TB & Cryptococcal Disease in Advanced HIV

CPD Webinar Series · Session 3

Key updates on TB & cryptococcal management — translating the 2026 National Consolidated HIV Guidelines into practice

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National Tuberculosis Programme · National Department of Health

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What do you expect to get out of this presentation?

Meet Thabo — setting the scene

A patient walks back in

Thabo, 34, was diagnosed with HIV 3 years ago. He started TLD but stopped about 8 months ago and disengaged from care. Today he returns to the clinic.

- 3 weeks of cough, drenching night sweats and weight loss
- 5 days of a worsening headache
- On exam: thin, oral thrush, low-grade fever — but no neck stiffness and a normal level of consciousness

78 **CD4 count**
cells/µL — the number that changes everything today

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Hold these five questions

1. What does that CD4 trigger — today, before he leaves the room?
2. First-line TB test — and if it is negative, is TB excluded?
3. His serum CrAg returns positive but the headache is mild — the next step?
4. He is off ART. When do we restart it?
5. Which preventive therapies must each be considered?

In one word — what most often delays a TB or cryptococcal diagnosis in your AHD patients?

SESSION FOCUS

Why this matters in Advanced HIV Disease

Both TB and cryptococcal disease are leading causes of death before and after ART is started — usually from late presentation and delayed diagnosis. The updates are about finding them faster and treating at the right level of care.

AHD is defined as **CD4 ≤ 200 cells/µL** or a **WHO clinical stage 3 or 4 condition** (all children < 5 years are treated as AHD).

Tuberculosis

- The commonest opportunistic infection and cause of death in AHD
- Often paucisymptomatic at low CD4 — may have TB with no symptoms
- Negative first-line tests do NOT exclude it — keep looking

Cryptococcal disease

- A new positive serum CrAg → high risk of cryptococcal meningitis within ~3 weeks
- Meningitis carries high mortality and needs intensive hospital treatment
- Reflex CrAg screening lets us intervene before meningitis develops

Source: *2026 National Consolidated HIV Guidelines (AHD section, pp. 53–54, 73)*

Systematic TB screening: who, regardless of symptoms

Screen **everyone** for TB symptoms at every visit. In addition, these high-risk groups are **investigated for TB whether or not symptoms are present:**

- At HIV diagnosis / first evaluation for ART (incl. pregnant & breastfeeding women)
- Anyone with confirmed or presumed Advanced HIV Disease
- A new TB exposure / known TB contact
- Annual clinical review on ART (aligned with the annual viral load)
- Any HIV-positive woman with a new pregnancy diagnosis
- A past history of TB disease – In the last 2 years

If the patient is well with no symptoms, do not wait for results before initiating ART or TPT.

Source: *2026 National Consolidated HIV Guidelines, Systematic screening for TB (pp. 69)*

Urine LAM (U-LAM): who is eligible

All inpatients living with HIV

- Test every admitted PLHIV being investigated for TB
- In hospital, also send a urine TB-NAAT in symptomatic patients

Sample matters

- Use a mid-steam or in/out catheter sample — more reliable
- Bag specimens may cause false positives

Symptomatic outpatients — if any of:

- **CD4 ≤ 200** — within the last 6 months (or ≥25% if < 5 yrs)
- **Advanced HIV Disease** — confirmed or presumed
- **Current serious illness** — warranting admission

A positive U-LAM confirms TB but gives no drug susceptibility — **always do a TB-NAAT on anyone with a positive U-LAM.**

Source: 2026 National Consolidated HIV Guidelines, TB Investigations (pp. 66–68)

U-LAM: reading the result well

Positive U-LAM

- Provides clinical confirmation of TB disease in a person living with HIV
- Gives NO indication of drug susceptibility → always add a TB-NAAT

Negative U-LAM

- Does NOT exclude TB — interpret with symptoms, CXR and TB-NAAT
- Keep investigating, especially for extrapulmonary disease

Two traps to remember

False positives are common with bag specimens of urine — use a mid-stream or catheter sample.

