Cryptococcal Disease:
Proposed Algorithm for Screening

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Acknowledgements

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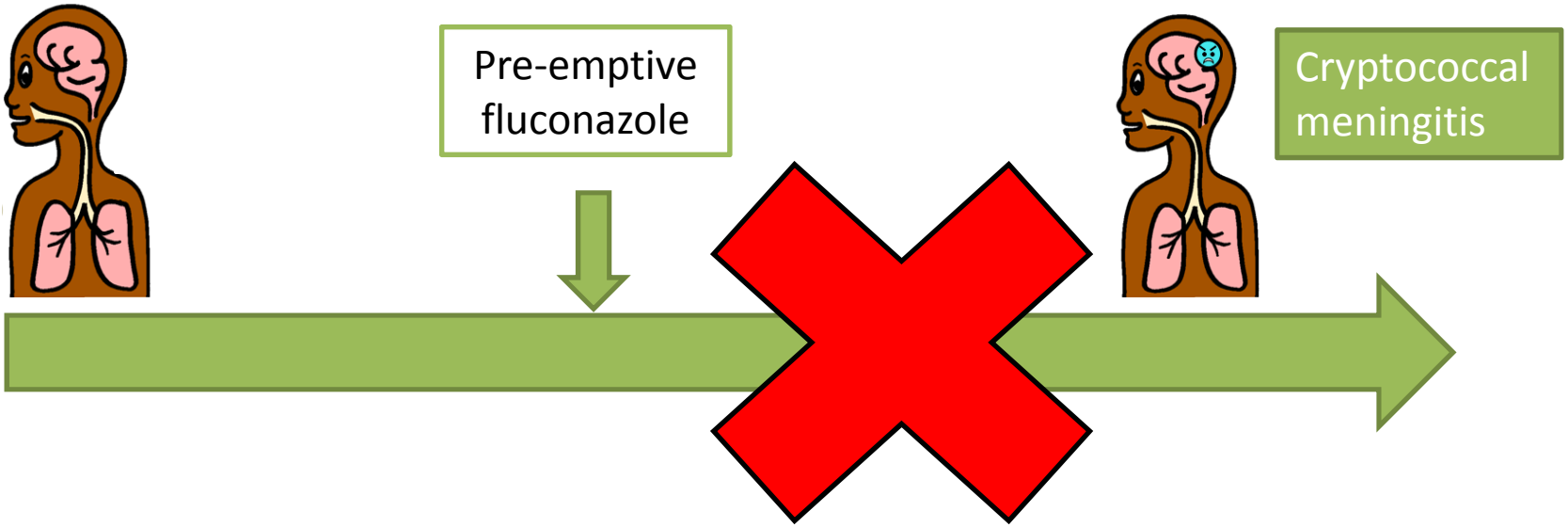
Proposed Algorithm for Screening

Overview of screening

- Screening principles
- Implementation in South Africa

Review of the screening algorithm

- Cryptococcal meningitis
- Asymptomatic cryptococcal antigenaemia

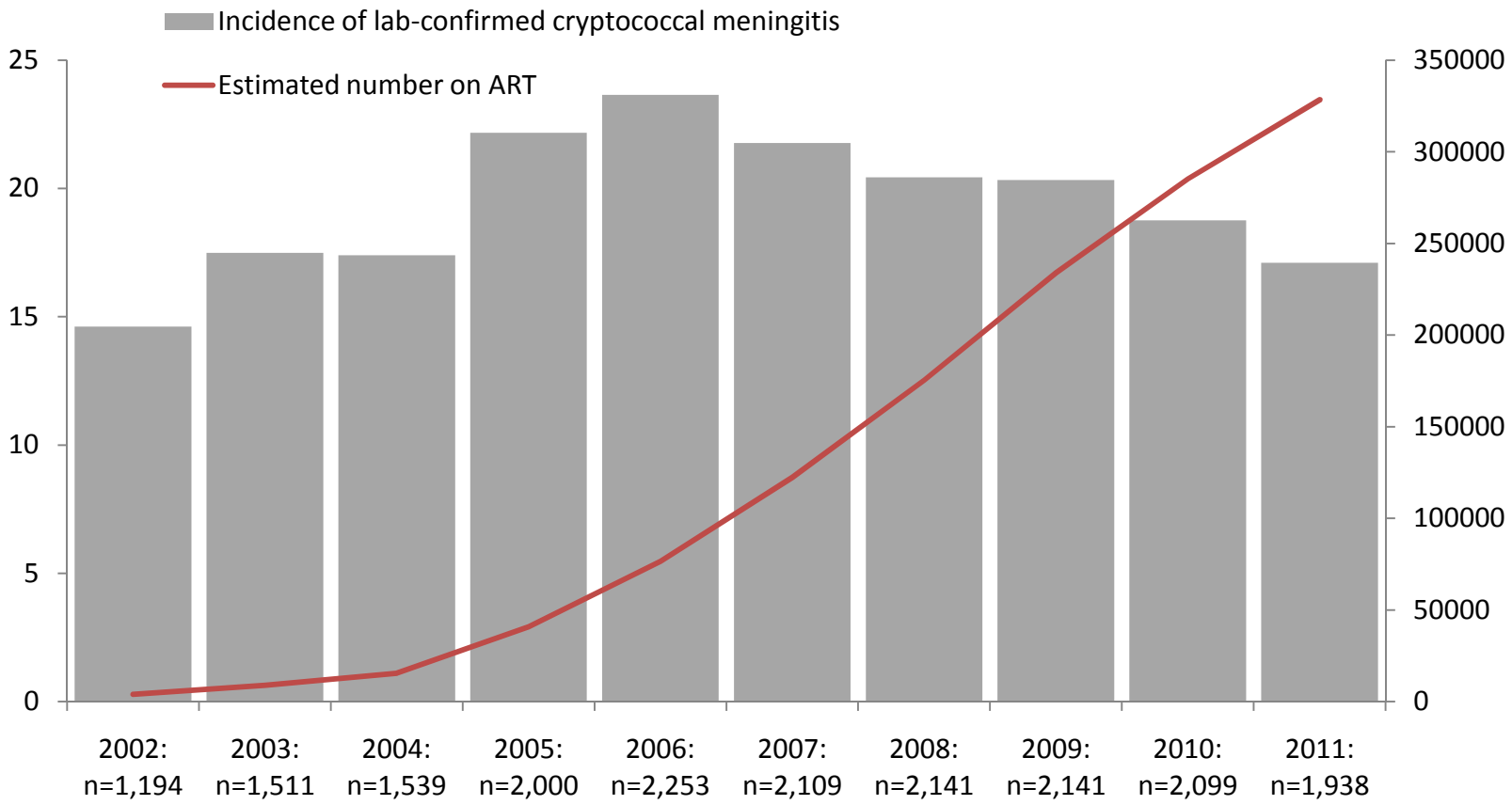


CRYPTOCOCCAL ALGORITHM

1. OVERVIEW OF SCREENING

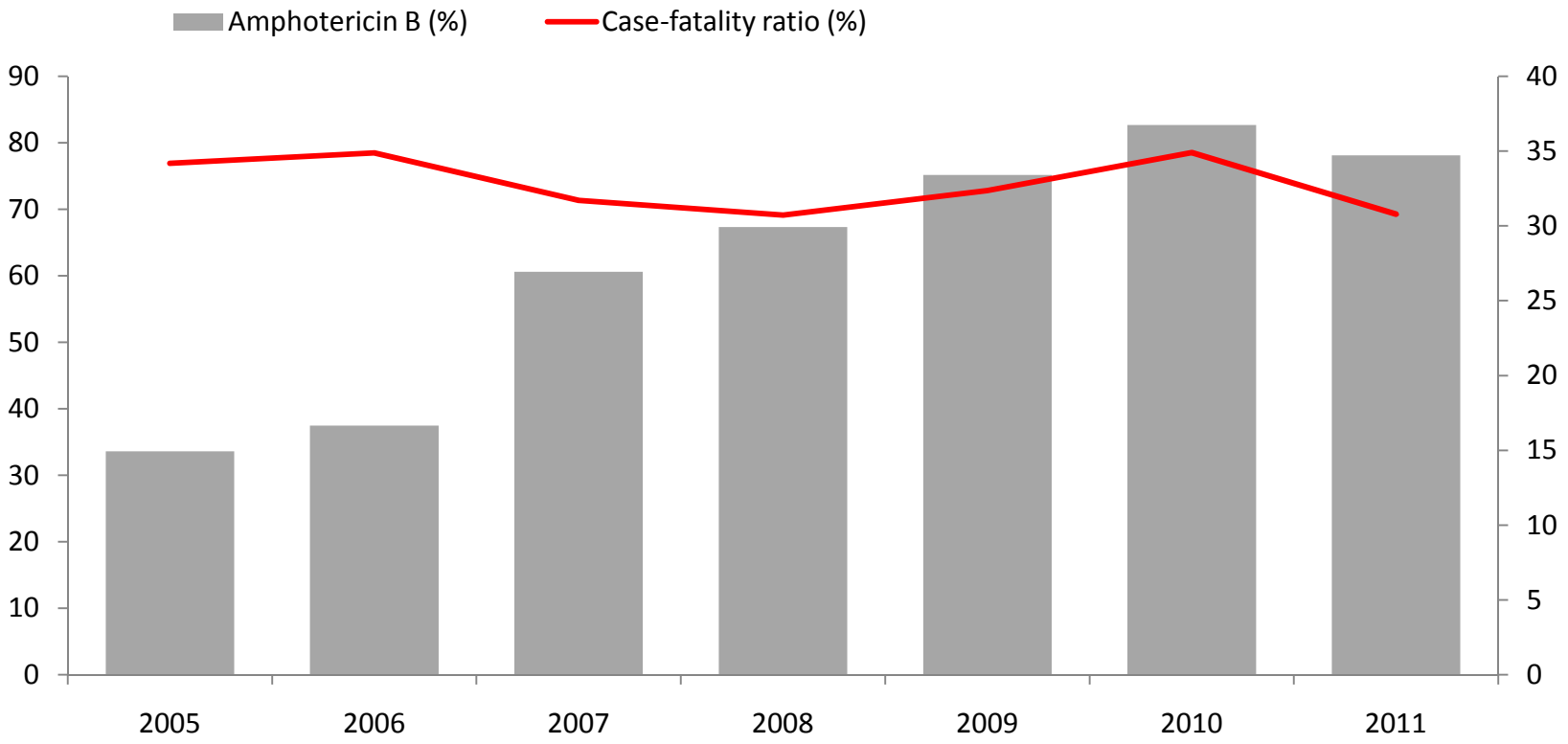
High burden of cryptococcal meningitis in South Africa

