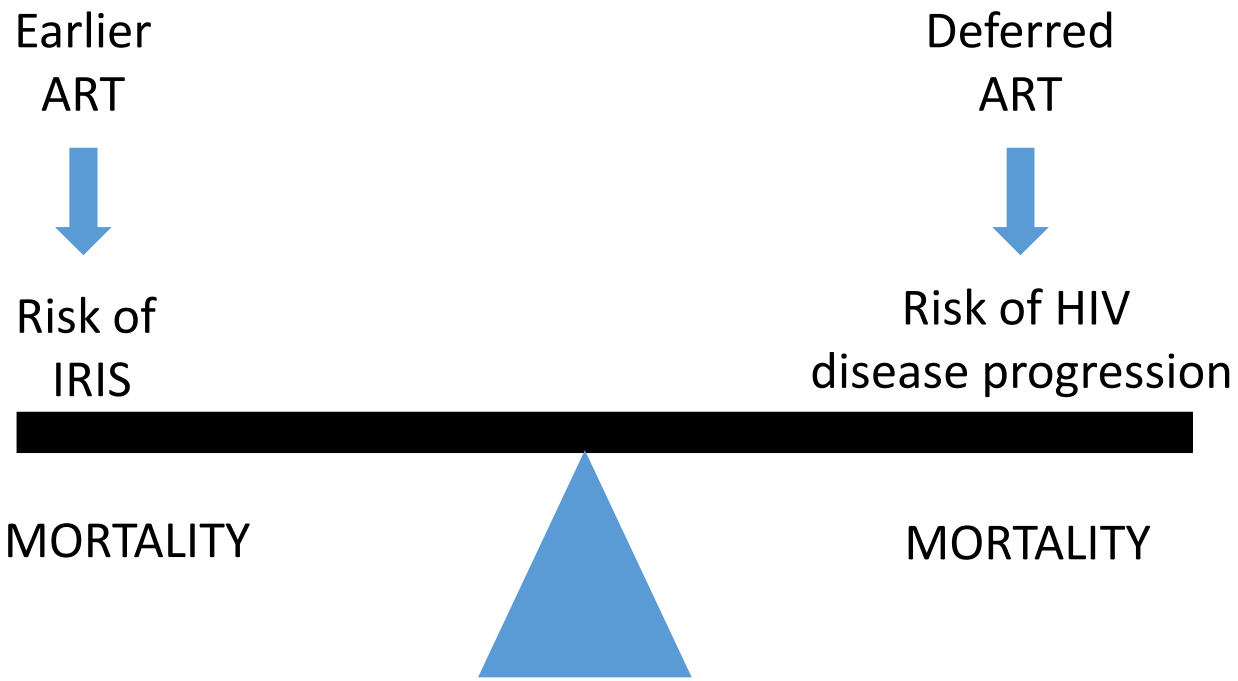
Govender NP, et al. S Afr J HIV Med 2019