Non-tuberculous mycobacteria (e.g. MAC) can also produce a positive U-LAM, especially at CD4 < 50 — consider mycobacterial blood cultures.

Source: *2026 National Consolidated HIV Guidelines, TB Investigations table (pp. 66–67)*

The TB test menu: what each test tells you

Test	What it tells you	Key caveat
TB-NAAT (GeneXpert)	Bacteriological confirmation; detects rifampicin ± INH resistance	A negative NAAT does not rule out TB, especially EPTB — treat on clinical/radiological grounds if the picture fits
Urine TB-NAAT	Adds yield in symptomatic admitted PLHIV (alongside U-LAM)	Hospital inpatients with TB symptoms
Culture / DST	Most sensitive; confirms viable bacilli; enables drug-susceptibility testing	Slow — never delay treatment waiting for it
Chest X-ray	Supports a clinical diagnosis; useful for EPTB patterns	A normal CXR does not exclude TB in a symptomatic person
U-LAM	Side-room confirmation of TB in PLHIV (see previous slide)	Always pair a positive result with a TB-NAAT

Source: *2026 National Consolidated HIV Guidelines, TB Investigations: the 'what', 'when' & 'how' (pp. 66–68)*

Thabo's sputum TB-NAAT is negative and his chest X-ray is normal. What's your next step?

Negative tests ≠ no TB: think extrapulmonary

A negative sputum TB-NAAT and a normal CXR in a symptomatic AHD patient does NOT exclude TB. Refer for, or continue, investigation for extrapulmonary TB.

Clinical clues that strongly support EPTB in an AHD inpatient

- Large peripheral lymph nodes
- Lymphocyte-predominant exudative pleural effusion
- Pericardial effusion
- Abdominal lymph nodes, ascites or splenic abscesses on ultrasound

Keep the threshold for empiric TB treatment low. These findings, with no clear alternative cause in an AHD patient, justify starting TB treatment while investigation continues.

Source: *2026 National Consolidated HIV Guidelines, EPTB clues in AHD (pp. 65–66)*

Systematic screening for tuberculosis

If a patient is clinically well and has no TB symptoms, there is no need to wait for the test results before 1) initiating/re-initiating ART or 2) initiating TPT if the patient is eligible for TPT. See *Table 25: TB screening and TPT eligibility on page 89*.

ART and TPT can be started on the same day

TB-NAAT / u-LAM negative and NO evidence suggestive of TB on CXR

Symptoms and signs NOT suggestive of TB

No TB Disease

Initiate ART if not already on ART and there are no other reasons to defer ART

Offer TPT if eligible (See Table 26), if TPT not already initiated

Symptoms or signs suggestive of TB[3]

Continue to investigate for TB and other diseases

No evidence for TB Disease

Treat most likely non-TB condition, if applicable

Follow-up on results of any culture and DST, as applicable.

