SAHCS
GUIDELINES

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY CLINICAL GUIDELINES FOR **HOSPITALISED ADULTS WITH ADVANCED HIV DISEASE 2022**

A publication of the Southern African HIV Clinicians Society

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY CLINICAL GUIDELINES FOR **HOSPITALISED ADULTS WITH ADVANCED HIV DISEASE 2022**

Authors: Tom Boyles,[1,2] Gary Maartens,[3] Jeremy Nel,[4] David Stead[5,6]

Author affiliation:

[1] Right to Care NPC, SA
[2] London School of Hygiene and Tropical Medicine, London, UK
[3] Division of Clinical Pharmacology, Department of Medicine, University of Cape Town
[4] Division of Infectious Diseases, Helen Joseph Hospital, University of the Witwatersrand
[5] Division of Infectious Diseases, Internal Medicine, Frere & Cecilia Makiwane hospitals, East London.
[6] Department of Medicine, Faculty of Health Sciences, Walter Sisulu University, Mthatha.

TABLE OF CONTENTS

ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ADR	adverse drug reaction
AKI	acute kidney injury
ALT	alanine transaminase
ANC	antenatal care
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate transaminase
ATV	atazanavir
ATV/r	ritonavir-boosted atazanavir
AZT	zidovudine
bd	twice daily
CM	cryptococcal meningitis
CrAg	cryptococcal antigen
CrCl	creatinine clearance
CNS	central nervous system
CSF	cerebrospinal fluid
CTX	cotrimoxazole
d4T	stavudine
ddI	didanosine
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DRV	darunavir
DRV/r	ritonavir-boosted darunavir
DTG	dolutegravir
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ETR	etravirine
FBC	full blood count
FTC	emtricitabine
Hb	haemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immuno-deficiency virus
ICU	intensive care unit
INH	isoniazid
INR	international normalised ratio
InSTI	integrase strand transfer inhibitor
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrom
LAM	lipoarabinomannan
LDL-C	low-density lipoprotein cholesterol
LP	lumbar puncture
LPV	lopinavir
LPV/r	ritonavir-boosted lopinavir
MTCT	mother-to-child transmission
MVC	maraviroc
NGT	nasogastric tube
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NTD	neural-tube defect
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OI	opportunistic infection
PAS	p-aminosalicylic acid
PCR	polymerase chain reaction
PI	protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PMTCT	prevention of mother-to-child transmission of HIV
PPIs	proton pump inhibitors
PrEP	pre-exposure prophylaxis
QTc	corrected QT interval
RAL	raltegravir
RCTs	randomised controlled trials
RIF	rifampicin
RFB	rifabutin
RNA	ribonucleic acid
RPV	rilpivirine
RTV	ritonavir
sCr	serum creatinine
sCrAg	serum cryptococcal antigen
TAF	tenofovir alafenamide
TAM	thymidine analogue mutation
TB	tuberculosis
TBM	tuberculosis meningitis
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TG	triglycerides
TST	tuberculin skin test
UDP	uridine 5'-diphospho
ULN	upper limit of normal
VL	viral load
WHO	World Health Organization
WOCP	women of childbearing potential

1. INTRODUCTION

In 2015, the World Health Organization (WHO) recommended that all people living with HIV (PLHIV) start antiretroviral therapy (ART) irrespective of clinical or immune status. However, despite this progress, up to half the people living with HIV continue to present to care with Advanced HIV Disease (AHD). The WHO defines AHD for adults and adolescents (and children five years and older) as having a CD4 cell count of less than 200 cells/mm^3 or WHO clinical stage 3 or 4 disease.

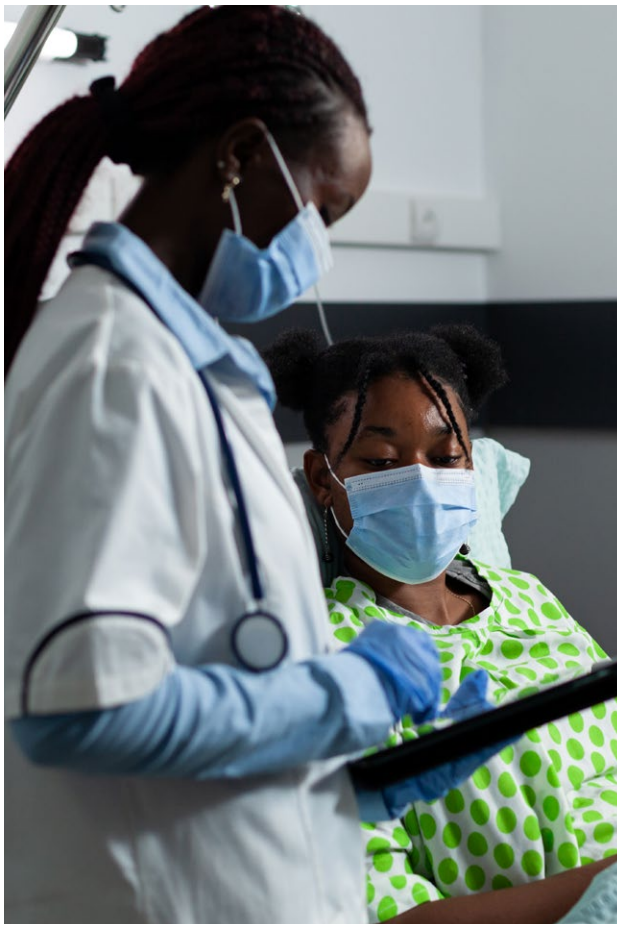
AHD includes people presenting to care for the first time following an HIV diagnosis and people who have treatment failure and consequent decline in CD4 cell count. Individuals who had previously initiated ART and are re-engaging with care after a period of ART interruption should be assessed for AHD. People presenting with AHD are at high risk of death, even after starting ART, with the risk increasing with decreasing CD4 cell count, especially with CD4 cell count cell count <100 cells/mm^3. AHD is also associated with increased health-care costs, increased risk of opportunistic infections, immune reconstitution inflammatory syndrome (IRIS), incomplete immune reconstitution, higher viral reservoirs, higher inflammation, increased risk of AIDS-related and non-AIDS-related comorbidities, use of more healthcare services, and more frequent monitoring needs.

Leading causes of mortality among adults with AHD globally include tuberculosis (TB), severe bacterial infections, cryptococcal disease, histoplasmosis, toxoplasmosis and *Pneumocystis jirovecii* pneumonia (PJP). Other invasive fungal infections have been recently estimated as contributing significantly to the number of people dying from AIDS-related causes.

CD4 cell count is the best indicator of disease stage and immediate risk of death and should therefore be used to identify people with AHD. If access to CD4 count is limited or unavailable, WHO clinical staging should be used.

To address these leading causes of morbidity and mortality among people with AHD, the WHO recommends that a package of interventions, including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions, be offered to everyone (all populations and all age groups) living with HIV presenting with AHD. However, this guidance is predominantly applied to ambulatory patients as it is based on two studies (REALITY and REMSTART) that excluded hospitalised patients.

The aim of this document is to provide clinical guidance in the care of hospitalised patients with AHD, who often present with complex problems and multiple opportunistic infections. The guidance is aimed predominantly at clinicians in South Africa but may be applicable more broadly. We generally provide an 'approach' to each condition with selected references for further reading. Each chapter has a primary author who wrote the first draft which was peer reviewed by the other three authors.



2. RENAL IMPAIRMENT

Primary Author: Jeremy Nel

Background

Patients with AHD commonly have abnormal creatinine levels. This chapter presents a useful approach to a patient with apparent renal impairment, beginning with asking if renal impairment is definitely present and whether it might be acute or chronic. It then gives an approach to dealing with both acute and chronic renal impairment.

Is the patient truly in renal failure?

Serum creatinine should not be used as the sole indicator of renal failure. One reason is that independently of renal function, creatinine also varies as a function of muscle bulk. Men, younger adults, and muscular men have a higher serum creatinine than women, older adults and wasted people, on average.

Rather than using creatinine therefore, it is far better to estimate the **glomerular filtration rate (GFR),** which considers many of the above factors. Commonly used calculations for this include:

- **Cockroft-Gault formula:** this uses sex, age, weight, and creatinine. It is relatively easy to calculate, and because weight is factored in, it's often more accurate for wasted patients such as might be seen with AHD. Technically, it measures creatinine clearance, not eGFR.
- **CKD-EPI:** this uses sex, race, age, and creatinine. It is often calculated automatically on lab reports. It is more accurate than Cockroft-Gault, apart from patients who are extremely wasted.

Both calculations are accessible on most medical Apps available on a smartphone.

Note: these equations are only meant to be used in chronic kidney disease, not acute kidney injury. In acute kidney injury, the glomerular filtration rates estimated by the above equations can be highly inaccurate. *In acute renal failure, look at the creatinine trend* too. A rapidly rising creatinine implies that the GFR is worse than the equations calculate. A falling creatinine implies that the GFR is better than the equations calculate.

Note: some medications inhibit creatinine's secretion directly, without affecting renal function. Dolutegravir is one such medication. Because the above equations use creatinine to estimate the GFR, a patient who is started on dolutegravir can expect their serum creatinine to rise and their eGFR to appears to fall, but *this does not reflect a true decline in renal function.* In the case of dolutegravir, the estimated rise in creatinine is usually <25%, and it occurs within the first few weeks after initiating the medication. A rise of >20-25% in serum creatinine, or a rise that occurs after the first month, should prompt workup for alternative causes (the median rise in creatinine seen in the ADVANCE trial was almost 20%).

Is the renal dysfunction likely acute or chronic?

This is a hard question to answer, but it has important implications. In acute kidney injury (AKI), urgent intervention is required for the kidney function to recover, whereas in chronic kidney disease (CKD), management is less urgent and often centers around risk factor modification to prevent gradual worsening, rather than on renal recovery.

Clues that suggest acute vs chronic kidney injury are shown in table 1.