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

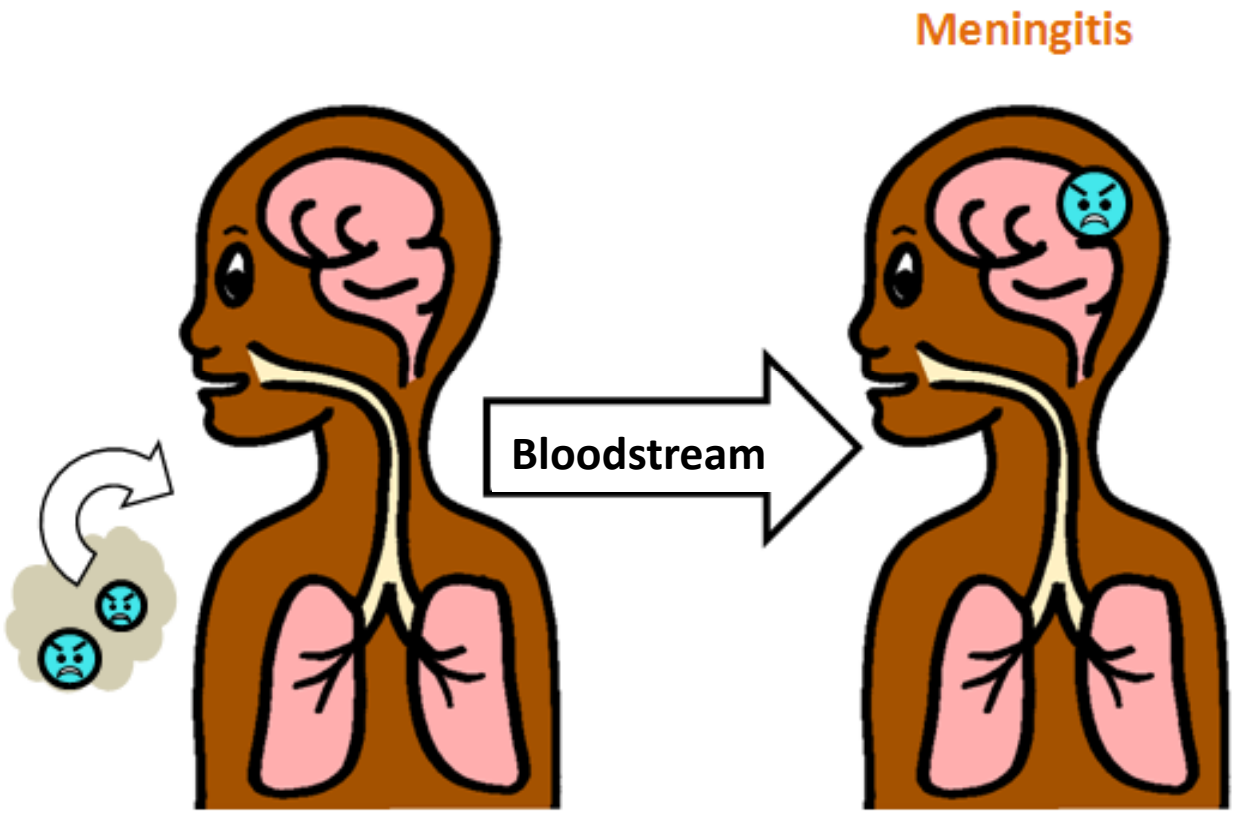


High in-hospital mortality in South Africa

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



Pathogenesis of disease



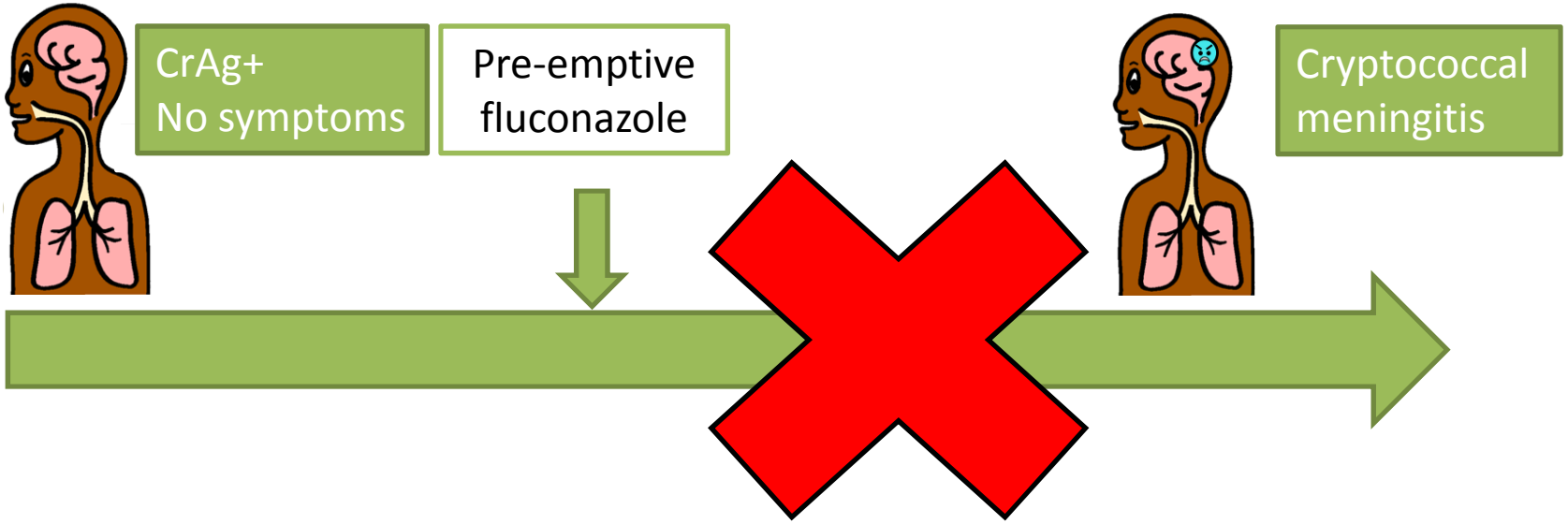
Latent infection

HIV-infected with low CD4 count

Garcia-Hermoso D, et al. *J Clin Microbiol* 1999
French N, et al. AIDS 2002.

How cryptococcal screening works

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



(Conditional) WHO Recommendation

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

a. patients with a CD4 count less than 100 cells/mm^3, **and**

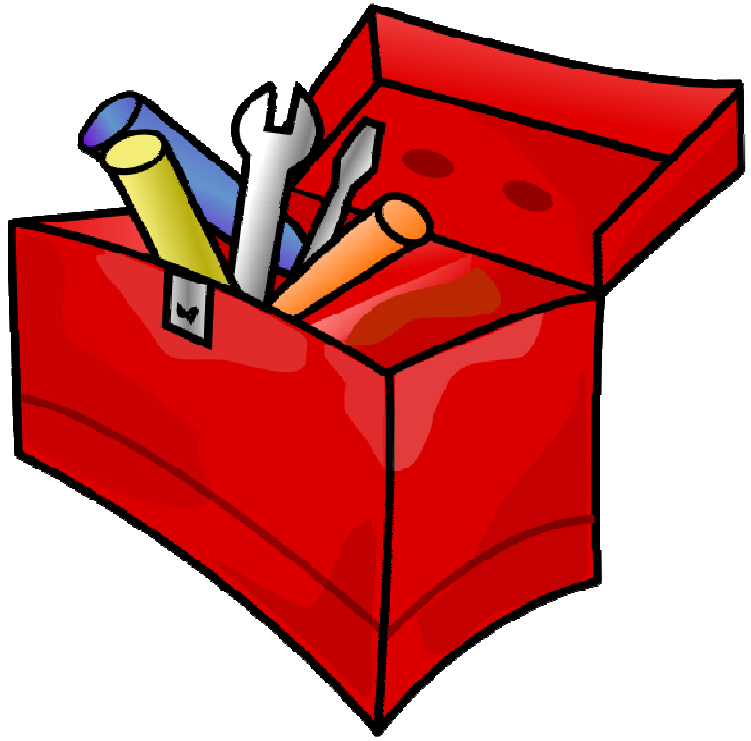
b. where this population also has a high prevalence of cryptococcal antigenaemia[13].

[Conditional recommendation, low quality of evidence]

WHO Rapid Advice Guidelines 2011.

A comprehensive screening programme

- Who should be screened and where?
- Develop clinical algorithm
- Integrate screening into ART and TB programmes
- Train healthcare personnel
- Educate patients
- Perform monitoring and evaluation to determine effectiveness



Strategy	Reflex screening	Clinician-initiated screening
Provinces	▪ Gauteng & Free State (Phase 1)	▪ Western Cape
Coverage of screening	▪ Potentially broader	▪ Restricted (depends on clinicians ordering/ performing test on a selected group
Location of laboratory testing	▪ CD4 laboratory	▪ Microbiology laboratory
Required specimen	▪ CD4 EDTA-blood sample	▪ Separate serum sample submitted by clinician
Test format	▪ Lateral flow assay	▪ Latex agglutination test
Test request	▪ Reflex	▪ Depends on clinician awareness
Clinician training	▪ Augmented clinician training required because test not specifically requested	▪ No clinician training
Selection of patients	▪ All samples screened regardless of clinical background – including repeat CD4 samples from the same patient	▪ Clinicians select patients, e.g. ART-naïve vs. ART-experienced, no prior CM, adult, asymptomatic, no prior screening test

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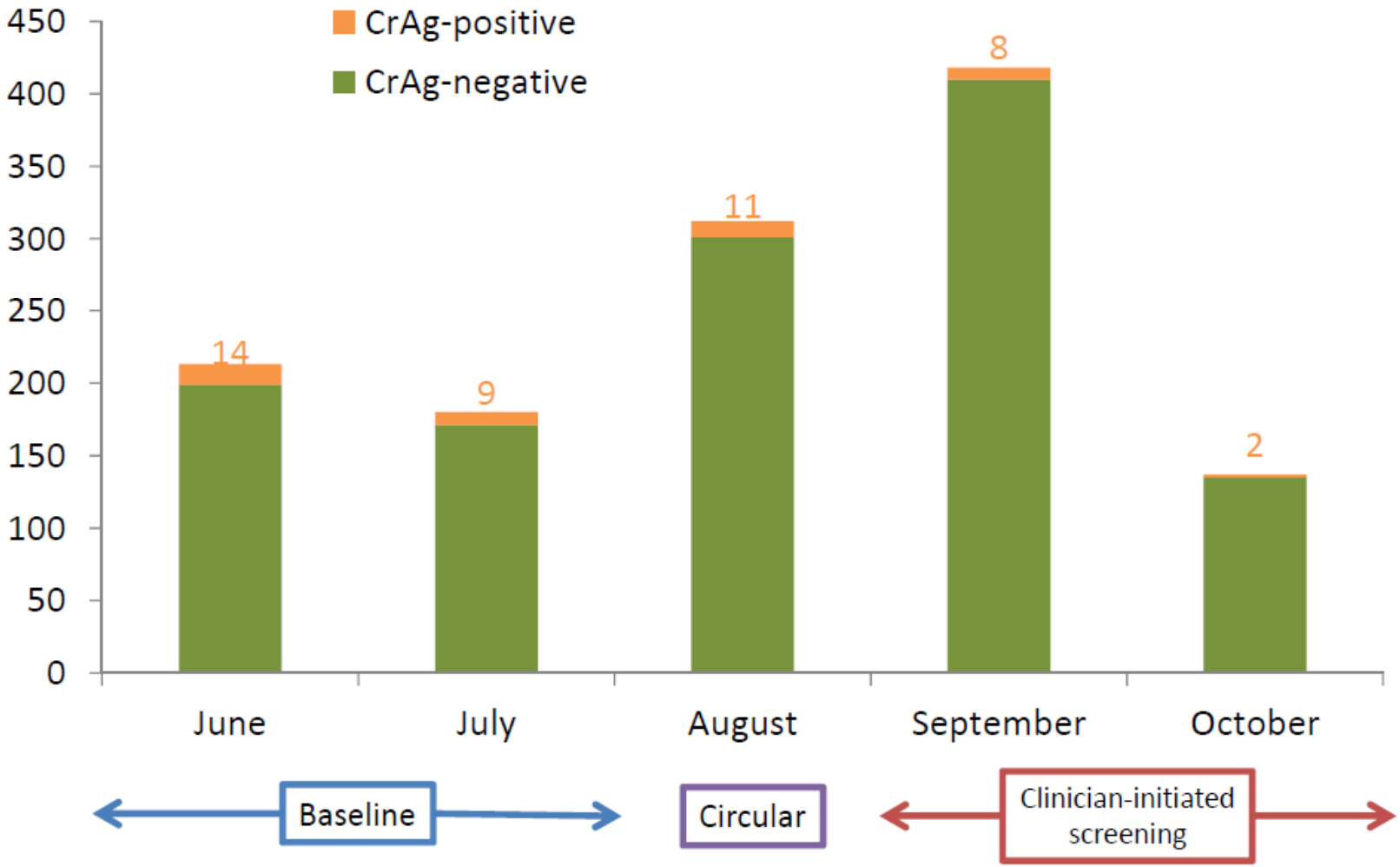
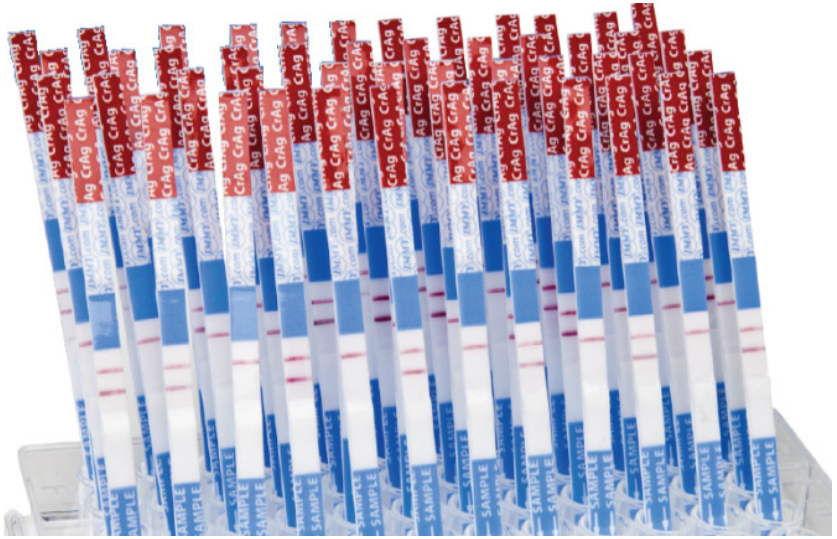
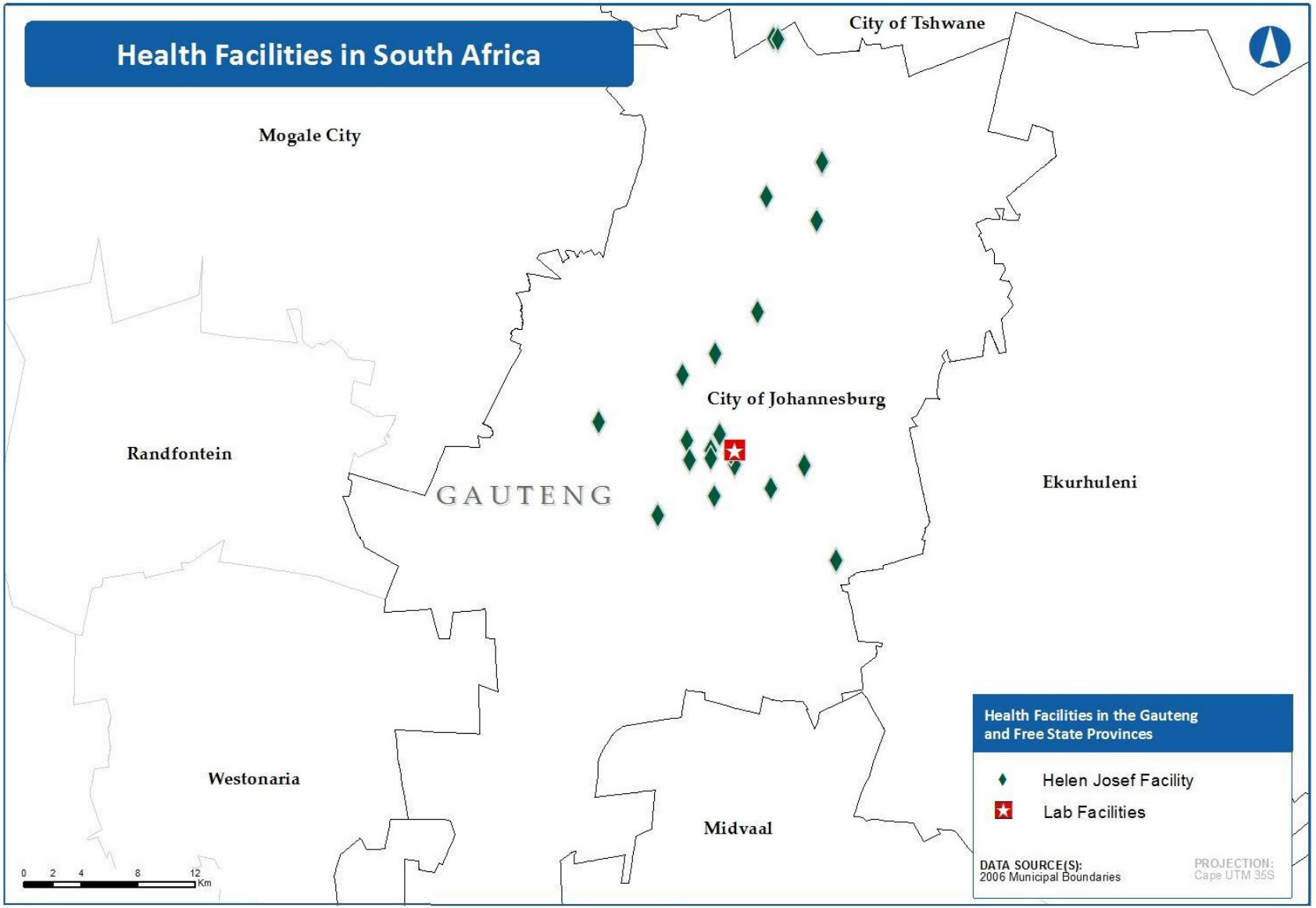
Figure 1: Number of blood specimens screened for CrAg at NHLS laboratories by month, Western Cape, 1 June to 8 Oct 2012