TB-NAAT / u-LAM positive or CXR suggestive of TB

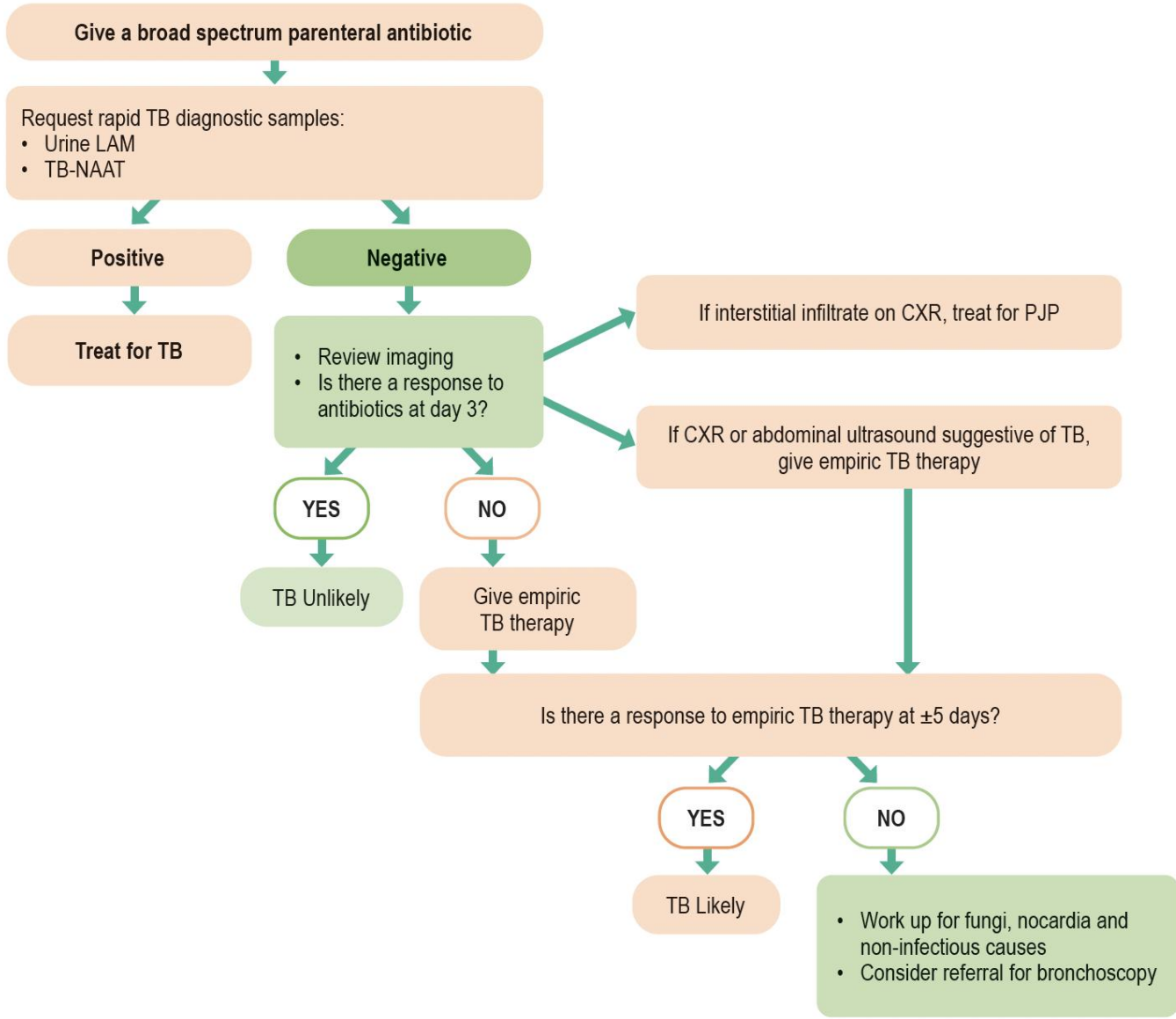
TB Disease (bacteriologically confirmed or clinically diagnosed)

Initiate TB Treatment.
Continue ART. If not yet on ART, defer ART as per Table **29**
Register and notify the patient

Ensure response to treatment, especially if TB was clinically diagnosed.

Source: *2026 National Consolidated HIV Guidelines, Figure 8: (pp.69)*

An approach to an inpatient with AHD and a pulmonary presentation



Source: *2026 National Consolidated HIV Guidelines, Figure 10 (pp.71)*

TB preventive therapy (TPT): prevent it

Rule out active TB first (clinical + testing). A TST is not required, TPT and ART can start the same day, and an asymptomatic patient need not wait for the NAAT result.