TABLE 1: Clinical clues to differentiate acute kidney injury (AKI) from chronic kidney disease (CKD)

Clue	This suggests	Comment
Small kidneys (< 9 cm) on ultrasound/CT scan	CKD	Note that some causes of CKD have normal/large kidneys (e.g. HIVAN, diabetic nephropathy, etc.)
A previous normal creatinine within the last 3 months	AKI	Chronic kidney disease is defined as renal dysfunction lasting at least 3 months.
Normal haemoglobin	AKI	99% of CKD patients have anaemia. Many patients with AKI also have anaemia from other causes, so anaemia itself isn't helpful – but the absence of anaemia is and would be suggest that it is not CKD
High serum phosphate	CKD	Not that phosphate levels can change quickly (within days)
Oliguria	AKI	Note that end-stage CKD patients will also be oliguric, and some AKI patients can be polyuric.

The clinical context is also important to distinguish between AKI and CKD. A patient with AKI is usually acutely ill in some obvious way (e.g. diarrhoea, pneumonia, dehydration, septicaemia).

However, a patient with CKD can develop a superimposed AKI ("acute-on-chronic renal dysfunction"). In that case the acute and chronic components will need separate management, as outlined below. If in doubt, treat as if it is AKI first, but be careful to watch for signs of fluid overload.

Acute renal failure (acute kidney injury – AKI)

Common causes of AKI are:

- **Pre-renal AKI** – hypoperfusion of the kidney, often from dehydration or sepsis. This will respond to fluids. If renal perfusion is not rectified, progress to acute tubular necrosis occurs (see below).
- **Acute tubular necrosis (ATN)** – from either ischaemia because of hypoperfusion, or from toxins (usually medications). Important medications that cause ATN include:
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Aminoglycosides
  - Amphotericin B
  - Tenofovir (rarely)
- **Acute interstitial nephritis** – this is inflammation of the interstitium with or without renal tubular injury. Urine eosinophils are virtually pathognomonic but are only present in the minority of cases. Important medications that can cause acute interstitial nephritis include:
  - Rifampicin
  - Cotrimoxazole (Bactrim)
  - NSAIDs
  - Herbal remedies

Management principles

Below is a list of management principles in acute kidney injury (AKI):

- Give a trial of fluids if there is a suspicion of a pre-renal component to the AKI (unless the patient is clinically overloaded). Most septic or dehydrated patients will respond at least partially to fluids. E.g., give 1 litre of an isotonic crystalloid like normal saline over 30 minutes, then 3 litres per day thereafter. Assess the patient carefully for signs of fluid overload before each litre. If signs are present, stop giving fluids.
- Stop all commonly nephrotoxic medications, like NSAIDs, tenofovir, and cotrimoxazole.
- Dose-adjust any other medications that trequire dose adjustment if there is renal compromise, like pyrazinamide and ethambutol.
- Attempt to correct any metabolic derangements. Pay particular attention to hyperkalaemia.
- Treat the underlying cause (e.g., diarrhoea, pneumonia).
- If there is reason to suspect urinary obstruction (e.g., a history of prostate enlargement, cervical cancer, or kidney stones), obtain an urgent ultrasound to exclude this possibility.
- Assess for the need for acute dialysis. Indications for dialysis include:
  - Acidosis refractory to medical therapy
  - Hyperkalaemia refractory to medical therapy
  - Refractory pulmonary oedema
  - Uraemic gastritis
  - Uraemic pericarditis
  - Uraemic encephalopathy

BOX 1: A note on tenofovir use in acute kidney injury (AKI)

- Tenofovir (TDF) should be stopped as it may be contributing to AKI, even if it's not the primary cause. However, don't stop all antiretrovirals– rather change the TDF to another antiretroviral (like abacavir).
- If there is a non-TDF cause for the AKI, TDF can be reintroduced aonce renal function normalises. If the patient has had severe renal dysfunction, it is advisable to wait at least 1-3 months after renal function normalises before reintroducing TDF.
- **Remember:** TDF is a very rare cause of AKI in the absence of a second insult to the kidneys. Therefore, never assume that all you need to do is to stop the TDF. Consider other causes as here is a very high probability that there is another issue as well.

Chronic kidney disease (CKD)

There are two main aspects to consider in CKD:

1. HIV-associated nephropathy (HIVAN)

HIVAN is a direct HIV infection of the renal cells, causing a changes in the glomerulus (collapsing variant of focal segmental glomerulosclerosis), interstitium (plasma cell infiltrate) and tubules (dilated tubules lined by flat epithelium with filled with proteinaceous material).

HIVAN can only be diagnosed definitively on renal biopsy, but a typical picture highly suggestive of HIVAN can be easily identified. This includes:

- Advanced HIV (high viral load and low CD4, though there are exceptions)
- Black race (HIVAN is strongly associated with a particular genetic variant of the APOL1 gene).
- Large or high to normal sized kidneys (typical size range is 10.5-15.5 cm)
- Nephrotic or subnephrotic ranged proteinuria
- Bland urinary sediment (no significant amount of red or white cells in the urine)
- Absence of significant oedema or hypertriglyceridaemia (which often accompanies other forms of nephrotic syndrome)

Management of HIVAN

This is in addition to the standard management of CKD (see below) and includes:

- Initiate antiretroviral therapy urgently (to prevent a rapid decline in GFR).
- Give an ACE-inhibitor if the patient is significantly proteinuric (>1g per day). The benefit of this in HIVAN is not well established and is largely extrapolated from the management of other causes of nephrotic syndrome. Following initiation, monitor the potassium and GFR for 2 weeks. A slight fall in GFR is expected with an ACE-inhibitor, but this is acceptable provided it does not exceed 20%. If it exceeds 20%, stop the ACE-inhibitor.

2. General management of chronic kidney disease (CKD)

CKD can be caused has many causes (whether HIVAN or other, e.g. diabetes, hypertension, etc.) and management includes the following, regardless of the cause:

- Control relevant risk factors to prevent worsening renal function:
  - Blood pressure < 130/80
  - HBA1c < 7.0%
  - HIV viral load undetectable
- Counsel the patient about avoiding nephrotoxic drugs (e.g. NSAIDs)
- Dose-adjust any drugs that need it.
- Refer to nephrologist if the GFR is < 30 ml/min

HIV-infected patients with CKD are candidates for chronic dialysis and renal transplant in many centres.

BOX 2: Recommended first-line regimen in chronic kidney disease (CKD)

The recommended first-line antiretroviral regimen for patients with chronic kidney disease is

lamivudine (or emtricitabine) + abacavir + dolutegravir

Lamivudine and abacavir are available as a fixed dose combination. It is no longer believed to be strictly necessary to dose adjust lamivudine in renal failure; therefore, the fixed dose combination can be safely used.

BOX 3: Chronic kidney disease (CKD) and hepatitis B

What about an HIV-infected patient with chronic hepatitis B who has chronic kidney disease?

- Although lamivudine or emtricitabine have anti-hepatitis B activity, hepatitis B develops resistance to these medications after a period of time (approximately 50% resistance at 1 year, and 90% resistance at 5 years). Therefore, these medications cannot be relied on for chronic control of hepatitis B.
- Dedicated anti-hepatitis B medication, such as entecavir, are available in South Africa and can be used but they are very expensive and not routinely available in the public sector.
- Tenofovir is therefore required for control of chronic hepatitis B in most patients, even those with chronic kidney disease. Tenofovir alafenamide fumarate (TAF) may be a better option in patients with chronic kidney disease in this scenario, if it is available. The dose of tenofovir (either TDF or TAF) should be adjusted according to eGFR (see table below), and an effective antiretroviral regimen constructed around this for their HIV (this is the case even if the patient's HIV is resistant to TDF; in which case the patient may sometimes require TDF and 3 other antiretroviral drugs). In patients with CKD in whom tenofovir is added, close attention should be paid to the creatinine clearance, which should be checked at 3 and 6 months after TDF initiation at a minimum, and thereafter 6 monthly.

TABLE 2: Medication dosage adjustments in renal failure				
ART drug dosage adjustments in renal failure [Sourced from: SA HIV Clinicians Society 2017 Adult ART Guidelines]				
Drug	CrCl (mL/min)[‡§]		Haemodialysis (dose after dialysis)	Peritoneal dialysis
	10 – 50	< 10		
TDF	300 mg 48-hourly (GFR 30-50) or 72-96 hourly (GFR 10-29)	300 mg once weekly	TDF	300 mg 48-hourly (GFR 30-50) or 72-96 hourly (GFR 10-29) Unknown
TAF	25mg daily	Unknown	Unchanged	Unchanged
ABC	Unchanged	Unchanged	Unchanged	Unchanged
3TC	150 mg daily	50 mg daily	50 mg first dose and thereafter 25 mg daily[†]	50 mg first dose and thereafter 25 mg daily[†]
AZT	Unchanged	300 mg daily	300 mg daily	300 mg daily
d4T	15 mg 12-hourly	15 mg daily	15 mg daily	Unknown
NNRTIs	Unchanged	Unchanged	Unchanged	Unchanged
PIs	Unchanged	Unchanged	Unchanged	Unchanged
InSTIs	Unchanged	Unchanged	Unchanged	Unchanged

†It is no longer believed to be strictly necessary to dose adjust lamivudine in renal failure, and thus if it is more convenient (e.g. a fixed dose combination is available), the full dose may be given.

Recommended references

1. Yahaya I, Uthman OA, Uthman MM. Interventions for HIV-associated nephropathy. *Cochrane Database Syst Rev.* 2013;2013(1):CD007183. Published 2013 Jan 31. doi:10.1002/14651858.CD007183.pub3
2. Bigé N, Lanternier F, Viard JP, et al. Presentation of HIV-associated nephropathy and outcome in HAART-treated patients. *Nephrol Dial Transplant.* 2012;27(3):1114-1121. doi:10.1093/ndt/gfr376
3. Selhorst P, Combrinck CE, Manning K, et al. Longer-Term Outcomes of HIV-Positive-to-HIV-Positive Renal Transplantation. *N Engl J Med.* 2019;381(14):1387-1389. doi:10.1056/NEJMc1903013
4. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. *N Engl J Med.* 2019;381(9):803-815. doi:10.1056/NEJMoa1902824

3. DIARRHOEA

Primary Author: David Stead

Background

Diarrhoea is common in AHD, affecting 40-80% of HIV-infected people not on ART. The resulting dehydration and hypokalaemia is a frequent cause of hospital admission, with significant mortality. Chronic diarrhoea caused 10- 25% of early mortality on ART in a systematic review of low- and middle-income countries.