Reflex laboratory screening

CD4 <100





CMJAH NHLS CD4 lab node and 25 facilities

Laboratory Statistics	Number
Number of NHLS CD4 laboratories enrolled in screening programme	1
Number of NHLS CD4 laboratories reporting data	1
Number of CrAg screening tests performed	1458
Number of Crag-positive tests/ number of specimens tested (%)	71/1458 (4.9%)

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

Source: Monthly NICD Surveillance Report (Nov 2012)

A comprehensive screening programme

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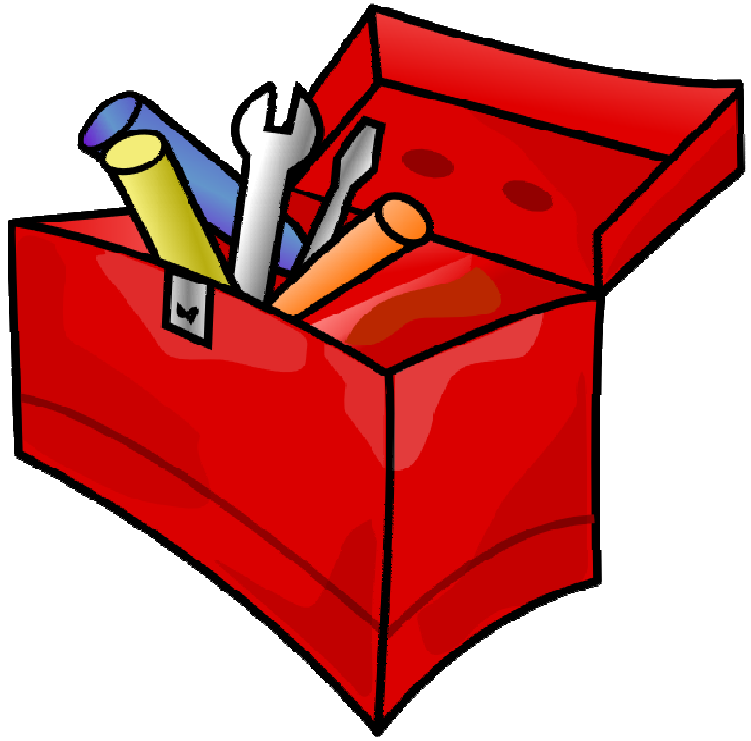


2. REVIEW OF THE SCREENING ALGORITHM

CASE

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

CASE

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

National Health
Laboratory Service

(Pr5200296)
NHLS Laboratoratoy Complex
Johannesburg Hospital
Jubilee Street,
Parktown, 2193

Call Centre 24 hours
Tel: (011) 489-8571/2/4/5
Fax: (011) 489-8409/10
After Hours
Tel: (011) 489-8433

Johannesburg Hospital Laboratory Complex

Patient

Age(Sex)DoB

Ref Dr
Ward-Hosp

Hosp No
Taken
Report

LABORATORY REPORT

Clinical data No clinical details supplied
Specimen Blood
Tests ordered CD4,Crypt

LYMPHOCYTE SUBSET ANALYSIS		**Flags**	**Ref Ranges**
CD45 +ve White Cell Count	9.27 x 10^9/l		
CD4% of Lymphocytes	2.63 %		
Absolute CD4	20 X 10^6/l	**L-**	500 - 2010

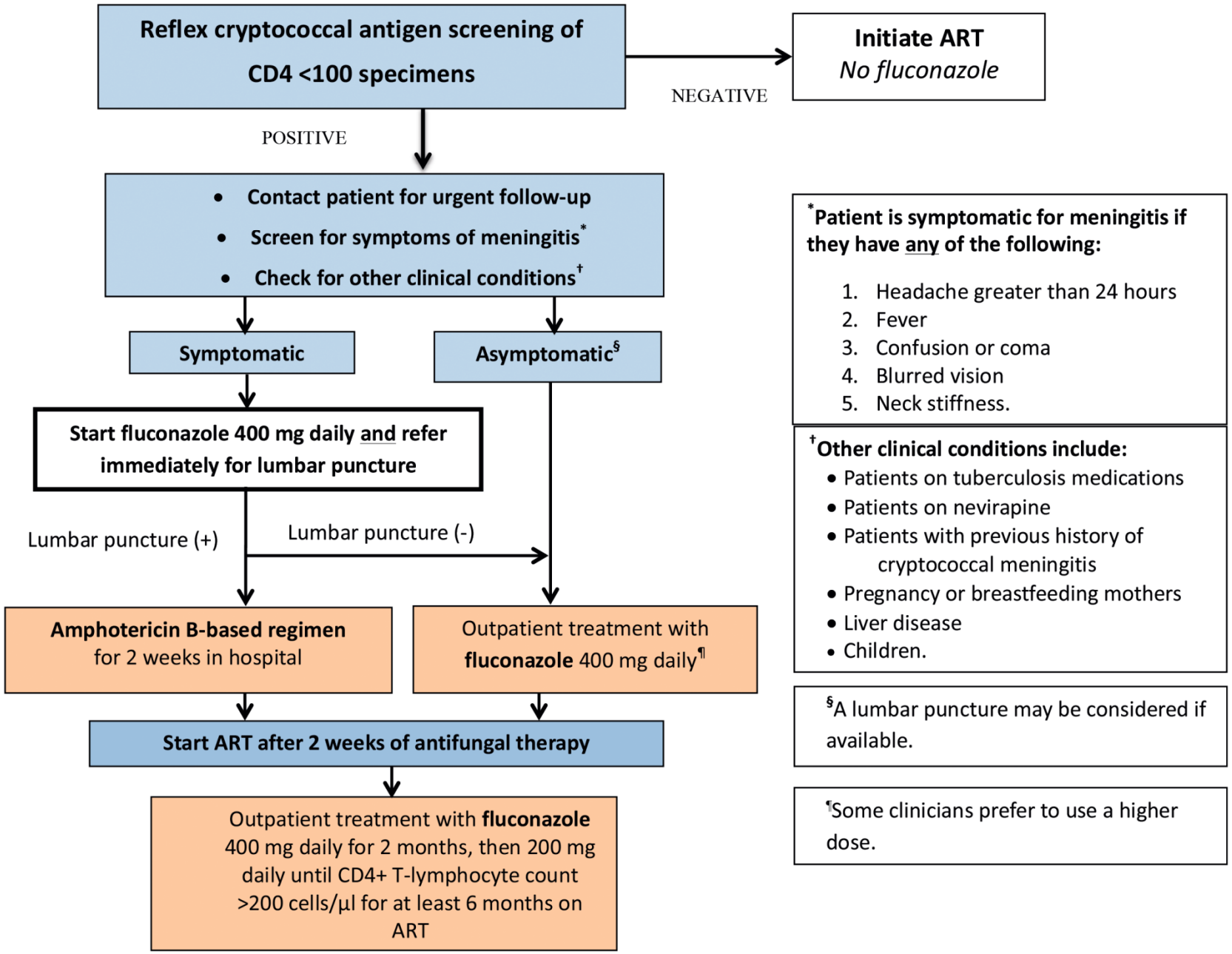
CRYPTOCOCCAL ANTIGEN TEST
Cryptococcal antigen ..... **Positive**

Reflex testing for cryptococcal antigen has been performed because the patient's CD4+ T-cell count is below 100 cells/µl. Cryptococcal antigen ***has*** *been detected.*
If the patient has been previously diagnosed with cryptococcal disease, please ensure that the patient continues antifungal treatment.
If this is a new diagnosis, the patient should be evaluated for signs and symptoms of disseminated disease, including meningitis. Symptomatic patients will need a lumbar puncture to exclude meningitis while asymptomatic patients should be started on fluconazole after evaluation for special conditions.

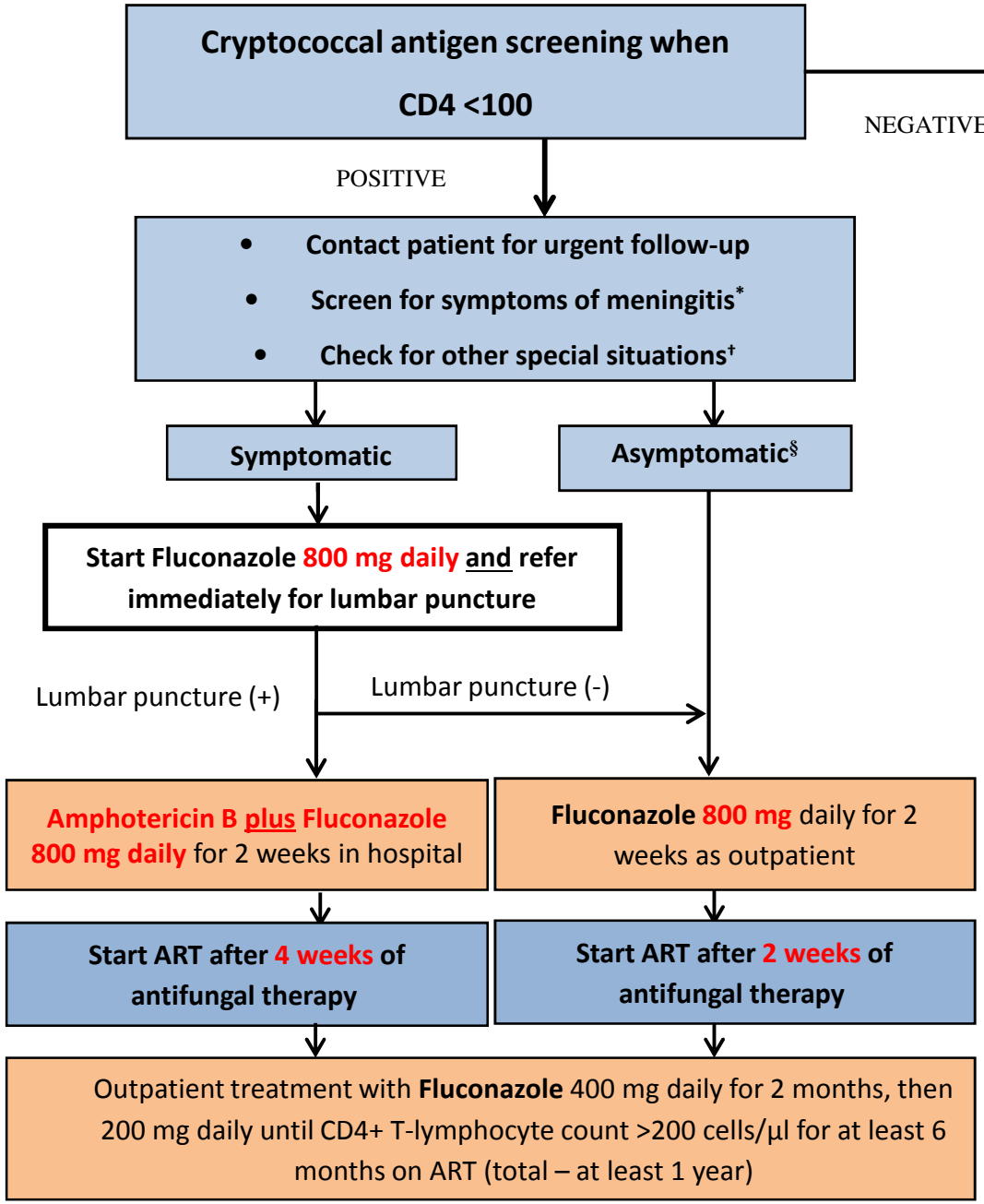
Authorised by :