Who	Regimen	Notes
Adults & adolescents ≥15 on / starting DTG	12H — isoniazid 300 mg daily × 12 months + pyridoxine 25 mg	Preferred regimen for DTG initiators
≥25 kg & virally suppressed (VL<50) on DTG	3HP — weekly isoniazid + rifapentine × 3 months	NOT for new DTG starters; avoid with PIs or oral/injectable contraceptives
Children < 15 yrs / < 25 kg	6H — isoniazid 10 mg/kg/day × 6 months + pyridoxine	6H preferred on DTG to avoid interactions
Pregnant women	12H — only if AHD (CD4 ≤200 or WHO 3/4)	If CD4 >200, defer TPT to post-partum; keep screening for TB

Contraindications: active liver disease · alcohol misuse · painful peripheral neuropathy · previous MDR-/XDR-TB · isoniazid hypersensitivity.

Source: 2026 National Consolidated HIV Guidelines, TPT eligibility & dosing (pp. 89–90)

TB/HIV co-treatment: DTG dosing & ART timing

Rifampicin lowers DTG levels

- Double the DTG: add DTG 50 mg 12 hours after the TLD dose
- Continue the extra dose until 2 weeks after rifampicin stops

Already on ART?

- Continue the DTG regimen and add boosting while on rifampicin
- Virally suppressed on EFV: continue EFV (no interaction), switch to DTG ≥2 weeks after TB treatment ends

When to start ART after TB treatment (defer table)

Situation	When to start ART
DS-TB, non-neurological, CD4 < 50	Within 2 weeks of starting TB treatment
DS-TB, non-neurological, CD4 ≥ 50 (adults/adolescents)	Defer to 8 weeks after starting TB treatment
DR-TB, non-neurological	After 2 weeks, once improving and TB treatment tolerated
TB meningitis / neurological TB	Defer until 4–8 weeks after starting TB treatment

Source: *2026 National Consolidated HIV Guidelines, co-treatment & indications to defer ART (pp. 91–92)*

Cryptococcal screening: reflex CrAg

Reflex CrAg at CD4 ≤ 200

- Lab runs a serum CrAg automatically on any CD4 ≤ 200
- Screen at ART initiation, at treatment failure, and on re-entry to care after disengagement
- Not routinely screened in children < 10 years

CrAg vs "CLAT" — clearing the confusion

- CrAg is the clinical entity — cryptococcal antigen, detected on serum and CSF
- LFA / CLAT are methodologies — SA labs use the CrAg lateral-flow assay (IMMY)
- Don't re-screen a prior CM patient: CrAg stays positive for life → use CSF culture for relapse

Every new positive serum CrAg means cryptococcal antigenaemia — and it must be acted on.

- All antigenaemia requires antifungal treatment
- A first positive serum CrAg carries a high risk of developing cryptococcal meningitis within the next ~3 weeks
- **So every new positive serum CrAg needs a lumbar puncture — see next slide**

Source: *2026 National Consolidated HIV Guidelines, Cryptococcal disease (pp. 73)*

Thabo's serum CrAg is positive, but his headache is mild and he has no neck stiffness. What now?

Every new positive serum CrAg → lumbar puncture

Do an LP and CSF CrAg to find out whether disease has reached the meninges — even if there are no meningitis symptoms.

Serum CrAg POSITIVE

Cryptococcal antigenaemia

→

Lumbar puncture + CSF CrAg
Do it regardless of symptoms — asymptomatic CM may be present

CSF CrAg negative → antigenaemia, no meningitis

CSF CrAg positive → cryptococcal meningitis

High-stakes window: a first positive serum CrAg has a high likelihood of progressing to cryptococcal meningitis within ~3 weeks — the LP is what catches it early.

If the LP or amphotericin will be delayed

Start fluconazole 1200 mg immediately rather than waiting — then complete the appropriate induction once the CSF result is known.