There are **different definitions** of diarrhoea, but a practical one is the passing of 3 or more loose/ liquid stools per 24 hours.

It is important to differentiate acute from chronic diarrhoea, and again there are various cut-offs, but for this guideline acute will be defined as diarrhoea lasting < 2 weeks, and chronic will be defined as diarrhoea lasting ≥2 weeks. This chapter gives a point-by-point approach to a patient with AHD and diarrhoea.

Key features to identify on history & examination:

History:

- Duration and severity of diarrhoea. Previous episodes.
- Stool consistency and presence of mucous or blood.
- Presence of constitutional symptoms: fever, night sweats, weight loss.
- Potential drug causes: protease inhibitors, recent antibiotic use.
- Recent travel or possible contaminated water exposure
- HIV control: if currently taking ARVs Or not, last HIV viral load and CD4. **Note:** opportunistic infections that cause diarrhoea occur mostly with severe immunosuppression e.g. CD4 <200 (Cryptosporidium and *Cystoisospora belli*) and CD4 < 50 cells/mm^3 (*Cytomegalovirus* (CMV) and *Mycobacterium avium complex* (MAC))

Examination:

- Hydration status
- Blood pressure, pulse
- Temperature
- Signs of TB (adenopathy, chest signs etc.)
- Abdominal examination:
  - Tenderness in the left iliac fossa (suggestive of acute colitis)
  - Other features of generalised tenderness are non-specific
- Fundoscopy for features of CMV retinitis (haemorrhages and exudates)

Distinguishing small bowel vs large bowel diarrhoea

It is helpful to identify if the diarrhoea is small or large bowel related. This is not always possible or clear on history. Table 3 indicates suggestive findings of which it might be.

TABLE 3: Differentiating small bowel diarrhoea versus large bowel diarrhoea.

	Small bowel diarrhoea (enteritis)	Large bowel diarrhoea (colitis)
History	• Large volume, watery stools • Bland in nature • May have malabsorption • Nausea and vomiting more common	• Low volume, frequent stools • Red and white cells or mucous • Tenesmus
Examination	• Often apyrexial	• May be pyrexial • Left iliac fossa tenderness

Differential diagnosis

Common infectious pathogens will differ by geographical region, hence the need to adapt empiric treatments according to local microbes.

For example, whether the patient has been in an area endemic for amoebiasis or giardiasis, and possible exposure risk to untreated water. There is currently no useful published epidemiological data on stool pathogens among HIV infected adults in South Africa. Causes can be divided into infectious and non-infectious related causes:

Infectious causes

Table 4 shows the infectious causes of diarrhoea in AHD and indicates suggested investigations, and treatment for each.

Non-infectious causes

These include:

- Medications: protease inhibitors (lopinavir/ritonavir > darunavir/r > atazanivir/r)
- Malabsorption syndromes
- Malignancies: Non-Hodgkin's Lymphoma and Kaposi sarcoma.

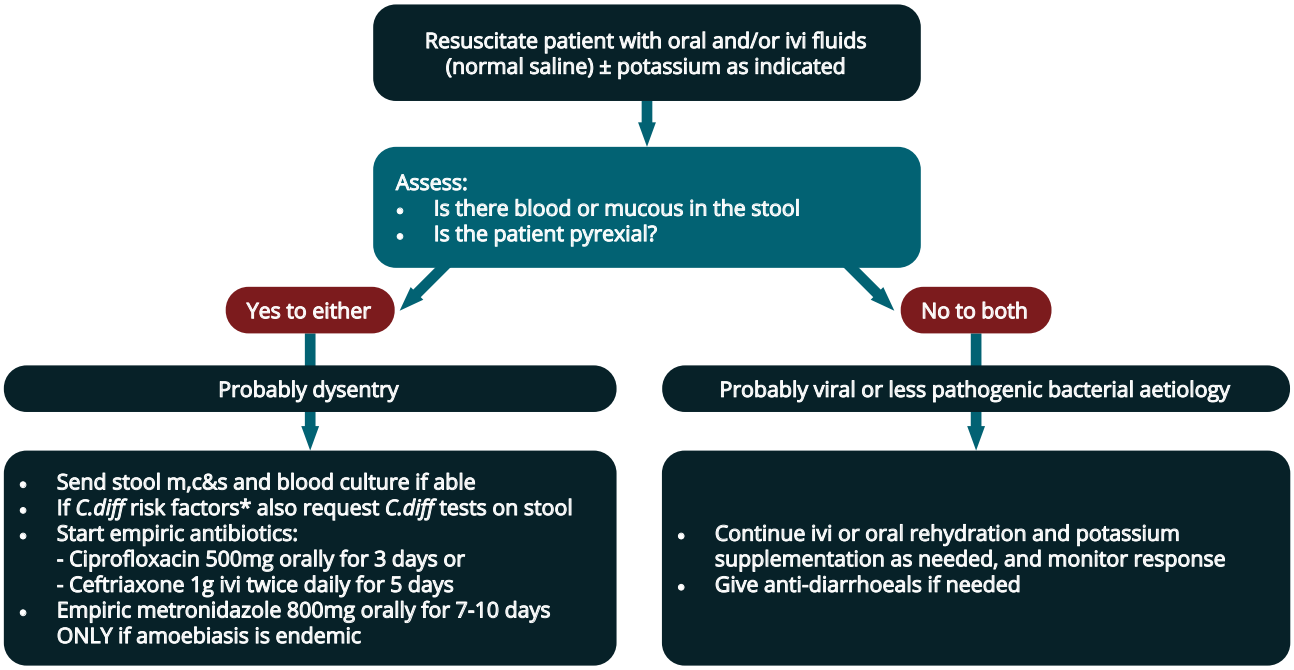
TABLE 4. Infectious causes of diarrhoea in AHD with suggested investigations and treatment

Protozoa	Presentation	Diagnosis	Specific treatment
• Coccidia	Small bowel		
Cryptosporidium		stool modified auramine	Nil
Cystoisospora belli (previously Isospora belli)		stool modified auramine	• Co-trimoxazole (CTX) (80/400mg) 4 tablets orally 12 hourly for 10 days • If allergic to CTX: give instead ciprofloxacin 500mg orally 12 hourly for 10 days.If no response, see section on refractory *Cystoisospora belli*
Microsporidia spp.		Stool calcofluor stain	Albendazole 400mg orally 12 hourly for 4 weeks
• Giardia	Small bowel	Stool microscopy	Metronidazole orally 400mg 8 hourly for 5 days or 2g daily for 3 days
• Amoebiasis	Large bowel	Stool microscopy	Metronidazole 800mg orally 8 hourly for 10 days
Bacteria	**Large bowel**		
Salmonella typhi		Stool culture	Fluoroquinolone
Shigella		Stool culture	Fluoroquinolone
Campylobacter		Stool culture	Macrolide
Clostridium difficile (C.diff)		Stool toxin, GDH & C. *diff* PCR	• Metronidazole 400mg orally 8 hourly for 10-14 days • *Second line:* Vancomycin 125mg orally 6 hourly
Mycobacteria	**Small bowel**		
M.TB		Urine LAM Culture/biopsy/ultrasound	Anti-TB therapy
M. avium-complex (MAC)		Blood or bone marrow TB culture (LAM may also be positive but non-specific)	Azithromycin & Ethambutol
Viral			
CMV	Large bowel	Biopsy	Ganciclovir
HIV	Small bowel	Exclude other causes	Antiretrovirals

Initial recommended investigations

- Bloods:
  - Electrolytes, urea and creatinine
  - Full blood count (raised WCC with neutrophilia suggestive of a bacterial cause)
  - HIV Viral load and CD4 (if not done in the last 3 months)
  - Blood cultures:
    - Bacterial: if suspecting dysentery and the patient is pyrexial
    - Mycobacterial: if disseminated TB or MAC suspected
- Stool analysis:
  - Acute diarrhoea:
    - Stool MC&S If mucous or blood
    - Request stool C.diff testing if clostridium difficile suspected (see figure 1):
  - Chronic diarrhoea:
    - **All** require stool MC&S *plus* a **modified auramine stain** for coccidian parasites (some labs do this routinely, but best to request this specifically)
    - Send up to 3 sequential stool samples as parasites shed ova intermittently, therefore the initial samples may be negative despite infection being present.
- Urine TB-LAM test, especially if chronic diarrhoea and accompanying constitutional symptoms
- Radiology:
  - Chest X-ray: if pulmonary TB is considered
  - Abdominal X-rays:
    - Not routine unless suspecting bowel obstruction or perforation
    - If severe colitis to diagnose toxic megacolon
  - Abdominal ultrasound: only if disseminated TB is being considered
- Endoscopy:
  - This is seldom an initial investigation, but useful for patients with non- resolving symptoms after negative initial stool analyses (see figure 2). Endoscopy with biopsy (histology, bacterial and mycobacterial culture, and CMV PCR) yields an additional diagnosis in 30-70% of cases.
  - Initial endoscopic route:
    - If large bowel presentation, start with flexible sigmoidoscopy and proceed to full colonoscopy if inconclusive.
    - If small bowel presentation, start with gastroscopy, and duodenal aspirate and biopsy or and terminal ileoscopy (some suggest there is a higher yield with this option)