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

--- End of Laboratory Report ---



Govender NP, et al. *S Afr Med J* 2012. In press



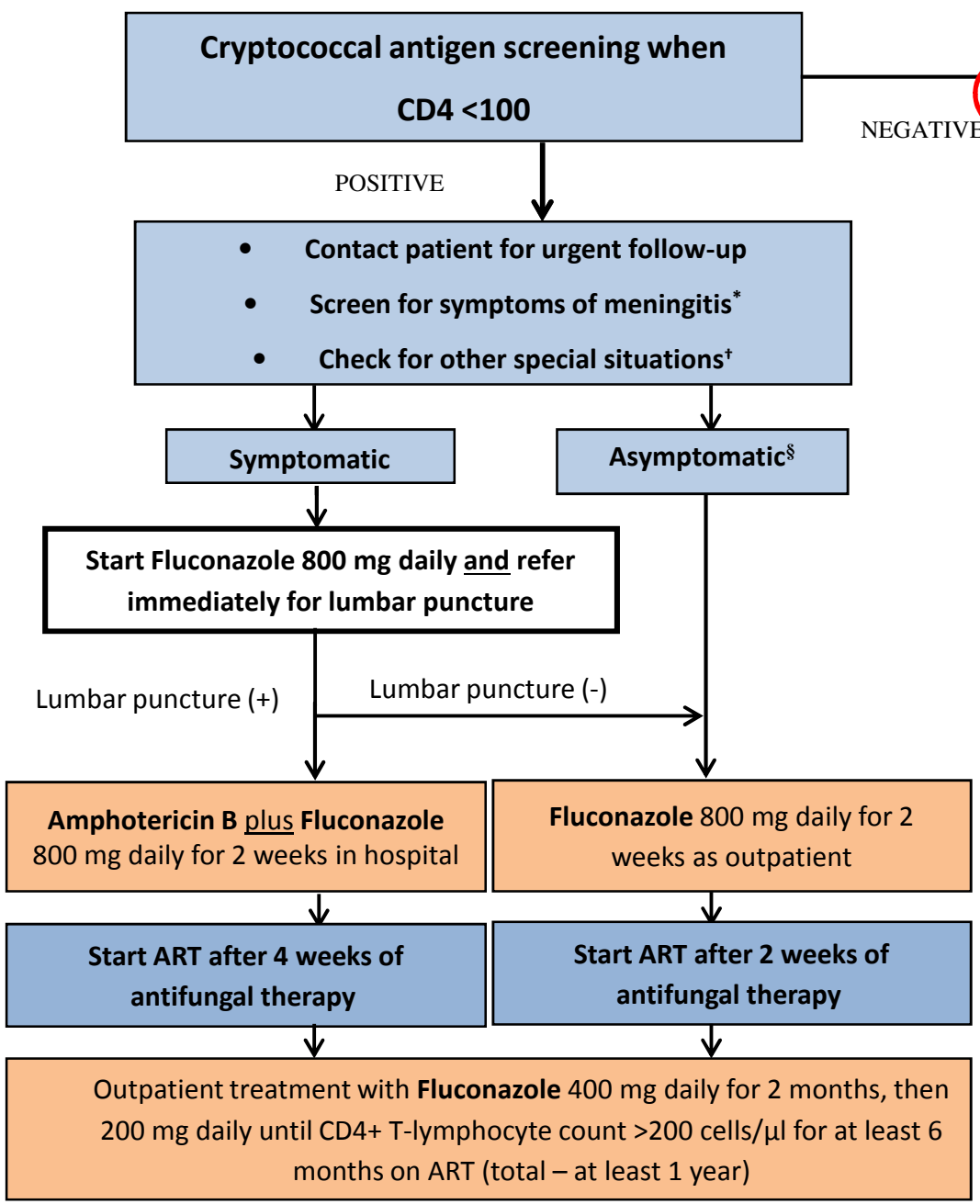
*Patient is symptomatic for meningitis if they have any of the following:

1. Headache
2. Confusion

†Other special situations include:

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

§ A lumbar puncture may be considered if available.



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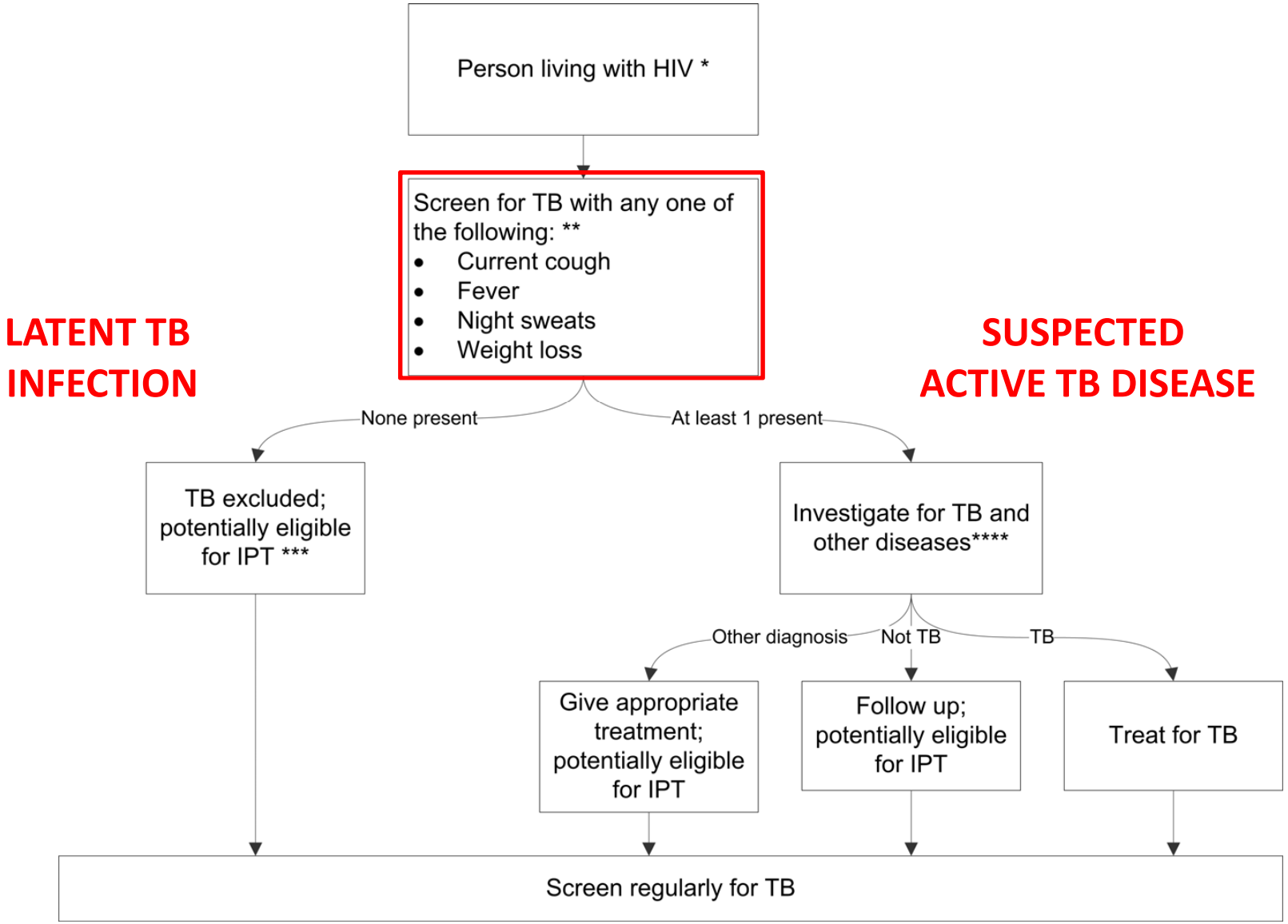
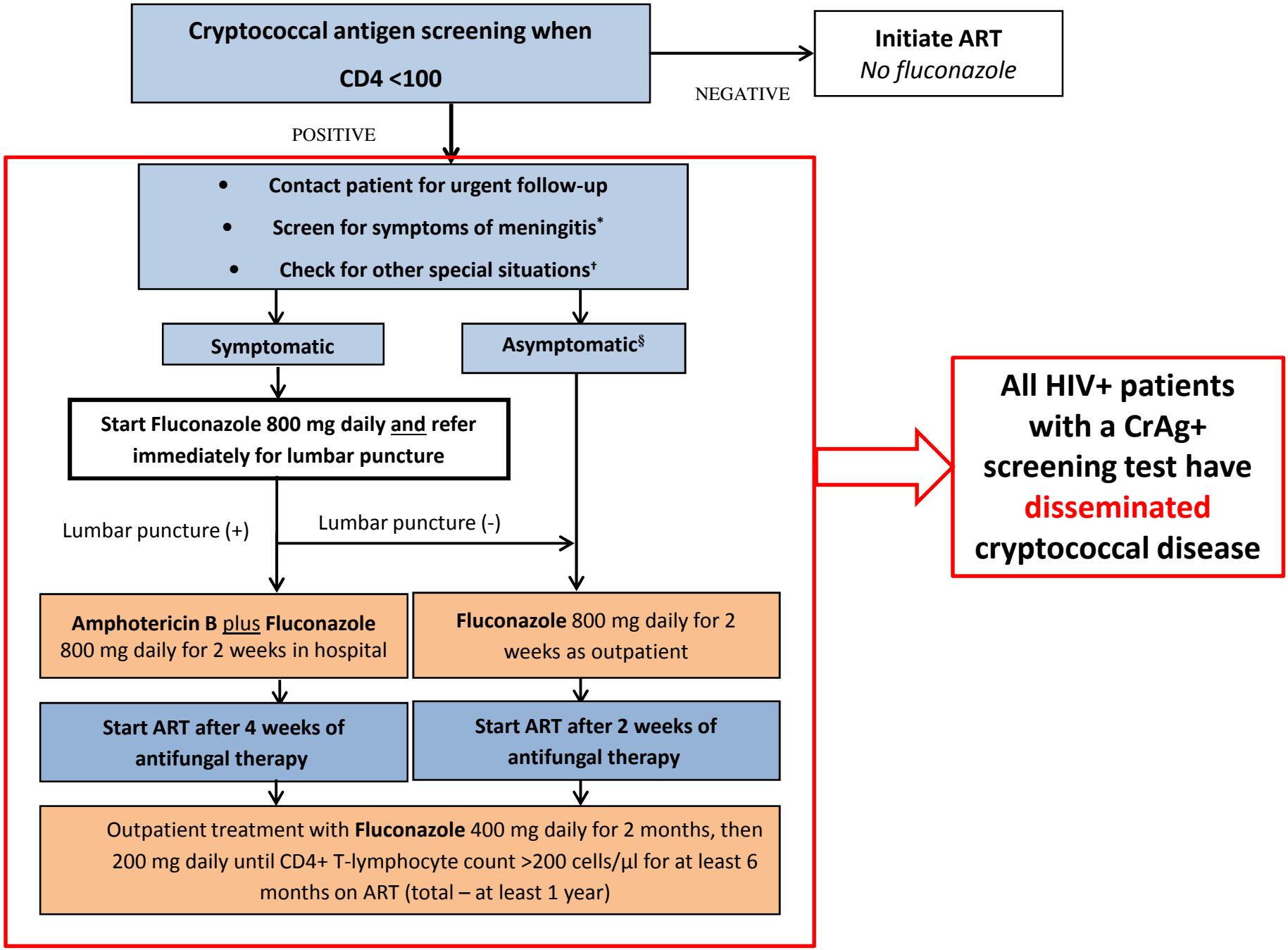
TB Symptom Screening and IPT

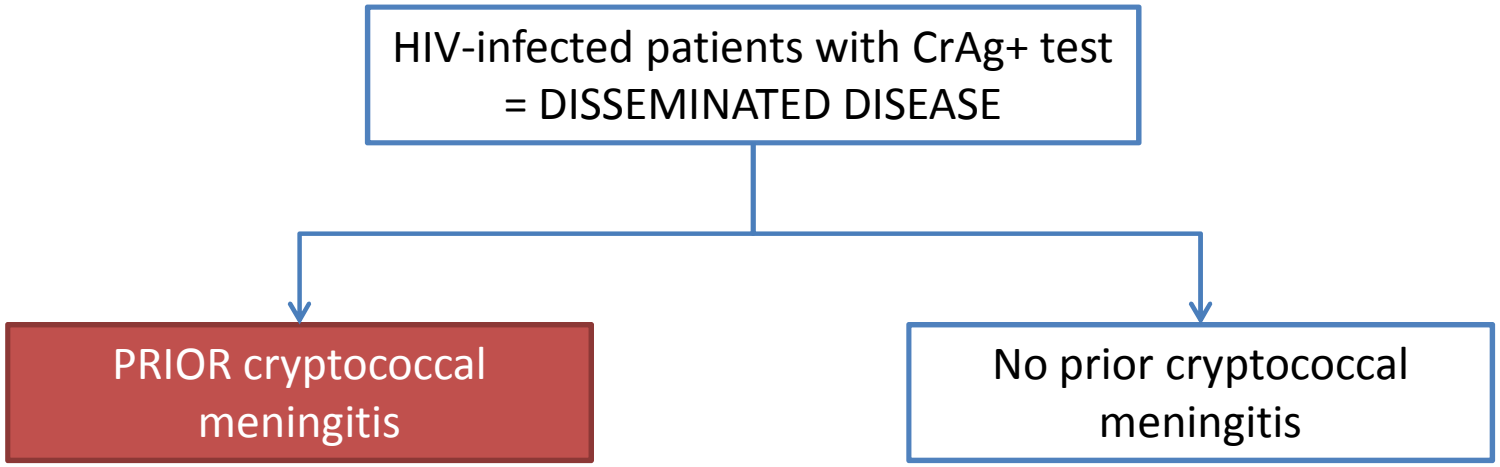


Getahun H, et al. *PLoS Med* 2011.