Source: *2026 National Consolidated HIV Guidelines, investigating cryptococcal disease (pp. 73–77)*

Antigenaemia vs meningitis: the ART consequence

Antigenaemia WITHOUT meningitis

Serum CrAg positive · CSF CrAg negative

- Oral fluconazole-only induction: 1200 mg daily for 14 days
- Start ART immediately — no need to delay
- Then consolidation and maintenance fluconazole (next slide)

Cryptococcal MENINGITIS

Serum CrAg positive · CSF CrAg positive

- Admit for intensive induction antifungal therapy (next slide)
- DEFER ART until 4–6 weeks after starting antifungal treatment
- Earlier ART increases the risk of death — do not rush it

Source: *2026 National Consolidated HIV Guidelines, treatment & indications to defer ART (pp. 76, 92)*

Thabo turns out to have cryptococcal meningitis AND pulmonary TB. When do you restart his ART?

Induction therapy for cryptococcal meningitis

PREFERRED (Option 1) — 14 days

Liposomal amphotericin B 10 mg/kg IV — single dose (over 2 h)

+ Flucytosine 25 mg/kg orally 6-hourly × 14 days
+ Fluconazole 1200 mg orally daily × 14 days

If the preferred drugs aren't available — alternative 14-day inductions

No liposomal ampho B	Amphotericin B deoxycholate 1 mg/kg/day IV (7 d) + flucytosine 25 mg/kg 6-hrly (7 d), then fluconazole 1200 mg daily (7 d)
No flucytosine	Amphotericin B deoxycholate 1 mg/kg/day IV × 14 d + fluconazole 1200 mg daily × 14 d
Neither amphotericin available	Fluconazole 1200 mg daily + flucytosine 25 mg/kg 6-hrly × 14 days

Antigenaemia without meningitis uses fluconazole 1200 mg daily × 14 days only (no amphotericin). Then the maintenance and continuation phases

Source: *2026 National Consolidated HIV Guidelines, Table 16 — adult cryptococcosis regimens (pp. 77)*