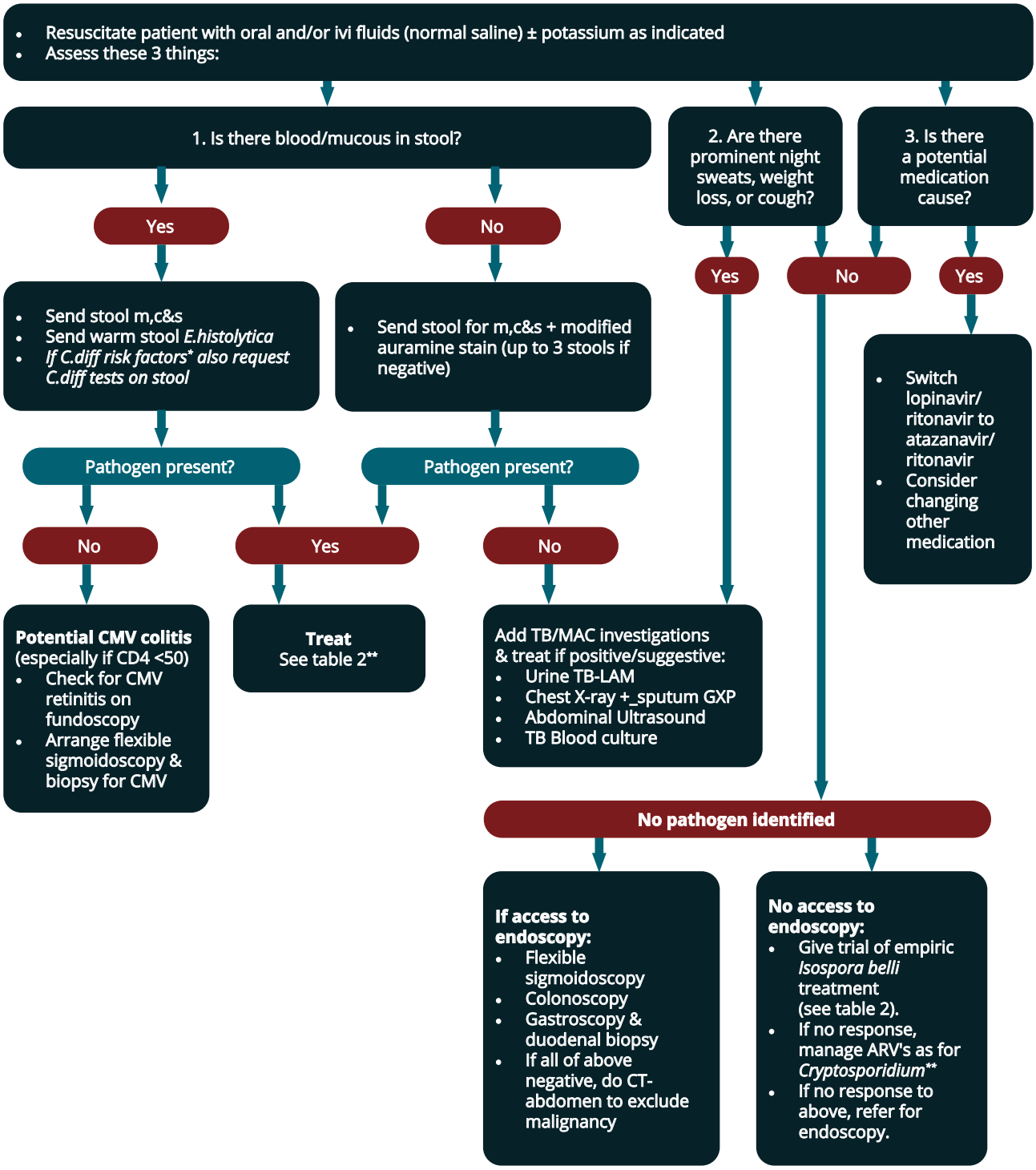
FIGURE 1: Management of acute diarrhoea



***Risk factors for *Clostridium difficil*e (C.diff)**

- Older age
- Current or recent hospital admission
- Current or recent (within last 1-3 months) antibiotic exposure, especially if broad-spectrum antibiotics
- Cancer chemotherapy

FIGURE 2: Management of chronic diarrhoea



***Risk factors for *Clostridium difficile* (C.diff)**
- Older age
- Current or recent hospital admission
- Current or recent (within last 1-3 months) antibiotic exposure, especially if broad-spectrum antibiotics
- Cancer chemotherapy

****Cryptosporidium**
- No effective specific treatment
- Urgently initiate ART if ARV-naive
- If on ART and faiiling/multiple defaults, consider switch to second line regimen.

Treatment of refractory *Cystoisospora belli* infections:

While most opportunistic infections causing chronic diarrhoea will resolve with treatment and effective ART and immune reconstitution, a patient with *Cystoisospora belli* will experience refractory diarrhoea despite a rising CD4 count and sustained HIV virological suppression. This is a poorly understood phenomenon, but is important for clinicians to be aware of, as it can cause significant morbidity and mortality. ***All*** these suspected cases should be managed in conjunction with an infectious diseases specialist.

A suggested definition of refractory *Cystoisopora belli* is: Relapsing episodes (>1) of confirmed Cystoisospora belli diarrhoea despite the following:

- Correct treatment with co-trimoxazole (or ciprofloxacin in allergic to co-trimoxazole) *and*
- Effective ART and immune reconstitution (VL<400 copies/ml and CD4 > 200 cells/mm^3) *and*
- Other causes have been considered (e.g., protease inhibitors)

A suggested treatment approach to such cases includes:

- Give prolonged cotrimoxazole (CTX) treatment for recurrent diarrhoea episodes i.e., CTX (80/400mg) 4 tablets orally 12 hourly for 1 month.
- If the diarrhoea improves, wean CTX slowly (3 tablets twice daily for 1 month, then 2 tablets twice daily for 1-2 months, then 2 tablets daily ongoing as prophylaxis.
- If there is a poor response to the higher dose of cotrimoxazole, try instead ciprofloxacin 500mg orally twice daily for 10 days. It is important to note that extending the ciprofloxacin duration any further is discouraged due to the risks of selecting for ciprofloxacin resistant enterobacteria and TB.
- Anti-diarrhoeals may need to be continued for symptomatic relief.
- There is weak evidence for some success with atovaquone and nitazoxanide. These may be considered in refractory cases despite the above measures, and only in conjunction with an infectious disease specialist.

Common pitfalls when managing diarrhoea in AHD:

- Mis-diagnosing a chronic/intermittent diarrhoea as an acute episode.
- Failing to send stool samples for appropriate stains and therefore missing the opportunity to definitively treat for a specific pathogen e.g., *Cystoisospora belli.*
- Discharging a severe cryptosporidium case after apparent successful ivi rehydration and potassium replacement to initiate outpatient ART. These cases frequently land up being re-admitted in the same state as before starting their ART. Cryptosporidium should be considered a condition for **urgent** ART initiation, usually in-hospital, and as soon as any other serious opportunistic infections have been excluded that would prevent immediate ART initiation e,g cryptococcal meningitis and disseminated TB. The only treatment for cryptosporidium is immune reconstitution, hence the urgency for effective and early ART initiation.
- Overuse of loperamide with a protease inhibitor. This can result in severe ileus as the protease inhibitor inhibits loperamide metabolism. A suggested maximum dose is 1 tablet 12 hourly until symptom relief.

Recommended references

1. Feasey NA, Healey P, Gordon MA. Review article: The aetiology, investigation and management of diarrhoea in the HIV-positive patient. *Aliment Pharmacol Ther.* 2011;34(6):587-603. doi:10.1111/j.1365-2036.2011.04781.x
2. Gupta A, Nadkarni G, Yang WT, et al. Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): A systematic review and meta-analysis. *PLoS One*. 2011;6(12). doi:10.1371/journal.pone.0028691
3. Wilson D, Naidoo S, Bekker L-G, Cotton M, Maartens G. *Handbook of HIV Medicine.* 1st editio. Oxford university press Southern Africa; 2002.
4. MacArthur R, DuPont H. Etiology and pharmacologic management of noninfectious diarrhea in HIV-infected individuals in the highly active antiretroviral therapy era. *Clin Infect Dis*. 2012;55(6):860-867. doi:10.1093/cid/cis544
5. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66(7):e1-e48. doi:10.1093/cid/cix1085
6. Boyles TH, Black J, Meintjes G, Mendelson M. Failure to eradicate Isospora belli diarrhoea despite immune reconstitution in adults with HIV - A case series. *PLoS One*. 2012;7(8). doi:10.1371/journal.pone.0042844
7. Lindsay D, Weiss L. Isospora belli. Antimicrobe. doi:10.1016/j.cmi.2017.07.009

4. CEREBRAL SPACE OCCUPYING LESIONS

Primary Author: Tom Boyles

Background

Space occupying lesions in the brain are a common problem in patients with AHD. Patients usually present with either new onset or changing patterns of seizures, or with a gradually worsening focal neurological deficit such as hemiplegia. The approach to this problem is complicated in the Southern African setting as there is unequal access to CT scanning. This chapter provides an approach to the diagnosis and management of space occupying lesions depending on access to CT scanning.

4.1 When a CT scan has been performed

Space occupying lesions may be found incidentally on CT brain scans done for another reason, but the commonest signs and symptoms are seizures or a gradually worsening focal neurological deficit.

The differential diagnosis is broad and there are no high-quality studies that systematically report aetiology, making it difficult to be precise about how common each condition is. However, the differential diagnoses below are a rough guide to aetiology:

Differential diagnosis

- TB
- Toxoplasmosis
- Pyogenic abscess
- Neurocysticercosis
- Primary CNS lymphoma
- Secondary brain tumour
- Cryptococcoma
- Nocardia
- Syphilitic gumma

Management in the first few days

- The following are indications for urgent neurosurgical review (if available):
  - Obstructive hydrocephalus for potential VP shunt
  - Impending herniation
  - Possible mass effect/midline shift with reduced level of consciousness
  - Pyogenic abscess
- The findings of neurocysticercosis (NCC) on CT are variable so it may be difficult to exclude it as a diagnosis. However, sometimes the findings are pathognomonic of NCC. These include multiple cysts with dot lesions as shown in image 1 below.

There are very few other diagnoses that have pathognomonic CT findings, although there are sometimes findings that are suggestive of a particular diagnosis e.g., primary CNS lymphoma. Beware of radiology CT reports that are confident about aetiologies other than NCC.