Cryptococcal antigen screening when CD4 <100
NEGATIVE
Initiate ART
No fluconazole
POSITIVE
Contact patient for urgent follow-up
Screen for symptoms of meningitis*
Check for other special situations†
Symptomatic
Asymptomatic§
Start Fluconazole 800 mg daily and refer immediately for lumbar puncture
Lumbar puncture (+)
Lumbar puncture (-)
Amphotericin B plus Fluconazole 800 mg daily for 2 weeks in hospital
Fluconazole 800 mg daily for 2 weeks as outpatient
Start ART after 4 weeks of antifungal therapy
Start ART after 2 weeks of antifungal therapy
Outpatient treatment with Fluconazole 400 mg daily for 2 months, then 200 mg daily until CD4+ T-lymphocyte count >200 cells/µl for at least 6 months on ART (total – at least 1 year)
All HIV+ patients with a CrAg+ screening test have disseminated cryptococcal disease

CASE

- Printed laboratory report with CrAg-positive result was not noticed by busy clinic personnel
- Fortunately, the laboratory also phoned the clinic with CrAg-positive result
- NIMART-trained nurse contacted the patient and asked that she return to clinic the next day

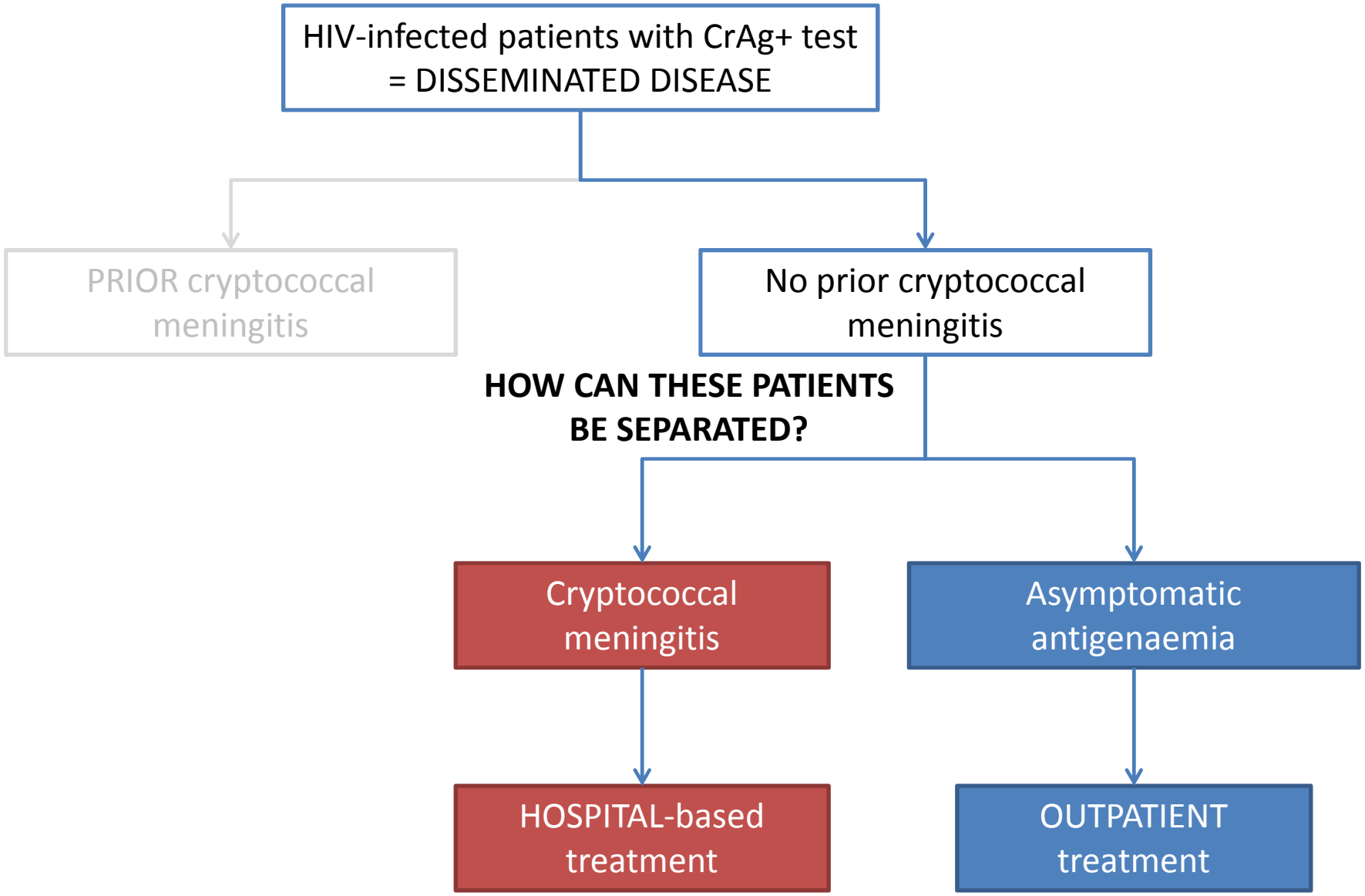


- CrAg may persist in body fluids for weeks to months after an episode of cryptococcal meningitis → may be detected by screening

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

CASE

- Patient returned to clinic a few days earlier than her appointment
  - No history of cryptococcal meningitis
  - Complained of a mild headache with prompting


HIV-infected patients with CrAg+ test
= DISSEMINATED DISEASE
PRIOR cryptococcal meningitis
No prior cryptococcal meningitis
HOW CAN THESE PATIENTS BE SEPARATED?
Cryptococcal meningitis
Asymptomatic antigenaemia
HOSPITAL-based treatment
OUTPATIENT treatment

HIV-infected patients with CrAg+ test
= DISSEMINATED DISEASE

PRIOR cryptococcal meningitis

No prior cryptococcal meningitis

LUMBAR PUNCTURE

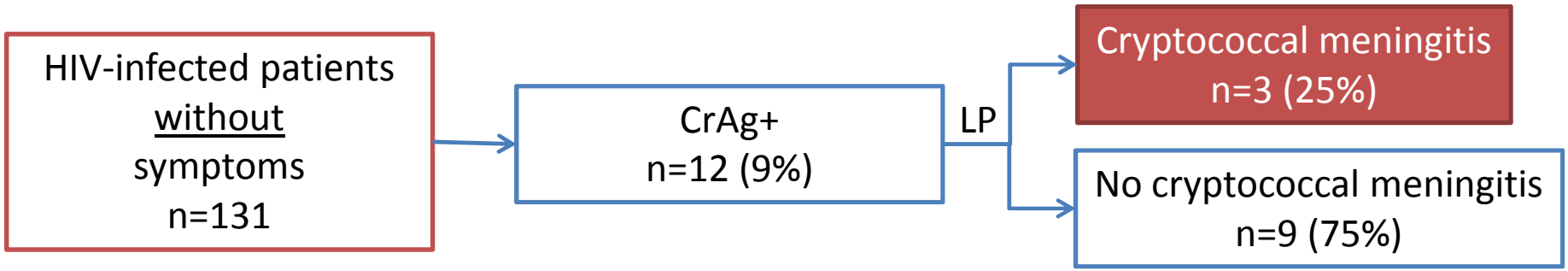
Cryptococcal meningitis

Asymptomatic antigenaemia

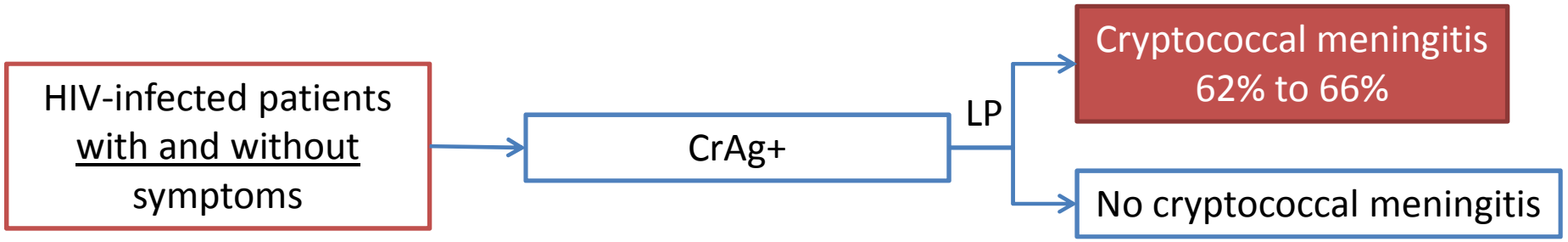
HOSPITAL-based treatment

OUTPATIENT treatment

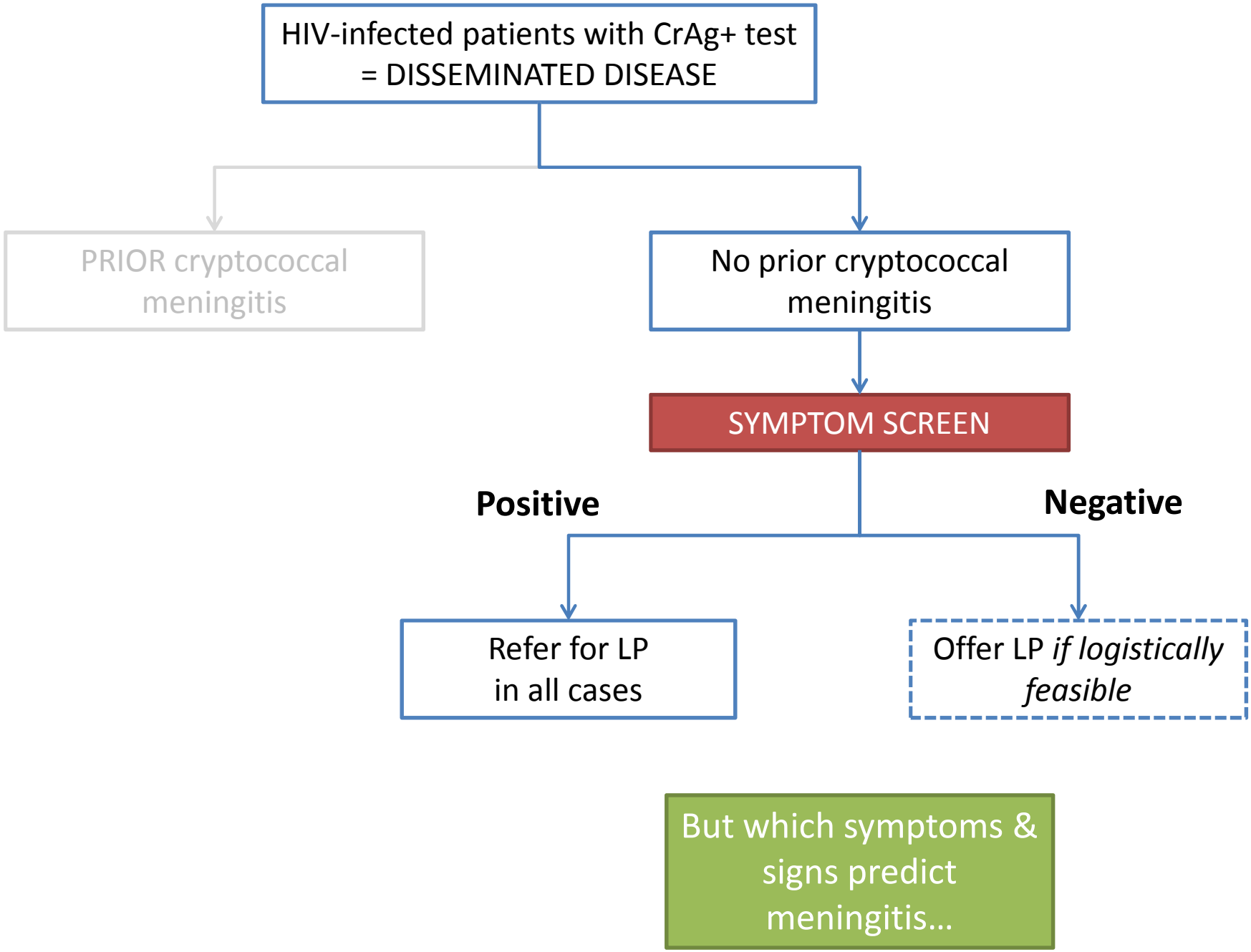
Lumbar puncture



Pongsai P, et al. J Infect 2010.



Tassie, et al. J Infect 2010; Desmet P, et al. AIDS 1989.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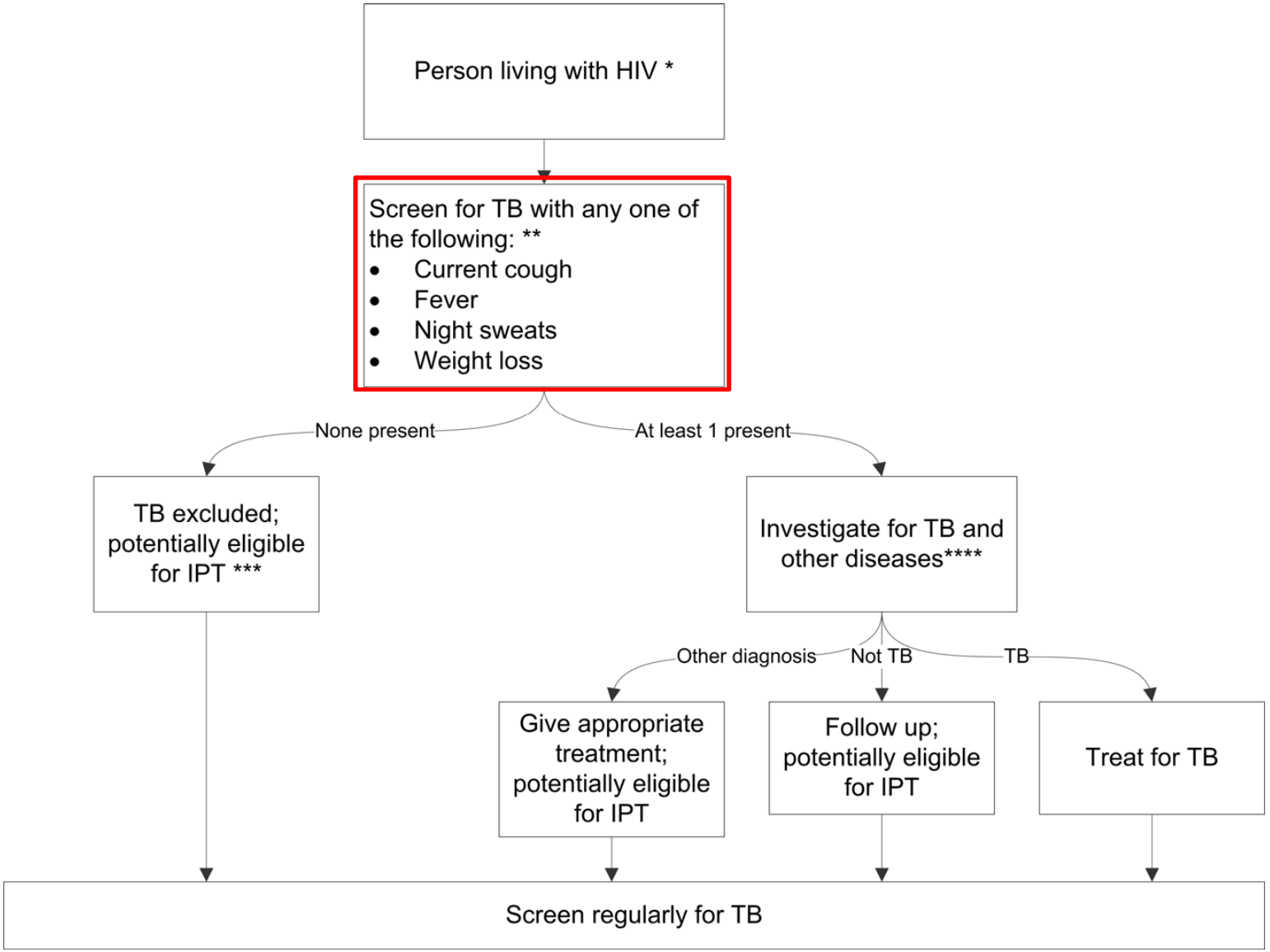
PRIOR cryptococcal meningitis
No prior cryptococcal meningitis
SYMPTOM SCREEN
Positive
Negative
Refer for LP in all cases
Offer LP *if logistically feasible*
But which symptoms & signs predict meningitis…