Fluconazole: pre-emptive & secondary prophylaxis

INDUCTION

Antigenaemia (no CM): fluconazole 1200 mg daily × 14 days

CONSOLIDATION

Fluconazole 800 mg daily × 8 weeks

MAINTENANCE

Fluconazole 200 mg daily (secondary prophylaxis) for ≥ 1 year

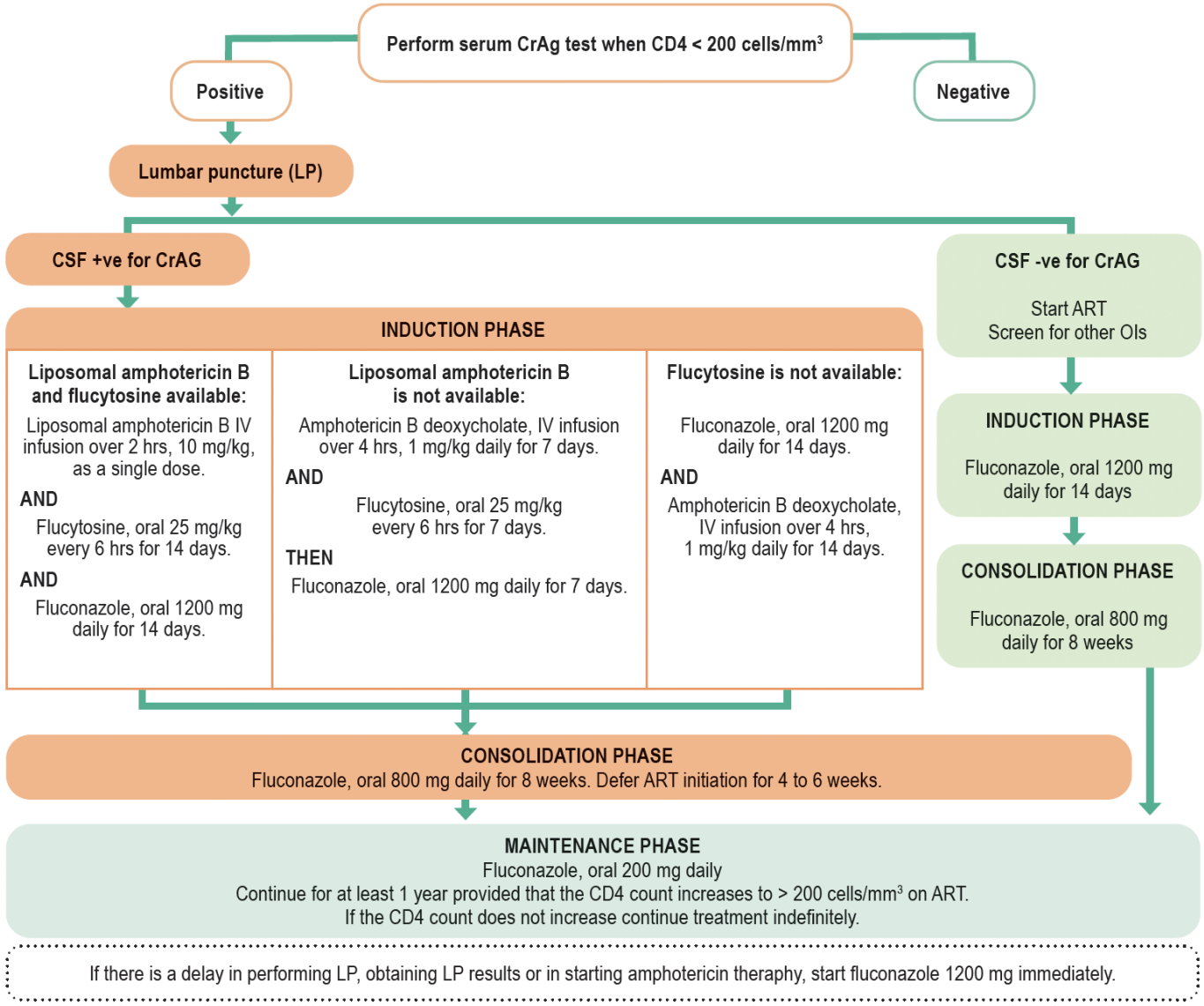
When can maintenance fluconazole stop?

Only after ≥ 1 year, once the CD4 count rises above 200 cells/µL on ART for at least 6 months AND the patient is virally suppressed. If CD4 does not recover, continue indefinitely.

Relapse is usually a prophylaxis failure. Symptomatic relapse most often follows inadequate or premature cessation of maintenance fluconazole — always check the adherence history. Diagnose relapse with a CSF culture, never with a repeat CrAg (which stays positive for months).

Source: *2026 National Consolidated HIV Guidelines, cryptococcal treatment phases (pp. 76–77)*

Algorithm for the diagnosis and management of cryptococcal disease in adults



Source: *2026 National Consolidated HIV Guidelines, Figure 11: (pp.76)*

Raised pressure & who does what

Therapeutic lumbar punctures

- Raised intracranial pressure drives much of the early mortality and morbidity in CM
- Indicated in symptomatic patients — do with pressure monitoring
- Remove CSF (up to 30 mL) to lower pressure to ~50% of opening pressure, but not below 20 cm H_2O
- Repeat daily until there is clinical improvement

Nurse (PHC)

Identify & act on a positive CrAg; refer all positives for LP; support adherence; switch to consolidation/maintenance per the discharge plan

Doctor (PHC)

LP for an asymptomatic CrAg-positive patient if a doctor is on site; refer symptomatic patients and confirmed CM to hospital

Medical officer (hospital)

Perform LP (or imaging if contraindicated), diagnose CM, and start the intensive induction phase

Source: *2026 National Consolidated HIV Guidelines, who/where of managing cryptococcal disease (pp. 74–75)*

Cotrimoxazole preventive therapy (CPT)

When to START

- Adults & children > 5 yrs: CD4 ≤ 200 or WHO stage 3 or 4
- Prevents PJP, toxoplasmosis, serious bacterial infections & diarrhoea
- Safe to use in pregnancy

When to STOP

- Stop once CD4 > 200 cells/µL, regardless of clinical stage
- Dose ≥ 25 kg: 2 single-strength tablets (800/160 mg) daily

Hypersensitivity: usually a maculopapular rash. If there are systemic features or mucosal involvement, stop cotrimoxazole immediately and permanently, and refer to hospital.