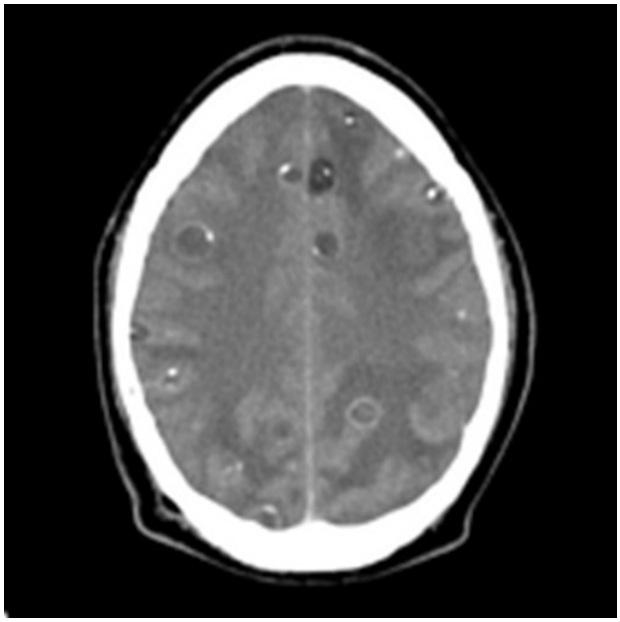


IMAGE 1: CT brain scan pathognomonic for neurocysticercosis: multiple ring and dot lesions.

- If there are no pathognomonic signs on CT, then the next 2 most common diagnoses are TB and toxoplasmosis, and the following approach is suggested:
  - Take a full history and examination
  - Do the following investigation:
    - CXR
    - CD4 and reflex CrAg
    - Toxoplasmosis serology
    - Syphilis serology
  - Search for extra-neural TB in the usual way (Xpert, LAM, USS abdomen)
  - Perform a lumbar puncture if it is not contraindicated. Send CSF for CrAg, TB Xpert Ultra and TB culture, EBV viral load if scan suggests PCNSL, syphilis serology (FTA-Abs and VDRL)

- While waiting for results:
  - Start co-trimoxazole treatment for toxoplasmosis
  - If CD4 count is already known to be >200 cells/mm^3, start TB treatment instead.
  - If CD4 count is unknown, decide if empiric TB treatment is required:
    - Firstly, assess if the patient is likely to come to significant harm if TB treatment is not started empirically while awaiting results. This includes a critically ill patient, lesions in critical place such as the brain stem and significant brain swelling with mid-line shift. In these cases it is likely TB treatment as well as steroids will be helpful.
    - If empiric TB treatment is not thought necessary, ***do not*** add steroids to the toxoplasmosis treatment. This can make interpretation of future CT scans difficult and has not been shown to improve outcome.

Could it be a pyogenic abscess?

Although a pyogenic abscess is a relatively uncommon cause for a space occupying lesion in a patient with HIV, it is an important diagnosis as a different management approach is required. This is difficult based on CT brain findings alone as there is no reliable way to differentiate a pyogenic abscess from another space occupying lesion. However, CT scan findings usually show patchy enhancement during early cerebritis which then evolves in to ring enhancement of the brain abscess: the brain abscess wall is usually smooth, 1 mm to 3 mm thickness and has surrounding parenchymal oedema. The ring enhancement may not be uniform in thickness. It can be relatively thin on the medial or ventricular surface in the deep white matter. Multi-location with subjacent daughter abscesses or satellite lesions is frequently seen. If gas is present this is suggestive of gas-forming organisms. Image 2 shows a typical brain abscess.

Entry of bacteria into the brain parenchyma is most likely from the paranasal sinuses, the middle ear, or the mastoid. Any lesions in these anatomically related structures should be considered as a possible abscess. Haematogenous spread, particularly emboli from infective endocarditis, is another possible route of entry. If a pyogenic abscess is likely based on either of these findings:

- Give ceftriaxone 2g ivi twice daily and metronidazole
- If available, urgently consult a neurosurgeon for possible surgical drainage

Unlike pyogenic abscesses in other parts of the body, the patient might not have a high fever, a high white cell count (WCC) or a raised CRP.

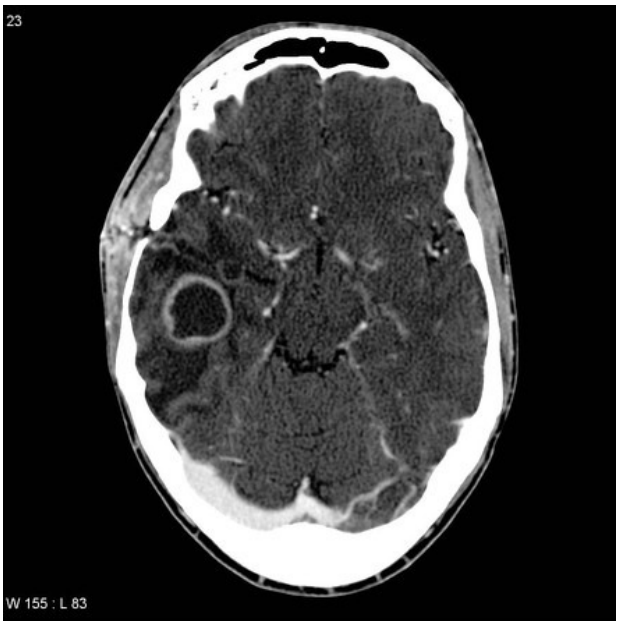


IMAGE 2: CT scan of a typical brain abscess showing ring enhancement.

Having done all of the above in the first few days, the patient will be taking some combination of co-trimoxazole, RHZE, and steroids. It is then important to adjust management based on the results received.

Adjust your treatment as results become available

- If the serum CrAg is positive, treat for cryptococcal meningitis **in addition** to the treatment you have already started. However, don't assume that the lesion(s) are cryptococcomas, and perform an LP if it is safe to do so, and has not been done already.
- Review the toxoplasmosis serology, and if negative stop the co-trimoxazole. Laboratories will generally provide toxoplasmosis IgM and IgG results. Toxoplasma encephalitis is a reactivation of latent infection so it is important to note that the IgG result will be positive, and the IgM result will be negative. IgM is seldom positive in this scenario.
- Review the CD4 count. If CD4 >200 cells/mm^3, toxoplasmosis is unlikely so stop co-trimoxazole and start TB treatment if not done already.
- If extra-neural TB is found, **add** TB treatment but don't stop the co-trimoxazole at this stage.
- If the serum treponemal antibody and confirmatory RPR are positive, consider the diagnosis of neurosyphilis, and perform an LP, unless contra-indicated and if not already done. CNS syphilitic gummata are very rare and other aetiologies are more likely. However, consider empiric syphilitic treatment if the RPR titre is high.

After about 2 weeks

If toxoplasmosis has not already been excluded by serology or CD4 count, repeat the CT brain scan:

- If the lesions are unchanged or worsening: stop cotrimoxazole and start TB treatment if not already started.
- If the lesions are smaller: continue co-trimoxazole. If the patient is on TB treatment, it is probably best to continue it as the steroids may have contributed to shrinking of the lesions.

Timing of ART initiation

- If cryptococcal meningitis or TB tuberculomas are diagnosed, start ART after 4 weeks.
- If toxoplasmosis is the only diagnosis, start ART after 2 weeks.

Follow-up CT scans

A routine follow-up CT brain scan is not indicated if the patient is responding to therapy. However, if the patient is not responding to treatment, repeat the CT scan after about 2 months

When a patient is not responding to treatment

If a patient has not responded to management, consider the following possibilities:

- Non-adherence
- IRIS
- Poor CNS penetration of drugs
- Resistance to drugs e.g., DR-TB
- Malabsorption of TB drugs
- The diagnosis is not toxoplasmosis, DS-TB or nocardia (which usually responds to co-trimoxazole)

Discuss the patient with an infectious diseases specialist and consider the following investigations:

- CSF EBV viral load. If negative, this excludes PCNSL.
- JC virus on CSF
- A biopsy of the lesion (but this may be difficult to obtain)

4.2 When there is a significant delay in accessing a CT brain scan

Managing a patient without immediate access to a CT brain scan is very difficult. This section provides a suggested approach in such cases.

If the patient presents with new onset seizures, first try to exclude other causes:

- Take a full history and examination, including:
  - Look for signs of endocarditis
  - If a focal neurological deficit such as hemiplegia is present, try to differentiate a growing lesion (which will have a gradual worsening of weakness) from a stroke (which will have a sudden onset)
- Check glucose
- Do renal and liver function tests
- Do a CXR

If a space occupying lesion is suspected clinically, avoid doing a lumbar puncture.

A reasonable general approach would be:

- Take a full history and examination
- Perform these tests:
  - CXR
  - CD4 and reflex CrAg
  - Toxoplasmosis serology
  - Syphilis serology
  - Search for extra-neural TB in the normal way (including doing a U-LAM)
- Start treatment for toxoplasmosis and TB
- Only add steroids if the neurological condition is severe
  - If the serum CrAg is positive, treat for cryptococcal meningitis **in addition** to the above. Don't assume that the lesion(s) are cryptococcomas.
- Only stop co-trimoxazole if toxoplasmosis serology is negative or the CD4 >200 cells/mm^3.
- Only stop TB treatment if there is no extra-neural TB and the patient's symptoms have markedly improved without steroids e.g. resolution of hemiplegia over 2 weeks. Start ART after 4 weeks.
- A delayed CT brain is still likely to be useful. It may show findings that exclude diagnoses such as TB or toxoplasmosis e.g., it shows signs suggestive of NCC, stroke or a pyogenic abscess. A delayed scan may also be useful as a baseline for comparison at a later date.

Recommended references

1. Pillay S, Ramchandre K. Audit of computed tomography brain findings in HIV-infected patients with space occupying infective lesions at a regional level hospital in KwaZulu-Natal. *SAGE Open Med.* 2018;6:2050312118801242. Published 2018 Sep 19. doi:10.1177/2050312118801242
2. See https://radiopaedia.org/articles/brain-abscess-1

5. ACUTE AND SUB-ACUTE/CHRONIC MENINGITIS

Primary Author: Tom Boyles

Background

Meningitis is a common presentation in patients with HIV. Clinical features are varied, and patients may be unable to provide a reliable history, which complicates diagnosis and management. This chapter covers both acute and chronic presentations with a suggested approach to investigation and management.