TB Symptom Screening



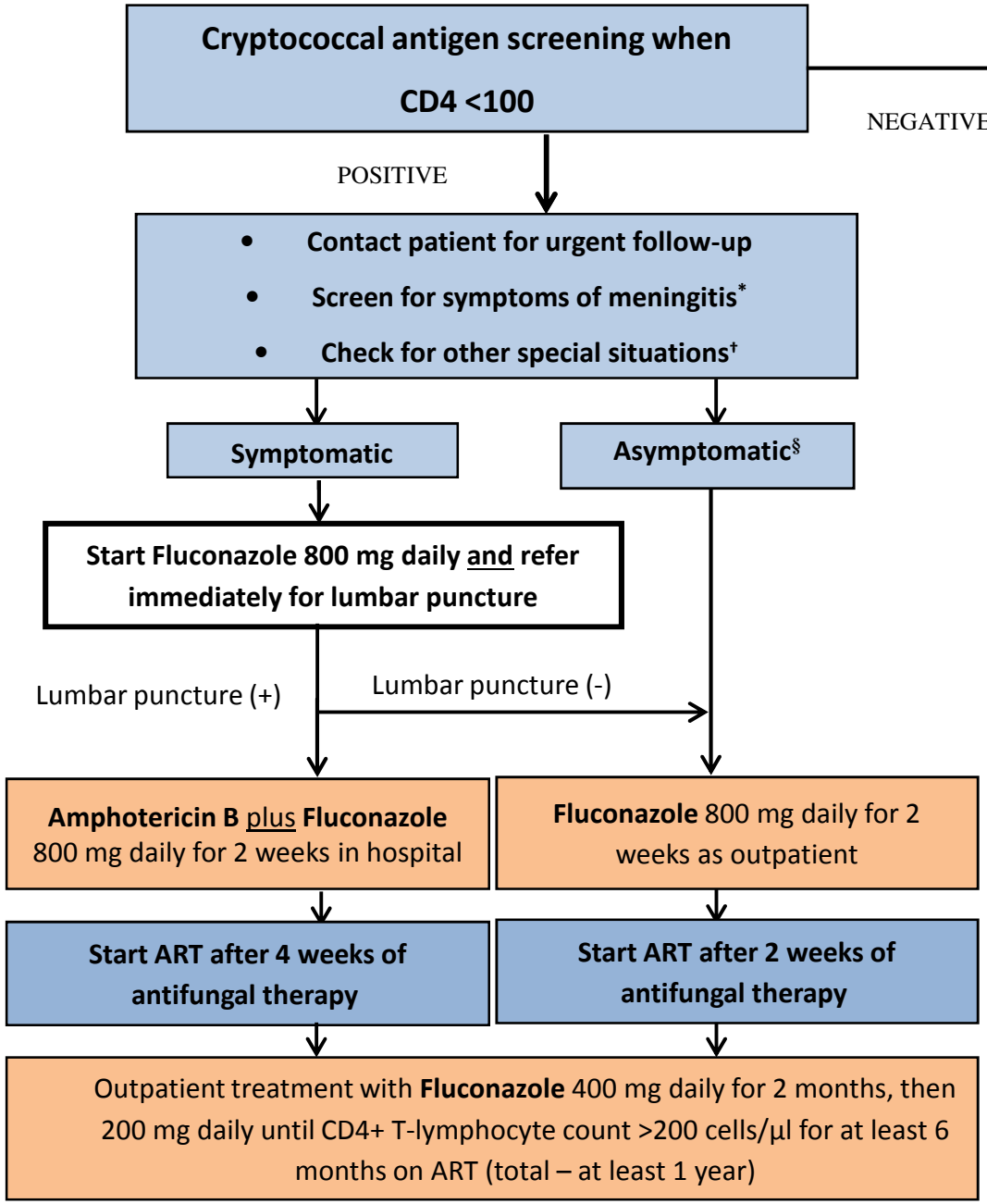
Getahun H, et al. *PLoS Med* 2011.

Symptoms and signs of cryptococcal meningitis

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

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

McCarthy KM, et al. *AIDS* 2006.



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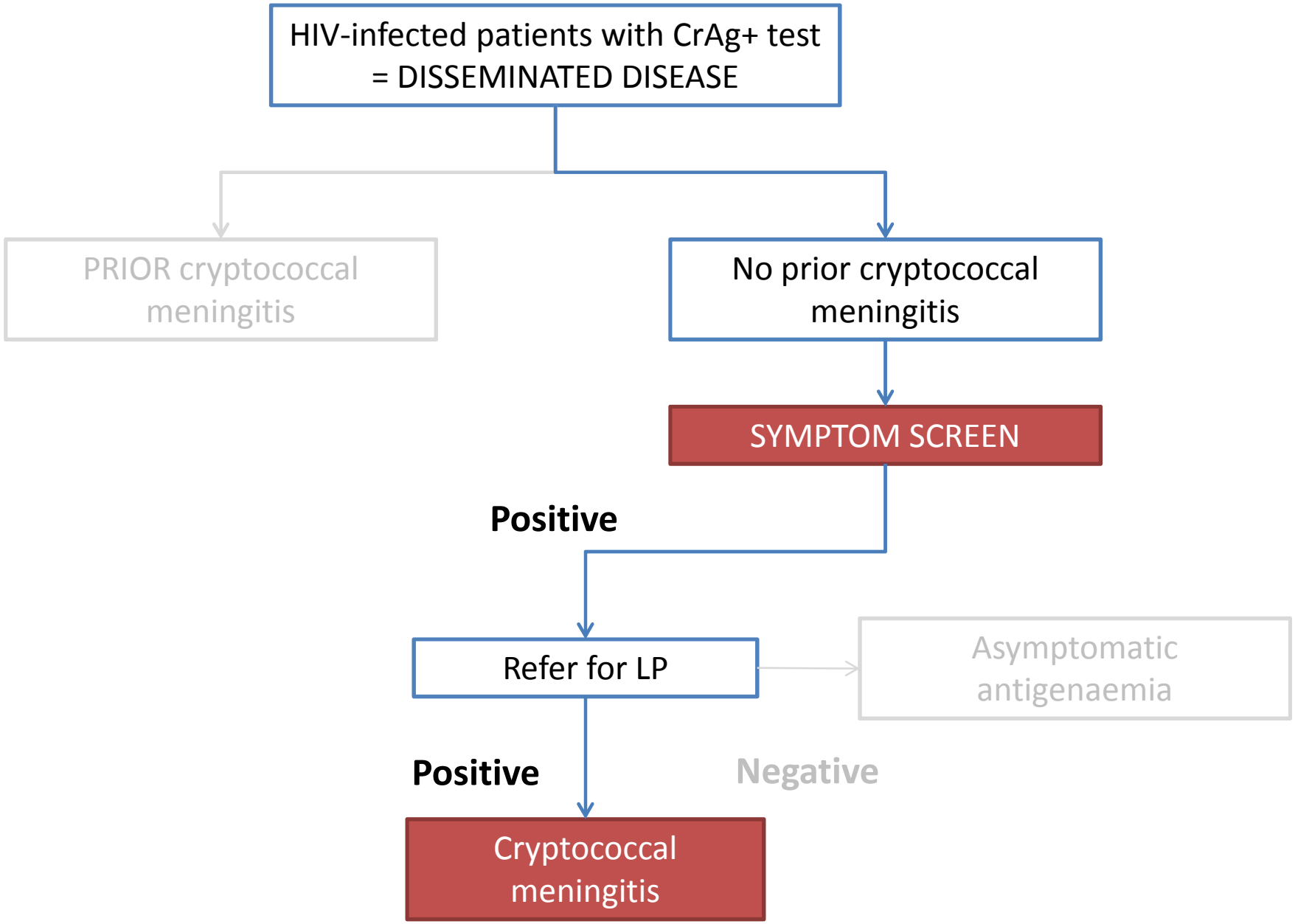
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SYMPTOM SCREEN
Positive
Refer for LP
Asymptomatic antigenaemia
Positive
Negative
Cryptococcal meningitis

Cryptococcal Meningitis: Antifungal treatment

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

WHO Rapid Advice Guidelines 2011.

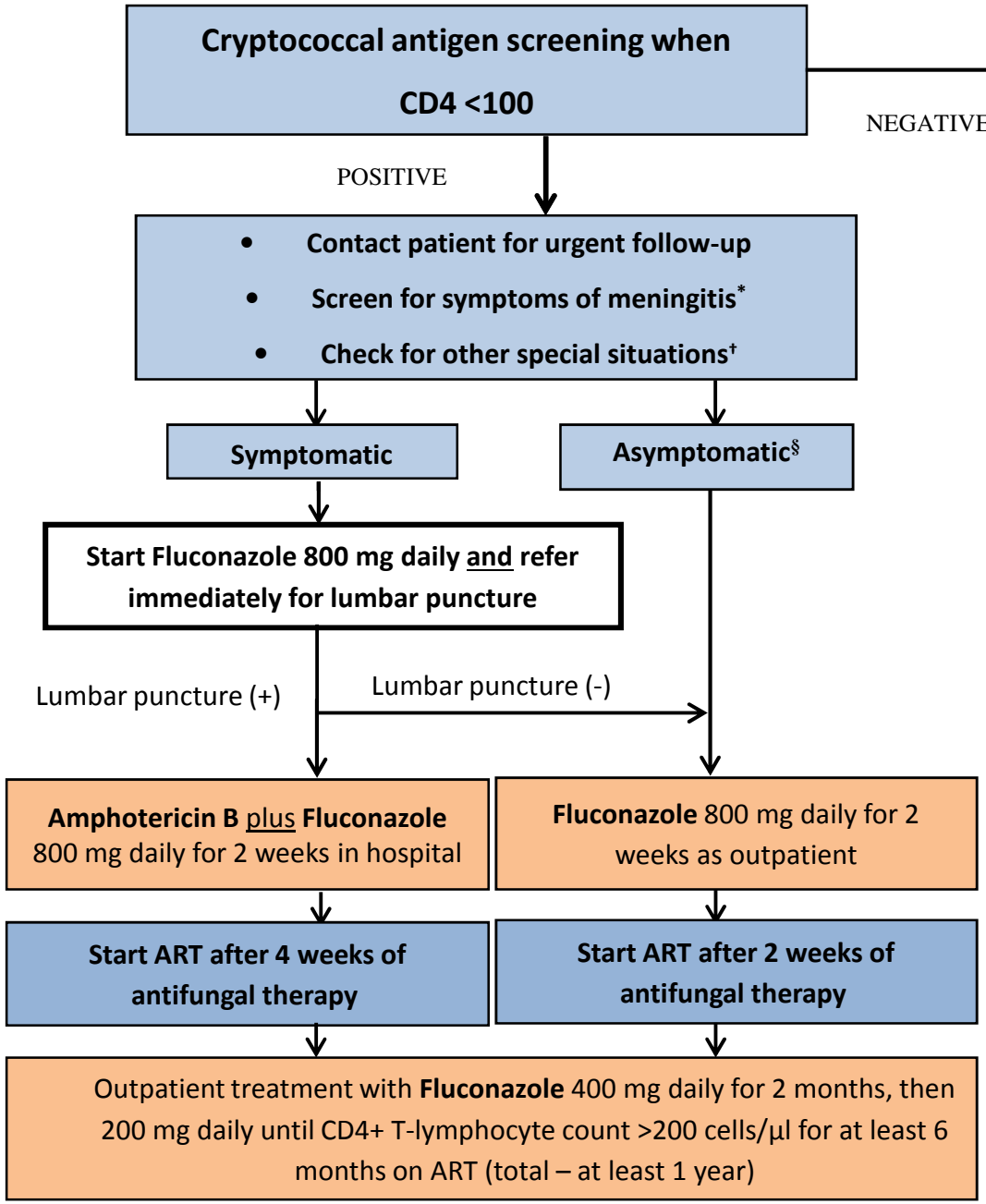
Cryptococcal Meningitis: Timing of ART

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

Induction regimen	Meningitis	Non-meningeal
Amphotericin B	2-4 weeks	2 weeks
Fluconazole	4-6 weeks	4 weeks

(Conditional recommendation, low quality of evidence)

WHO Rapid Advice Guidelines 2011.