Paediatric note: all HIV-positive infants < 1 year receive CPT regardless of CD4; children 1–5 years if CD4% ≤ 25% or WHO stage 3/4.

Source: *2026 National Consolidated HIV Guidelines, CPT indications & dosing (pp. 30, 86)*

The AHD prevention package: assess every patient

Step 4 of AHD care is "prevent OIs." Every patient with advanced HIV disease is assessed for all three of these — alongside the TB and CrAg screening that opens the pathway.

Cotrimoxazole (CPT)

CD4 ≤ 200 or WHO 3/4. Prevents PJP, toxoplasmosis & bacterial infection. Stop at CD4 > 200.

TB preventive therapy (TPT)

After active TB excluded. 12H for DTG initiators; 3HP only if already suppressed on DTG; 6H in children.

Fluconazole (pre-emptive)

For CrAg-positive antigenaemia without meningitis: induction → consolidation → maintenance (secondary prophylaxis).

Screen → diagnose & treat any OIs → prevent the rest. The bundle is only complete when CPT, TPT and fluconazole have each been considered.

Source: 2026 National Consolidated HIV Guidelines, Step 4: Prevent OIs (pp. 86–90)

CASE · RESOLVED

What happened to Thabo

1. **CD4 78 = advanced HIV disease.** Reflex serum CrAg sent, systematic TB investigation started, and cotrimoxazole begun — all at the same visit.

2. **TB confirmed.** Sputum TB-NAAT positive and rifampicin-susceptible; U-LAM positive. TB treatment started. A negative result would not have excluded TB.

3. **Serum CrAg positive → LP done despite mild symptoms.** CSF CrAg positive with raised opening pressure: cryptococcal meningitis. Admitted for induction (single-dose liposomal amphotericin B + flucytosine + fluconazole) with a therapeutic LP for pressure.

4. **He has BOTH meningitis and TB.** The meningitis deferral wins: ART restarted 4–6 weeks after antifungals, with DTG boosted while on rifampicin.

5. **Prevention considered, not assumed.** CPT started; fluconazole consolidation then maintenance after induction. TPT is NOT given now — he has active TB, so he is treated, not given preventive therapy.

SUMMARY

Three things to take back to the ward

1

Screen systematically, treat empirically

In AHD, negative first-line tests do not exclude TB or cryptococcal disease. Use U-LAM, keep a low threshold for empiric treatment, and investigate extrapulmonary TB.

2

Every positive serum CrAg gets an LP

Asymptomatic or not — the ~3-week meningitis risk demands it. CM defers ART 4–6 weeks; antigenaemia without CM does not delay ART at all.

3

Don't forget prevention

CPT, TPT and pre-emptive/maintenance fluconazole prevent the very deaths we've discussed. Consider all three in every AHD patient.

Source: *2026 National Consolidated HIV Guidelines (AHD section)*

Linking the levels of care

Diagnosis and induction often happen in hospital — but adherence, phase switches and follow-up happen at PHC.

Use the CrAg management summary as the handover tool. It carries the LP result, induction received, and the consolidation/maintenance plan back to the clinic — so fluconazole phases are continued and follow-up isn't lost.

Integrate TB and ART care at the same visit. Splitting them increases visits and the risk of disengagement — the single biggest threat to these patients after diagnosis.

Thank you — questions & discussion

How useful did you find this presentation?