Determine whether the clinical features are compatible with meningitis

Meningitis is typically defined as any 2 of: fever, headache, neck stiffness, and confusion; but other features may occur such as a rash, photophobia, and seizures.

Meningitis is often life threatening, particularly in patients with HIV, and in general there should be a low threshold for investigating for meningitis. Patients with more chronic forms of meningitis have an increased likelihood of atypical presentations and there should be an even lower threshold for investigating such patients.

There is overlap between the presentation and causes of meningitis and encephalitis, so it is important to consider this approach in conjunction with the approach to a patient with altered mental state (see **Chapter 7**).

Determine the duration of symptoms

A rough guide in deciding whether this is acute or sub-acute/chronic meningitis is the duration of symptoms – if <7 days, acute meningitis is more likely; if ≥7 days sub-acute/chronic meningitis is more likely. But remember exceptions do occur. Deciding on acute vs chronic meningitis and impacts the differential diagnosis and aspects of investigation.

Approach to acute meningitis

Differential diagnosis

The differential diagnosis is broad and it is difficult to predict aetiology on clinical grounds alone. Table 5 shows possible infectious causes. *Mycobacterium tuberculosis* and *Cryptococcus neoformans* usually cause chronic meningitis but an acute presentation can sometimes occur. The median duration of TB meningitis symptoms is 12 days, and it is rarely less than 4 days.

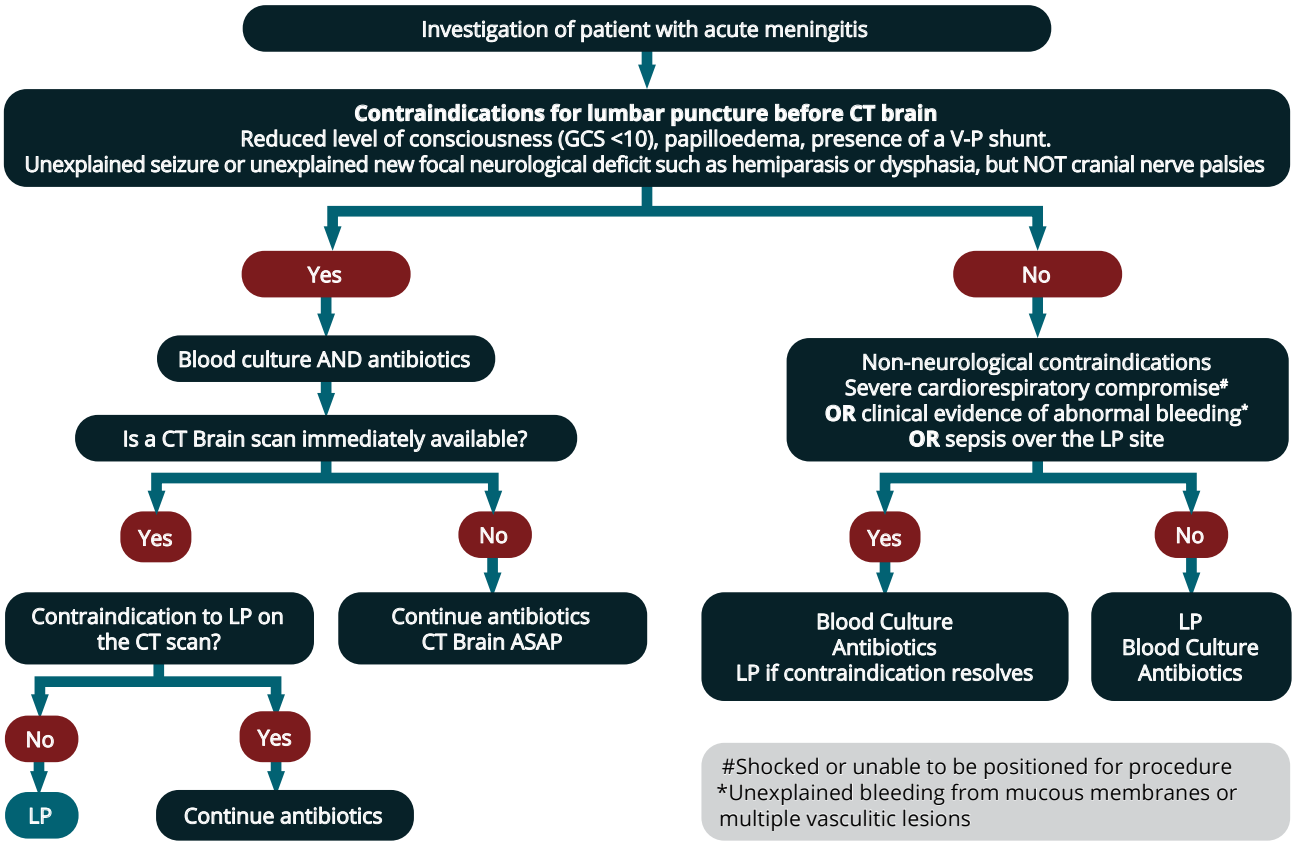
Initial hospital management

Acute meningitis is a medical emergency. The algorithm below shows an initial approach to suggested investigations and providing the first dose of antibiotics. Antibiotics should not be delayed while waiting for a CT scan.

TABLE 5: Infectious causes of acute meningitis in a patient with HIV

Bacteria	Viruses	Fungi
Streptococcus pneumoniae	Enteroviruses, including polio	*Cryptococcus neoformans*
Neisseria meningitidis	Human immunodeficiency virus	
Haemophilus influenzae	Herpes viruses	
Escherichia coli	Mumps	
Rickettsia species		
Leptospira species		
Staphylococcus aureus		
Salmonella non-typhi		
Listeria monocytogenes		
Streptococcus agalactiae (Group B)		
Treponema pallidum		
Mycobacterium tuberculosis		

FIGURE 3: Investigation of a patient with acute meningitis



Initial management:

- Administer ceftriaxone 2 g intravenously.
  - Use intramuscular or intraosseous routes if there is no vascular access.
  - Penicillin allergy is not a contraindication to ceftriaxone. Avoid ceftriaxone only if there has been documented cephalosporin anaphylaxis. Give instead vancomycin plus moxifloxacin *or* meropenem.
- If Listeria is suspected, *add* ampicillin 3 g intravenously six hourly.
  - *Listeria monocytogenes* is a relatively uncommon cause of bacterial meningitis but is intrinsically resistant to cephalosporins.
  - Suspect Listeria if patient > 50 years old or immunocompromised because of immunosuppressive drugs, alcoholism, liver cirrhosis, asplenia, end-stage renal failure or diabetes mellitus. HIV infection is not an indication.
  - In a patient with penicillin allergy give instead high dose co-trimoxazole.
- Provide adequate analgesia.

The yield of CSF and blood cultures post antibiotics will be lower but there will be no significant difference in CSF white blood cell count in the first 24 hours. However, CSF glucose and protein begin to normalise within a few hours of antibiotic therapy. Blood cultures are particularly important to increase the chances of isolating the causative organism and enabling targeted antibiotic therapy, especially in the case of a delayed LP.

Previously adjunctive corticosteroids were recommended for a patient with bacterial meningitis. Recently, an individual patient meta-analysis showed that adjunctive dexamethasone (the most widely studied corticosteroid) does not significantly reduce death or neurological disability. Therefore, corticosteroids are not recommended in a patient with bacterial meningitis.

Contraindications to lumbar puncture

An LP is considered an essential part of the assessment of a patient with suspected meningitis. However, there is a risk of transtentorial or cerebellar herniation if there is markedly increased pressure in the brain, or in one compartment compared to another. Evidence regarding clinical contraindications to LP in this setting is inadequate and guidance is based on the limited evidence available and expert opinion.

Neurological contraindications to lumbar puncture include:

- Coma or markedly decreased level of consciousness (Glasgow Coma Scale < 10).
- Papilloedema on fundoscopy.
- Unexplained new focal neurological deficit, such as a hemiparesis or dysphasia.

- A first generalised seizure in the preceding week, or changing pattern of seizures in a known epileptic.
- Presence of a ventriculoperitoneal shunt.
- Isolated cranial nerve palsies are not a contraindication to LP, but caution is advised if there is co-existing reduced level of consciousness.

CT of the brain should be performed as soon as possible in cases in which LP is delayed for neurological reasons. Taking blood cultures and provision of antibiotics should not be delayed if there is a delay in obtaining a CT scan. CT features of gross generalised brain swelling or significant hemispheral shift related to a mass lesion are contraindications to a LP. However, it is important to note, that a normal CT brain does not exclude the presence of raised intracranial pressure.

Non-neurological contraindications to lumbar puncture include:
- Severe cardiorespiratory compromise
- Severe coagulopathy
- Local sepsis at the LP site

In general, a patient who is shocked or unable to be positioned for an LP should have the procedure delayed until this has been corrected. In an emergency, it is unlikely that relevant laboratory values will be available, so unexplained bleeding from mucous membranes or multiple vasculitic lesions suggestive of disseminated intravascular coagulation should delay the LP. Once laboratory findings are known consensus opinion suggests that an LP is safe when the platelet count > 40 000/mm^3 and international normalised ratio is <1.5.