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

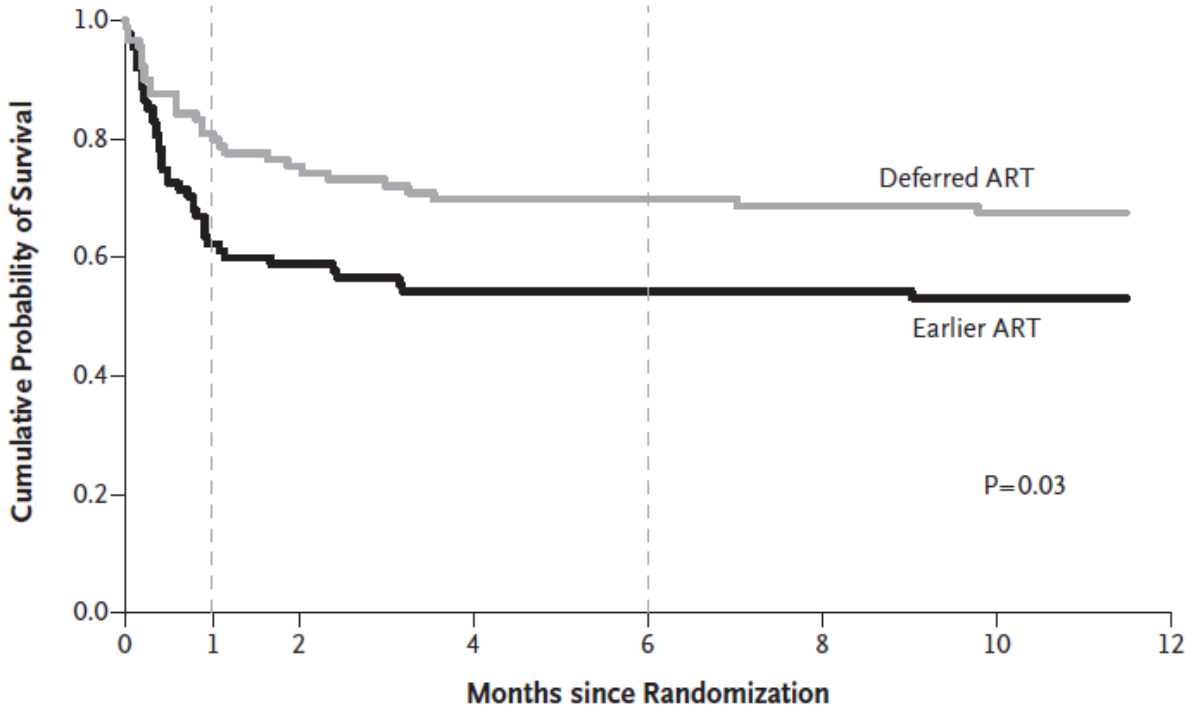
- *When should ART ideally be started after a CM diagnosis?*

*Though this is recommended for patients with multiple CSF culture+ relapse episodes



When to start ART <u>after</u> a diagnosis of CM?