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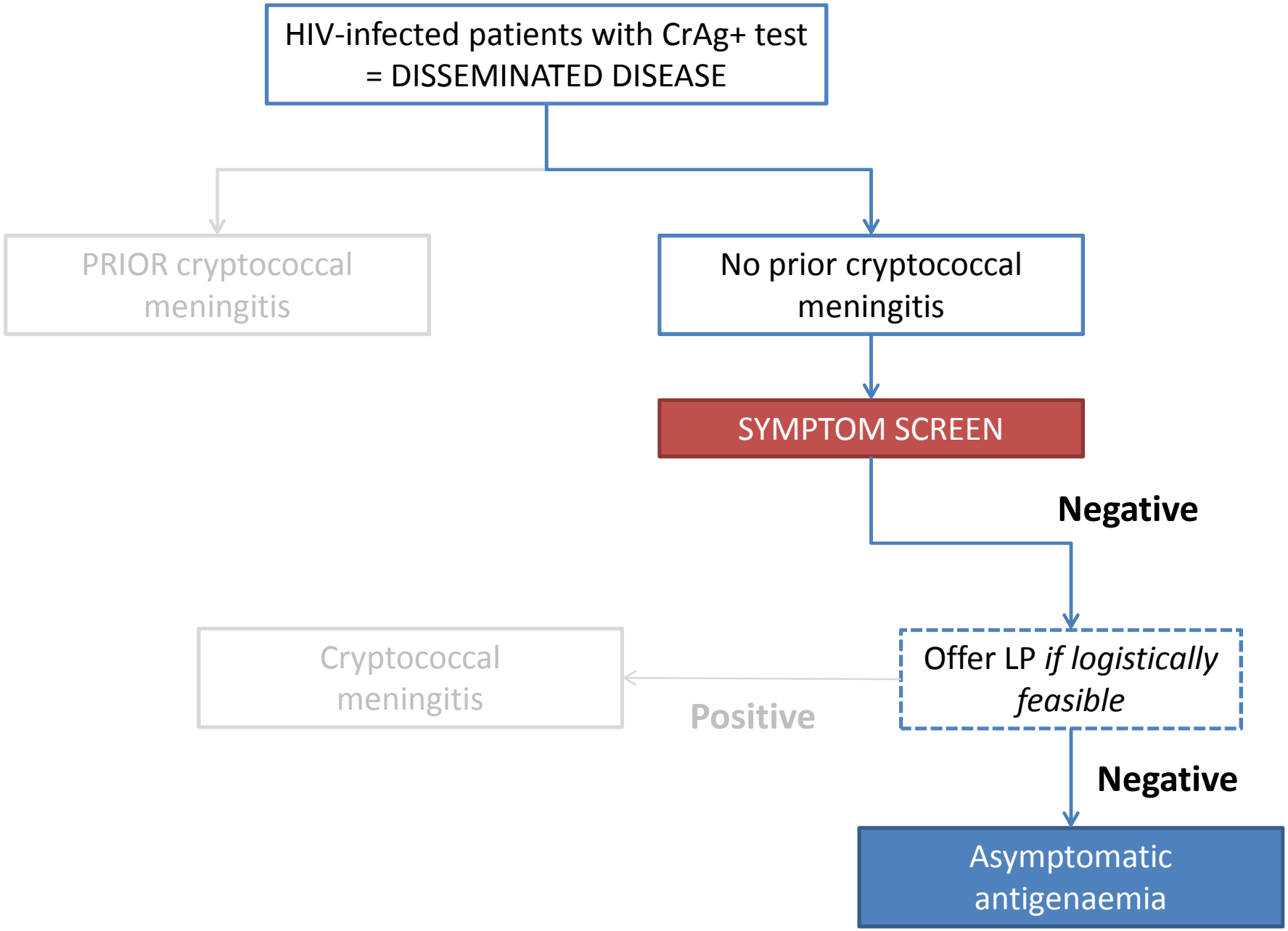
CASE

- Despite careful counselling, patient refused to be referred to the nearest hospital 100 km away for a lumbar puncture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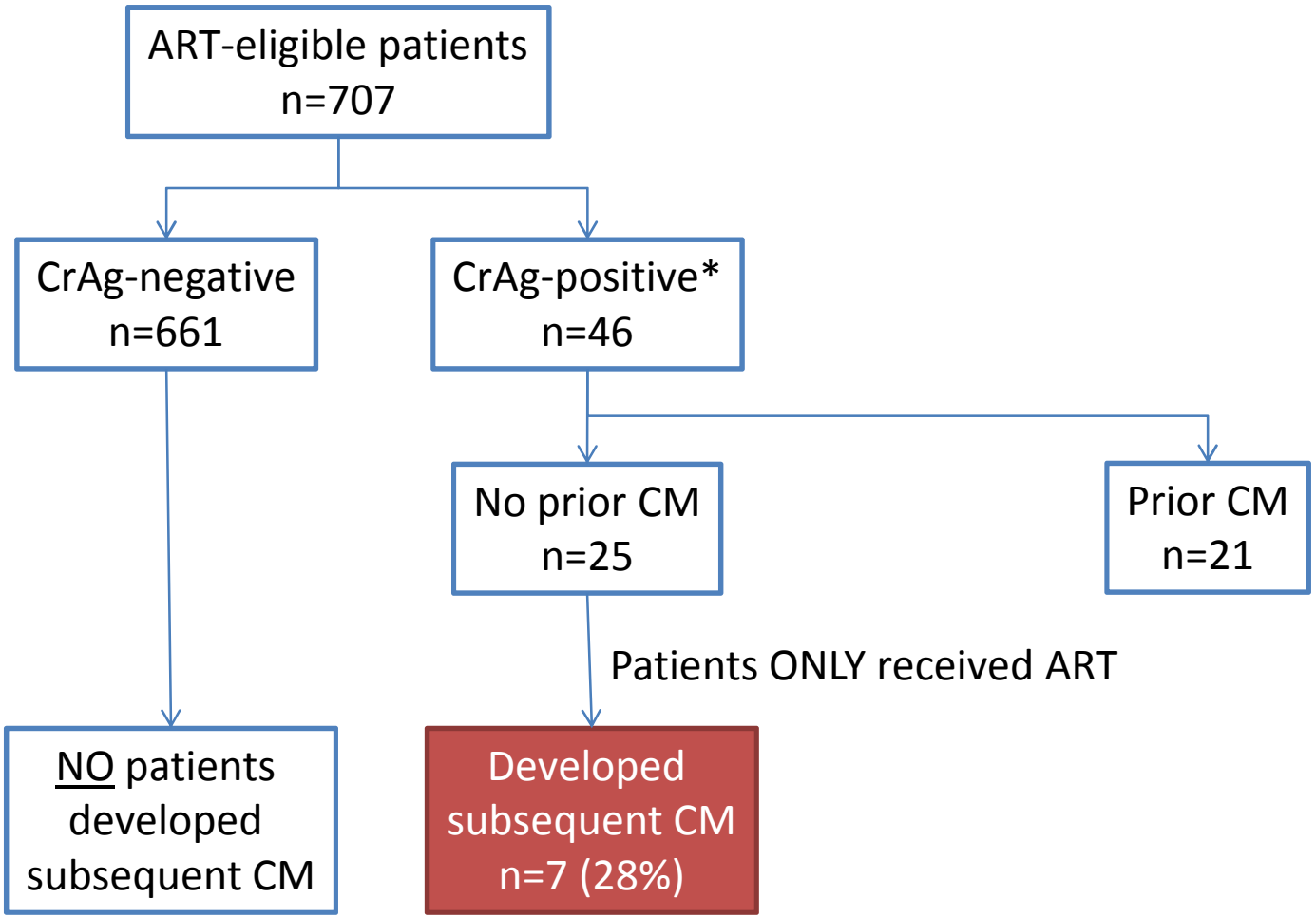
PRIOR cryptococcal meningitis
No prior cryptococcal meningitis
SYMPTOM SCREEN
Negative
Offer LP *if logistically feasible*
Positive
Cryptococcal meningitis
Negative
Asymptomatic antigenaemia

Asymptomatic antigenaemia predicts death during early ART

Unadjusted estimates ($n = 377$)			Multivariate estimates ($n = 364$)†			
Relative risk‡	95% Confidence interval	P	Relative risk‡	95% Confidence interval	P	Population attributable risk
5.20	1.73–15.61	0.0033	6.62	1.86–23.61	0.0036	0.18 (0.02–0.33)

Liechty CA, et al. *Trop Med Int Health* 2007.

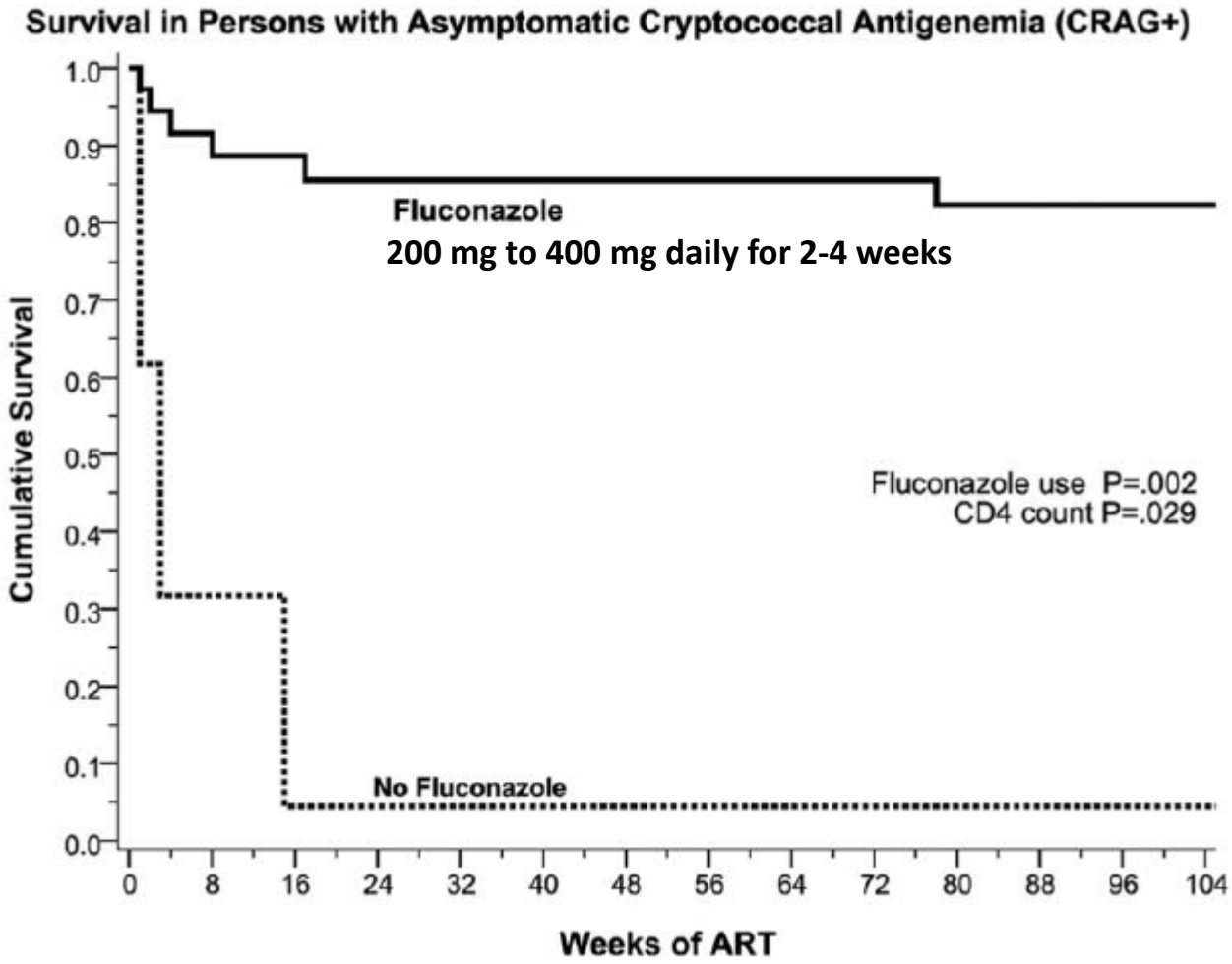
ART is not enough to treat asymptomatic antigenaemia



*All CrAg-positive patients were asymptomatic

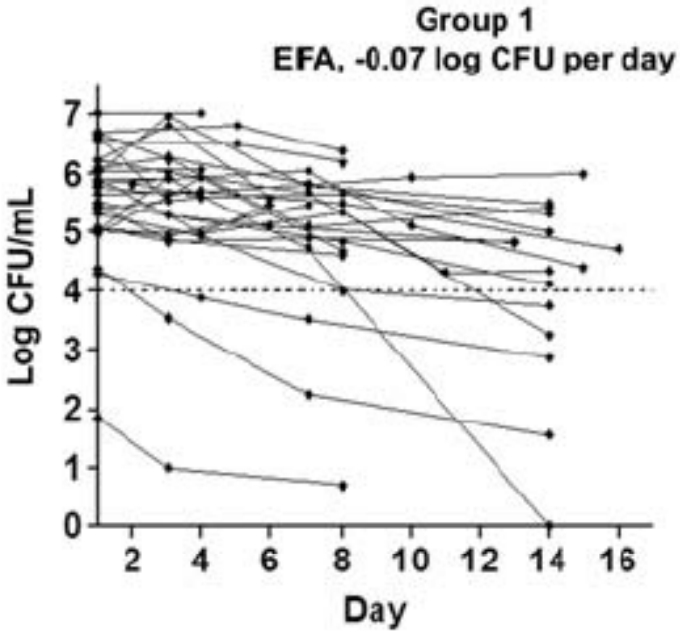
Jarvis JN, et al. *Clin Infect Dis* 2009.