Diagnostic tests

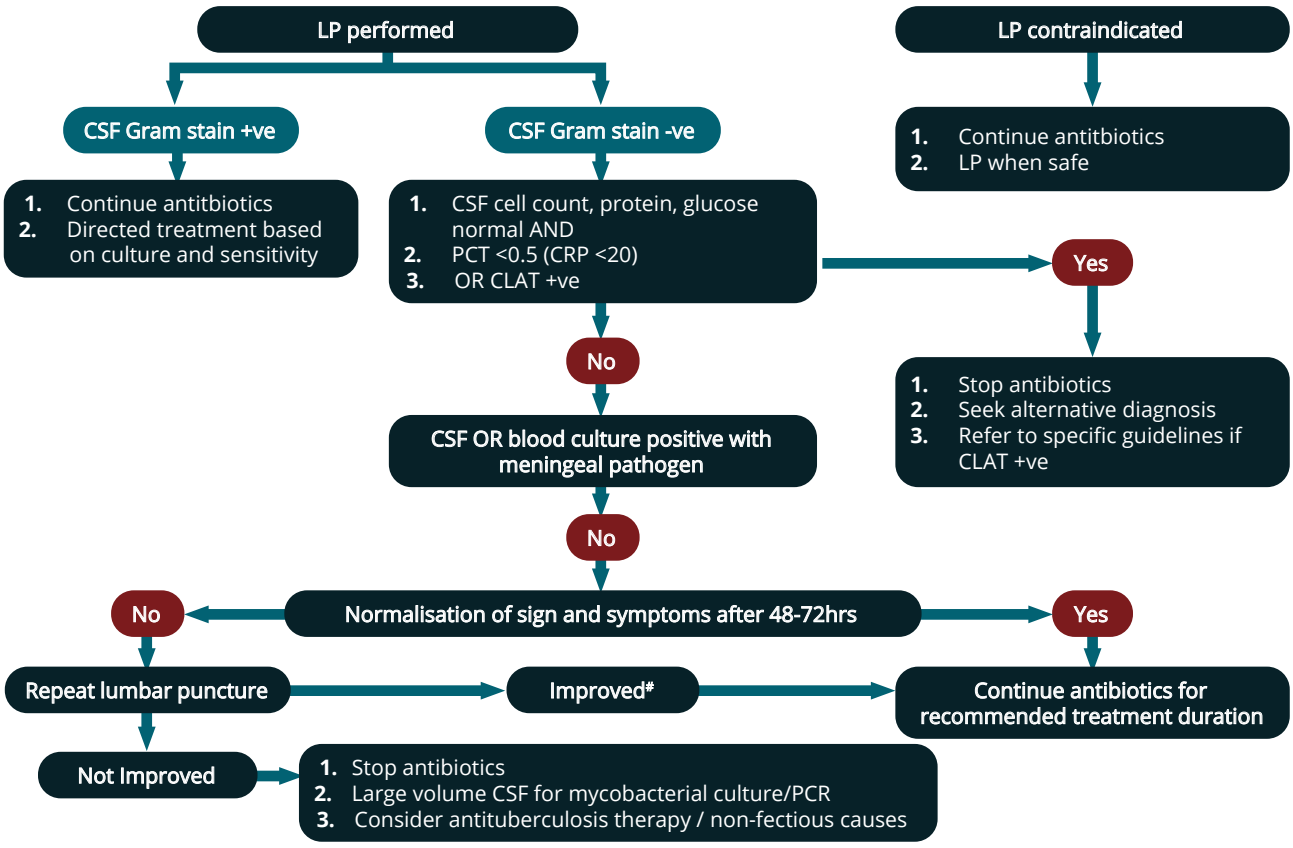
The following CSF and blood tests are required in all cases:
- Opening CSF pressure
- CSF differential cell count, glucose, total protein, gram stain, bacterial culture and sensitivity
- Cryptococcal antigen (CrAg)
- Serum glucose
- Peripheral white cell count and differential
- C-reactive protein (CRP)
- Store up to 10mls of CSF for future tests

CSF tests that are not usually useful are lactate, chloride and adenosine deaminase.

Interpretation of laboratory tests

A positive CSF gram stain is diagnostic of bacterial meningitis and treatment should be continued as outlined below. If the gram stain is negative, the diagnosis must be made using other CSF and blood results and clinical response to empiric therapy. There is considerable overlap in CSF results between aetiologies. An approach for making treatment decisions after the first dose of antibiotics, based on the availability of test results over time, is presented in figure 4 below.

FIGURE 4: Approach to meningitis following the first dose of antibiotics



#Opening pressure, protein, total WCC and % neutrophils reduced % Lymphocytes and CSF/serum glucose increased

↑ Back to Table of Contents

Second line tests

If meningitis is confirmed, consider requesting enterovirus PCR on the stored CSF. A positive result will allow you to stop antibiotics and discharge the patient. Other tests to consider are herpes simplex virus (HSV) PCR, varicella zoster virus (VZV) PCR and Xpert Ultra (ask lab to centrifuge sample).

Stopping antibiotics

Serum CRP < 20 mg/l has a negative predictive value for bacterial meningitis of 99%. If initial cell counts, protein, serum/CSF glucose ratio, and CRP are all normal, bacterial meningitis can be excluded, and antibiotics stopped.

Stopping ampicillin

If the CSF gram stain, culture or CLAT confirms an alternative pathogen, empiric ampicillin for Listeria can be stopped.

What to do if the diagnosis is unclear after 48-72 hours

It is common for patients to have negative CSF and blood cultures but abnormal CSF findings, particularly if antibiotics were given prior to taking CSF and blood cultures. In this case the diagnosis should be reviewed after 48-72 hours of antibiotics. Clinical improvement suggests a bacterial aetiology and therefore ceftriaxone should be continued for 10-14 days and, if initiated, ampicillin for 21 days. Clinical improvement cannot be quantified as signs and symptoms vary and they are age-dependent, but normalisation of fever and an improvement in most symptoms is suggestive.

If there is no clinical improvement or there is doubt about the significance of clinical improvement after 48-72 hours, the LP should be repeated. In bacterial meningitis, effective antibiotic therapy will lead to a reduction in CSF opening pressure, protein, total white cell count and percentage neutrophils, and an increase in percentage lymphocytes and CSF/serum glucose. If this does not occur bacterial meningitis is very unlikely, and antibiotics can be stopped. Alternative diagnoses, particularly tuberculous meningitis, should be considered. In this case, the stored CSF should be tested for TB with Xpert Ultra (ask lab to centrifuged sample first), and mycobacterial culture and sensitivity.

The section on chronic meningitis provides information for decision making if TB meningitis is likely.

Directed therapy

Table 6 details the recommended treatment based on a confirmed pathogen.

TABLE 6: Directed treatment based on a confirmed pathogen

Pathogen	Suggested antimicrobial	Alternative antimicrobial	Duration (in days)
Streptococcus pneumoniae **(penicillin MIC ≤ 0.06 µg/ml)**	Benzyl penicillin	Ceftriaxone	10-14
Streptococcus pneumoniae **(penicillin MIC > 0.06 µg/ml)**	Ceftriaxone	Vancomycin plus ceftriaxone	10-14
Streptococcus pneumoniae **(ceftriaxone MIC ≥ 1 µg/ml)**	Vancomycin plus ceftriaxone	Moxifloxacin plus rifampicin	10-14
Neisseria meningitidis	Benzyl penicillin	Ceftriaxone	5-7
Haemophilus influenzae	Ampicillin (if sensitivity confirmed)	Ceftriaxone	7-14
Listeria monocytogenes	Ampicillin plus gentamicin	Co-trimoxazole	21
Streptococcus agalacticae **(Group B)**	Penicillin	Ampicillin	14-21
Escherichia coli	Cefotaxime	Ceftriaxone	21
Salmonella non-typhi	Ceftriaxone	Ciprofloxacin	28

An approach to sub-acute/chronic meningitis

The differential diagnosis is broad. Table 7 below indicates possible infectious causes. Table 8 indicate possible non-infectious causes, which are also important to consider. The viruses HSV, VZV, and CMV more commonly cause encephalitis or ventriculitis (CMV) than meningitis. This is covered further in **chapter 8** Altered mental State.

TABLE 7: Possible pathogens causing sub-acute/chronic meningitis. Note: most common treatable causes in a patient with HIV in South Africa are indicated in **bold.**			
(Myco) bacterial	**Fungal**	**Viral**	**Parasitic**
Tuberculosis	**Cryptococcosis**	**Herpes Simplex (HSV)**	Toxoplasmosis
Syphilis	Candida	**Varicella Zoster (VZV)**	Cysticercosis
Listeria	Aspergillus	**Cytomegalovirus (CMV)**	Angiostrongylus cantonensis
	Mucormycosis	HIV	Gnathostomiasis
	Histoplasmosis		

TABLE 8: Possible non-infectious causes sub-acute/chronic meningitis. Note: this table excludes medication-related causes.	
Non-infectious (except drugs)	**Drugs**
Haematological malignancy	NSAIDS
Solid organ malignancy	Trimethoprim-sulfamethoxazole
Primary brain tumours	Isoniazid
Sarcoidosis	Azathioprine
SLE	
Vasculitis, Sjogrens, Behcet	

Does the patient require a CT brain before lumbar puncture?

It is important to determine if it is safe to perform an LP without first having a CT brain. There is limited evidence but in general the contra-indications to LP in sub-acute/chronic meningitis are similar to those for acute meningitis. It is particularly important to assess if the patient has papilloedema.

If there is a neurological contra-indication to LP, perform a CT brain. If there is a contra-indication to LP on the CT brain it is most likely a space occupying lesion (refer to space occupying lesion algorithm). If both CT brain and LP are not possible (this is rare), discuss with an Infectious Diseases specialist.

Initial tests on CSF

- CSF opening pressure
- Gram stain and bacterial culture
- Protein, cell count, glucose
- CrAg
- Syphilis
- Serum glucose
- Store up to 10mls of CSF for future tests

Initial treatment

There is no need to start empiric ceftriaxone and specific treatment can wait until the CSF results are received.

How useful are the initial CSF results?

The following are listed in order of usefulness:

- Gram stain - rarely positive but if it is, confirms diagnosis
- CrAg - if positive, confirms cryptococcal meningitis (unless previously treated)
- VDRL- if positive, confirms neurosyphilis
- FTA-Abs – a negative result excludes neurosyphilis
- CSF glucose - if <2.5, suggestive of TBM but bacterial cause cannot be excluded
- CSF protein - if around 1.5 suggestive of TBM, if > 5 suggestive of bacterial meningitis (but not definitive)
- Cell counts - not very useful- normal results are suggestive of no meningitis but up to 5% of cases with TB and bacterial meningitis may have normal results
- Very high polymorphs suggest bacterial or CMV meningitis

BOX 4: Typically normal result in a patient with HIV

- Glucose >3.5
- Protein <0.75
- 1 polymorph
- 5 lymphocytes

If the diagnosis remains unclear, consider the following tests on the stored CSF:

- Xpert Ultra (ask lab to centrifuge sample first)
- Mycobacterial culture (for future reference)
- Viral PCR – some laboratories offer a panel. If not, do HSV, VZV (rash may not be present), CMV, and enterovirus
- Bacterial PCRs, including Listeria

Next, think about other ways of making a diagnosis:

- Search for extra-neural TB, including urine LAM
- Examine for rashes suggestive of VZV or HSV
- Consider malignancy and autoimmune diseases
- Review medication history carefully and, if possible, stop any medications that may be implicated.