Overall Survival



No. at Risk

Earlier ART	88	54	51	47	47	46	42
Deferred ART	89	72	67	62	62	61	59

Boulware DR, et al. New Engl J Med 2014

Case

- Readmitted to hospital several months later with severe headache

- *How should a subsequent episode of CM be diagnosed and managed?*

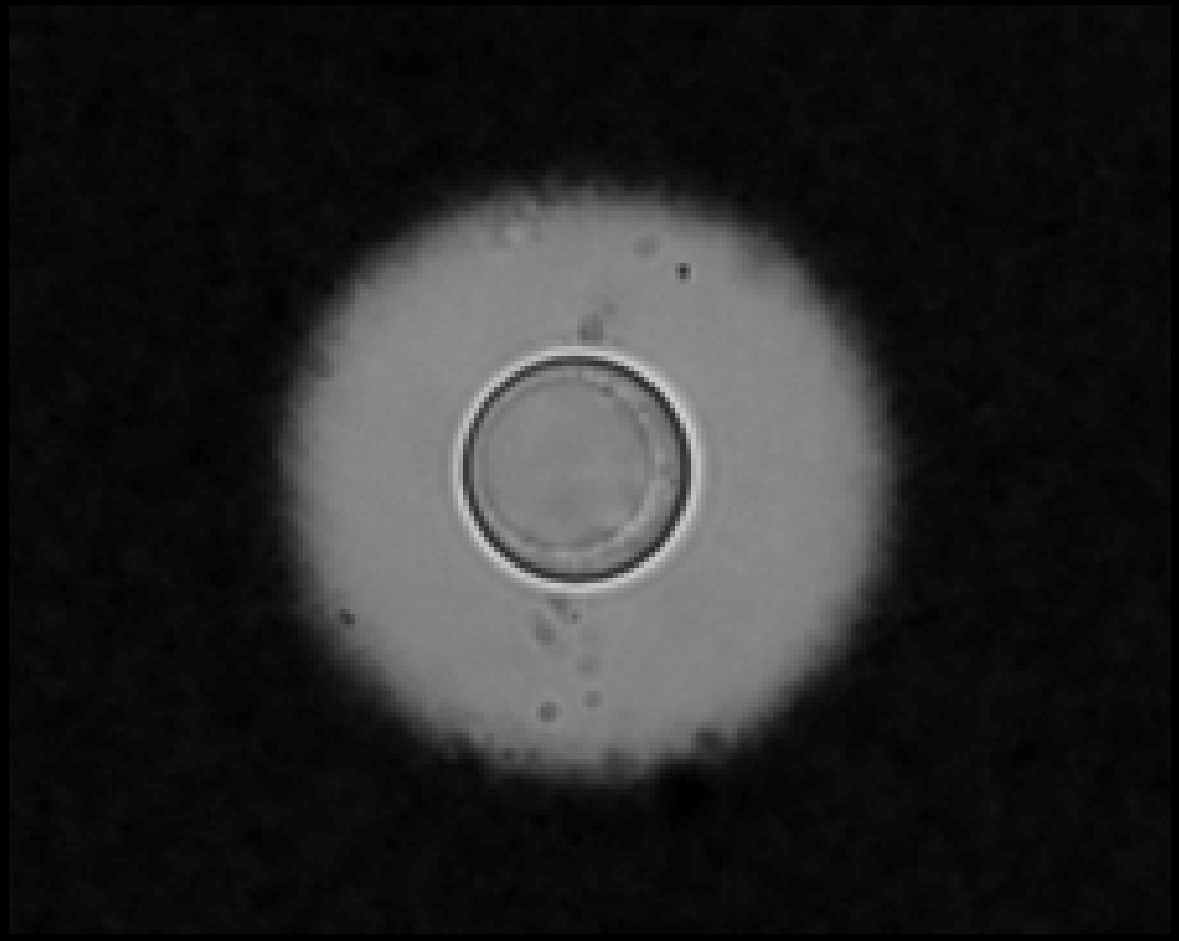
Careful clinical assessment

- 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)