Fluconazole is associated with improved survival

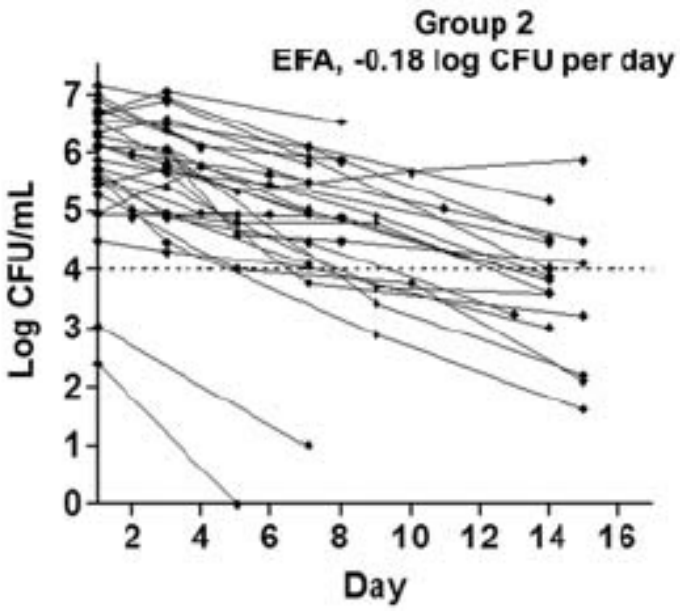


Meya DB, et al. *Clin Infect Dis* 2010.

High-dose fluconazole decreases time to CSF sterilisation

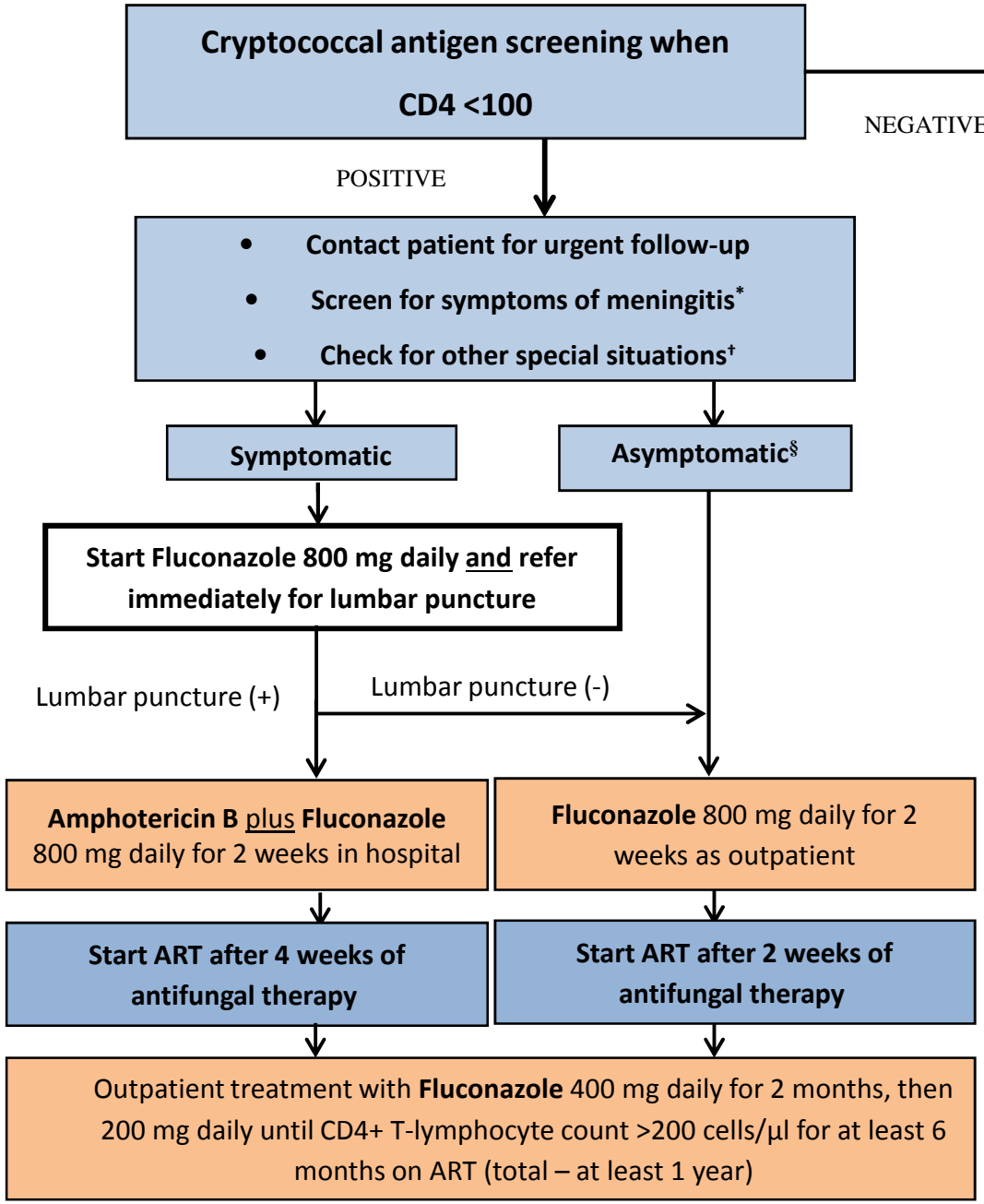


800 mg



1200 mg

Longley N, et al. *Clin Infect Dis* 2008.



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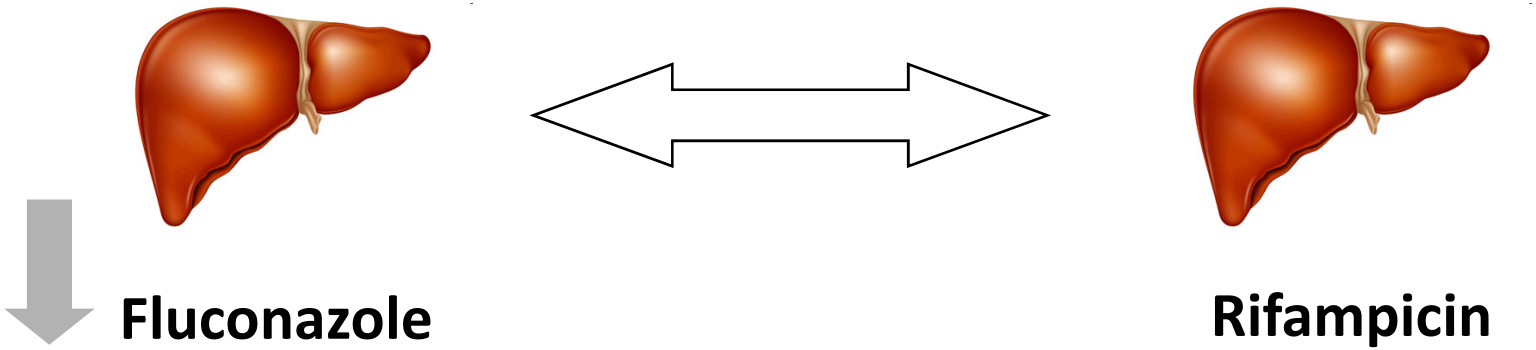
CASE

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



Fluconazole

Rifampicin

But no need for dose adjustment

CASE

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

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

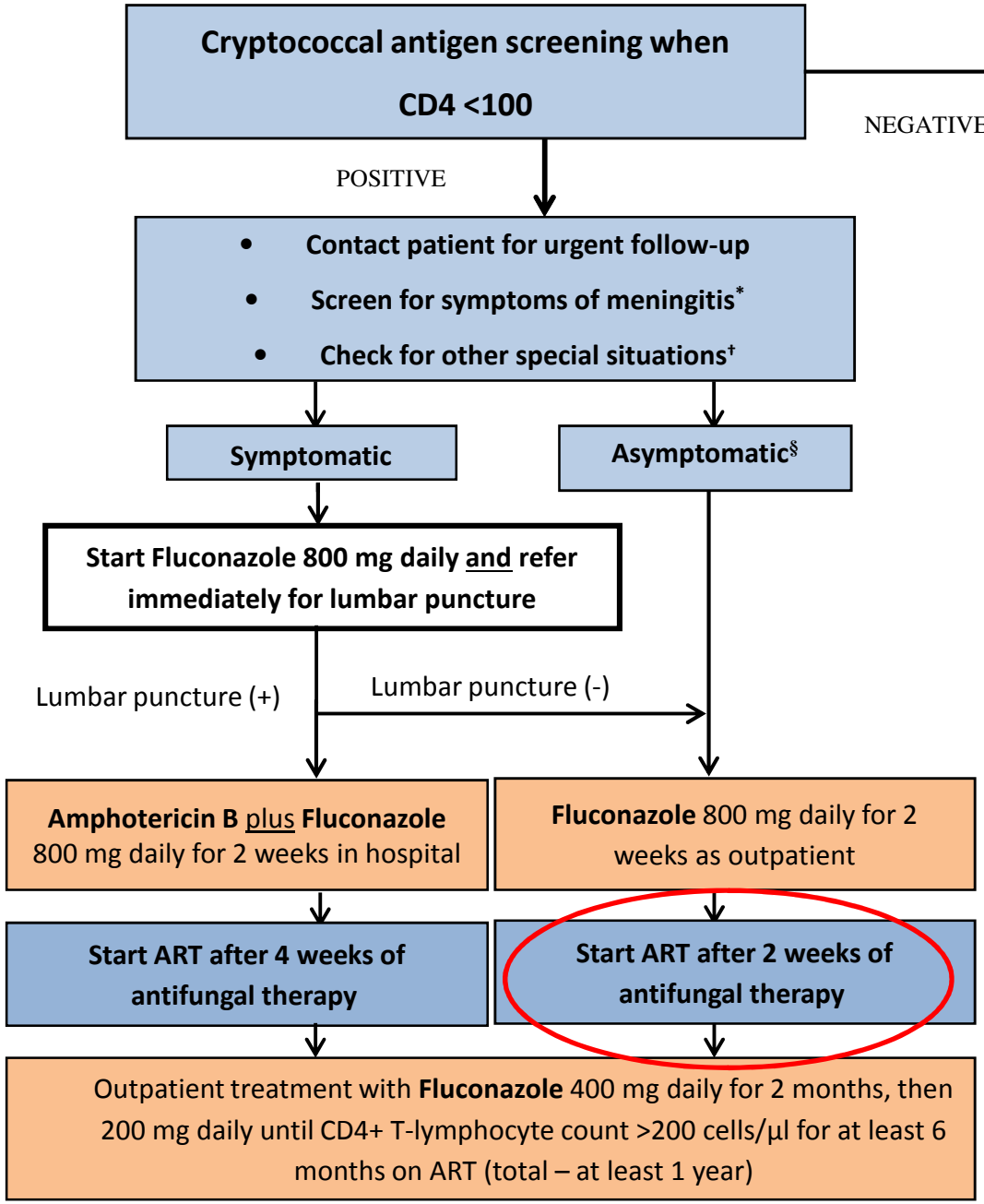
- Tolerated the medications better

Case discussion points

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

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

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



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

1. Headache
2. Confusion

†Other special situations include:

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

§ A lumbar puncture may be considered if available.

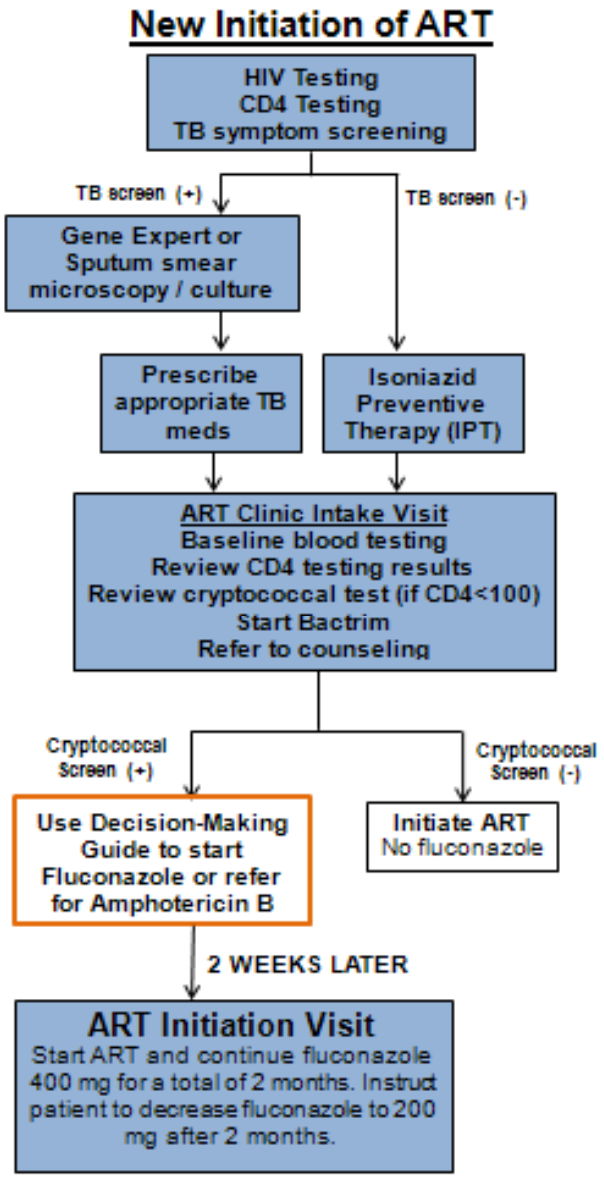
CASE

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

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

} Good counselling

Integration with routine HIV and TB care



Summary

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

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

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

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