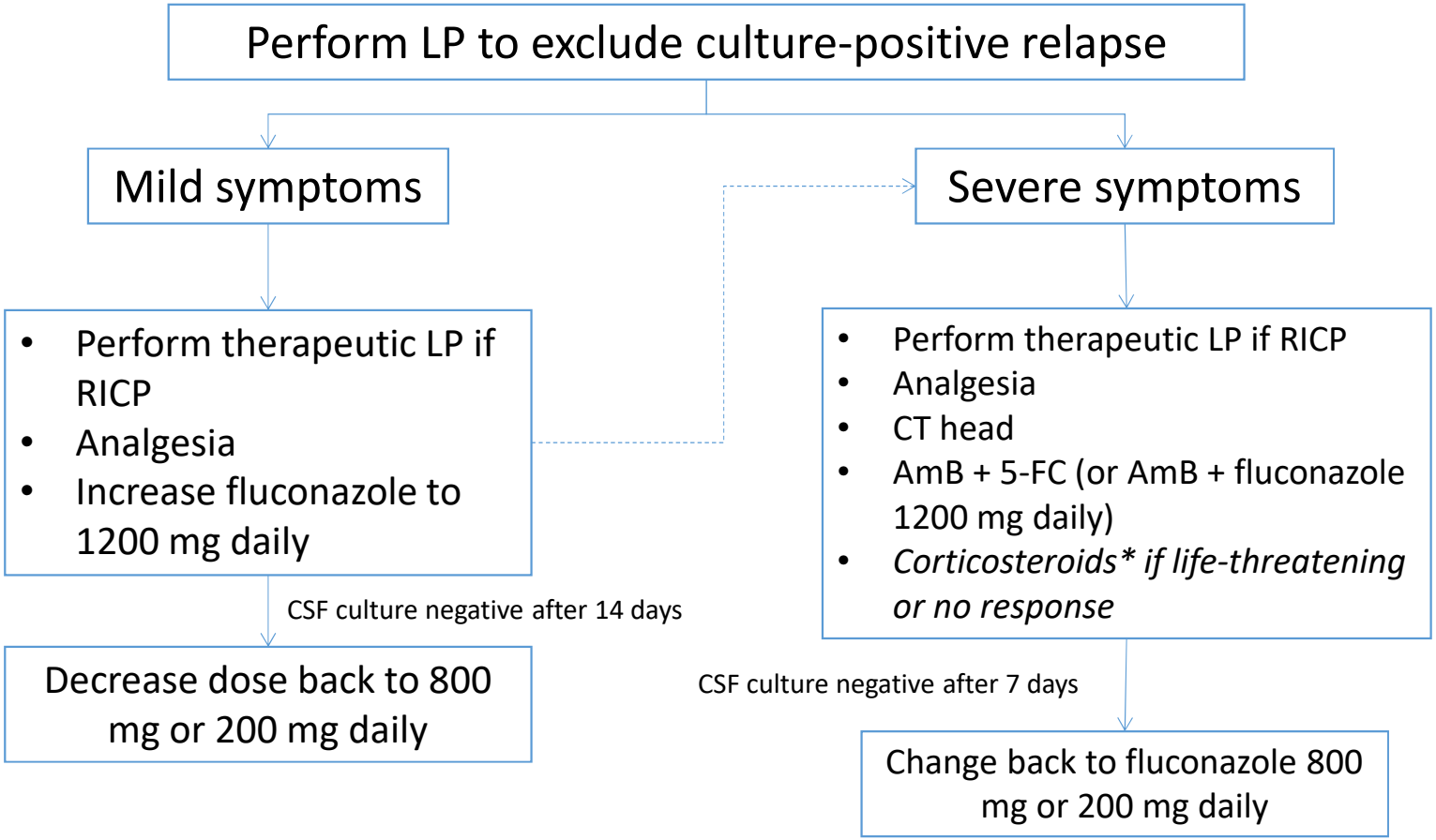
Dead or alive?



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



**Preferred if CSF culture is known NEGATIVE and other aetiologies excluded (TB, viral)*

When should fluconazole resistance be considered?

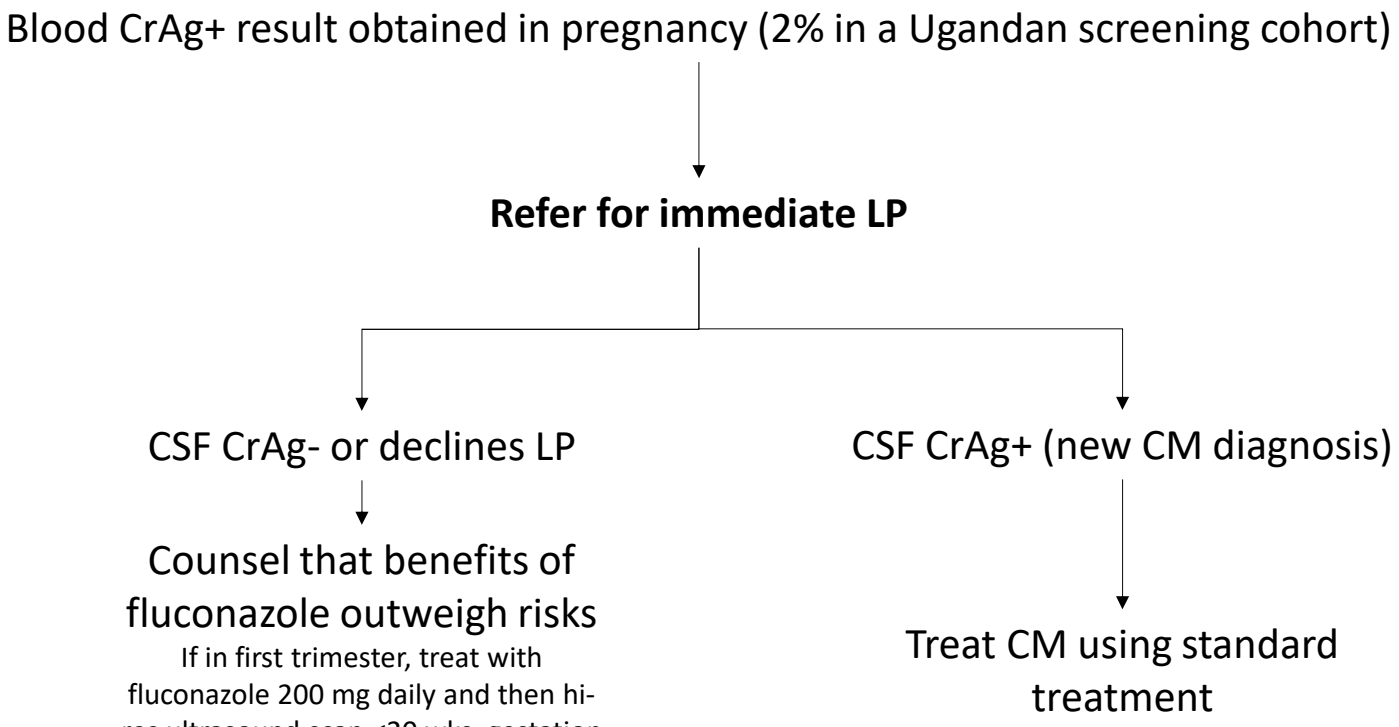
- At least 1 relapse episode and other causes excluded

- If fluconazole MICs are elevated, consider an alternative maintenance regimen:
  - Higher-dose fluconazole
  - Other triazole agents
  - Weekly amphotericin B

TABLE 10: Possible causes of recurrent symptoms and signs of meningitis in cryptococcal meningitis.

Symptoms	Causes
Attributable to CM	
CM relapse†	Possible causes of CM relapse (positive fungal culture) Fungal: • Inadequate induction therapy (e.g. suboptimal amphotericin B deoxycholate administration because of toxicity) • Non-adherence to fluconazole consolidation or maintenance therapy • Fluconazole resistance (uncommon if preferred induction regimens are used) • CNS cryptococcomas or gelatinous pseudocysts (requiring prolonged induction therapy) Immunological: • ART not initiated 4–6 weeks after CM induction therapy • Immunological failure because of virological failure of ART
Paradoxical IRIS	Features of IRIS (most cases have negative CSF fungal culture) • Occurs weeks to months after ART initiation • Because of an inflammatory response directed at antigens of non-viable fungus • Associated with higher CSF white cell counts, compared to the initial (culture positive) episode of CM • Frequently accompanied by raised intracranial pressure and can be associated with focal brain inflammation and/or mass lesions
Persistently elevated ICP	Thought to be mediated by occlusion of arachnoid granulations by fungi and fungal capsule; this does not necessarily imply CM treatment failure.
Unrelated to CM	
New diagnosis	Possible causes: • Tuberculous meningitis • Viral or bacterial meningitis • Space-occupying lesion with cerebral oedema (e.g. tuberculoma, CNS malignancy) or hydrocephalus • Non-infective (e.g. tension headache)

How to manage a blood CrAg+ result in a pregnant woman



Pastick K, et al. Med Mycol 2019
Govender NP, et al. S Afr J HIV Med 2019

Key differences between SAHCS and NDOH guidelines

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

http://www.health.gov.za/index.php/component/phocadownload/category/286-hospital-level-adults
https://sahivsoc.org/SubHeader?slug=ndoh-and-who-guidelines

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- National AHD task team
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- Ambition-CM trial consortium for sharing some teaching aids

DREAMM
Driving Reduced AIDS-associated Meningo-encephalitis Mortality

AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

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