Most tests take time, except for Xpert Ultra. If the Xpert Ultra is negative, there is confirmed meningitis and test results are outstanding, consider the following empiric therapies in this order:

- Consider TBM therapy – refer to box 5
- Treat for HSV - meningitis does not have as high mortality as encephalitis but treatment has limited side-effects
- Treat for neurosyphilis (unless the FTA-Abs are negative) - if VDRL is negative, then syphilis is less likely. It is important to consider suggestive neurological signs
- Give ampicillin - Listeria is uncommon outside of an outbreak but consider empiric treatment if the patient is > 50 years old, on chronic immunosuppressive medication or has brainstem signs and symptoms

BOX 5: Decision making in TB meningitis

- TB meningitis has a very high mortality, even with appropriate treatment.
- The consequences of withholding treatment from a patient with possible TBM are extremely serious (almost certain death).
- Therefore, the threshold for initiating treatment is low, particularly if the patient is clinically unstable.
- The incidence of TBM in patients with HIV in South Africa is high.
- Therefore, in a patient with confirmed sub-acute/chronic meningitis, with no evident alternative diagnosis, consider empiric TBM therapy.
- If an alternative diagnosis becomes evident later on (e.g., VZV PCR is positive) stopping TB treatment may be considered.

How to follow-up a patient who improves on treatment

In general, once empiric therapy has been started and the patient is improving clinically, completion of the full course is necessary, unless an alternative cause is found. This includes a patient who improves on TB treatment but has a negative CSF culture as this is not sufficient to exclude the diagnosis. However, if the patient develops signs of treatment related toxicity, the diagnosis should be reviewed including re-consideration of the CSF culture result.

How to follow-up a patient who does not improve on treatment

Full investigations should be guided by the likely reason for deterioration. In general, if the patient deteriorates despite TB treatment and the CSF culture is negative, it is unlikely that the diagnosis was TBM. Possibilities for not improving include IRIS, non-adherence, poor drug absorption, drug-drug interactions or incorrect diagnosis.

Recommended references

1. Boyles TH, Bamford C, Bateman K, et al Guidelines for the management of acute meningitis in children and adults in South Africa. South Afr J Epidemiol Infect 2013;28(1):5-16.
2. Govender NP, Meintjes G, Mangena P, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019;20(1):1030. Published 2019 Nov 8. doi:10.4102/sajhivmed.v20i1.1030
3. Seddon JA, Tugume L, Solomons R, et al. Tuberculous Meningitis International Research Consortium. The current global situation for tuberculous meningitis: epidemiology, diagnostics, treatment and outcomes. Wellcome Open Res. 2019;4:167. Published 2019 Nov 5. doi:10.12688/wellcomeopenres.15535.1

6. RESPIRATORY PRESENTATION

Primary Author: Gary Maartens

Background

Pulmonary presentations (respiratory symptoms and/or pulmonary infiltrate on chest x-ray) are the commonest reason for hospitalisation in people with advanced HIV disease (AHD). The mortality rate is high and early initiation of appropriate therapy is essential. Most (80-90%) patients will have tuberculosis (TB), bacterial pneumonia, and/or *Pneumocystis jirovecii* pneumonia (PJP). Co-infections occur commonly. This chapter provides an approach to diagnosing the most common causes of a respiratory presentation in a patient with AHD.

Tuberculosis

Most patients with AHD who have TB have disseminated TB, and pulmonary involvement is very common. The WHO TB symptom screen (cough of any duration, fever, night sweats, weight loss) is of minimal predictive value in inpatients with suspected TB. However, cough duration of >2 weeks has some predictive value. TB in a patient with AHD can present like severe bacterial sepsis with delirium and multi-organ failure.

It is important to examine carefully for accessible lymph nodes and other features of extrapulmonary TB as these are potentially important sources of specimens for microbiological confirmation.

Imaging plays a key role in diagnosis:

- Abdominal ultrasound features predictive of TB include effusions (ascites, pericardial, or pleural), intra-abdominal nodes ≥10 mm, and splenic hypodensities.
- Abdominal ultrasound is more sensitive but less specific than chest X-ray (CXR).
- CXR features suggestive of TB are miliary infiltrates, hilar/mediastinal nodes, or nodules >3 and large pleural effusions.
- Cavitation on CXR is very uncommon in AHD with pulmonary TB – it usually is a consequence of prior TB and has been shown not to be predictive of TB in inpatients.
- The upper lobe predominance seen on CXR in immunocompetent patients with TB is much less common in AHD.
- CXR is normal in about 20% of inpatients with AHD and confirmed pulmonary TB.
- Lymph nodes with central hypodensity and rim enhancement on contrast on CT/MRI are strong predictors of TB.

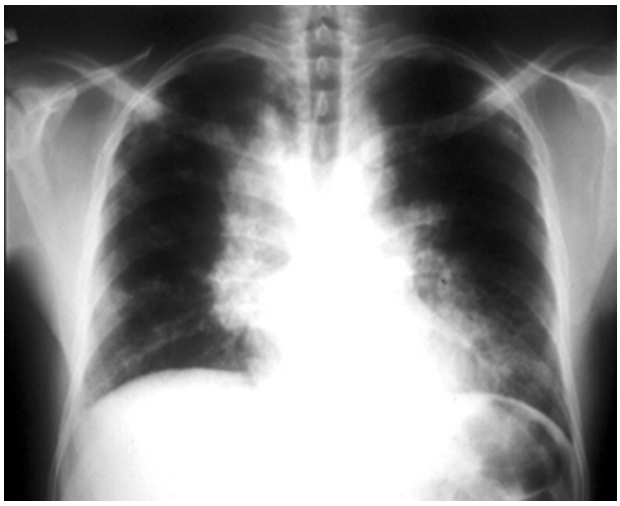


IMAGE 3: Large right paratracheal and hilar nodes – strongly suggestive of TB

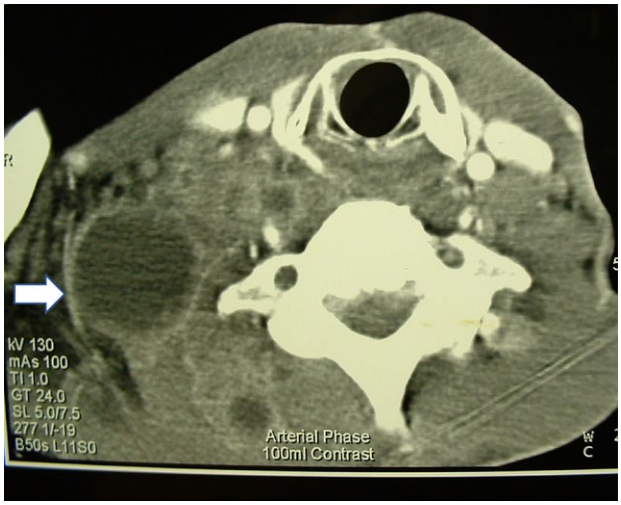


IMAGE 4: Large right supraclavicular node (arrowed) with rim enhancement and central hypodensity representing caseous necrosis on CT – typical appearance of a TB node.

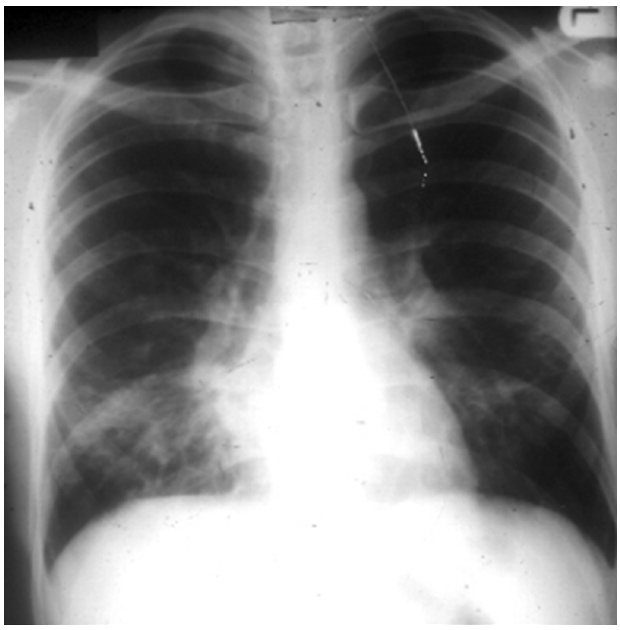


IMAGE 5: Asymmetric lower zone infiltrates with nodules due to TB in a patient with AHD.

Full blood count is diagnostically helpful:

- Anaemia is a very strong indicator of TB
- Elevated white cell count is against TB

Microbiologic confirmation of TB includes the following:

- Urine lipoarabinomannan (LAM) should be the first diagnostic test as it has a yield of about 40% in inpatients with AHD and is a good "rule in" test for TB.
- Sputum has the highest diagnostic yield – Xpert MTB/RIF Ultra should be requested. Note that the specificity of Xpert MTB/RIF Ultra on sputum is lower in patients with prior TB, especially if this was in the last 2 years.
- Many inpatients with AHD are unable to produce sputum – sputum induction using hypertonic saline driven by an ultrasonic nebuliser is often successful and gives a higher yield on microbiologic testing than spontaneously produced sputum.
- Lymph node fine needle aspirate (FNAB) flushed with 2 mL of saline has a very high yield on Xpert MTB/RIF Ultra.
- Xpert MTB/RIF Ultra on other extrapulmonary specimens (e.g., CSF, effusions, pus from cold abscesses) has a sensitivity of 50-90%.
- TB culture should only be requested if specimens are negative on Xpert MTB/RIF Ultra or to confirm positive Xpert MTB/RIF Ultra results in a patient with prior TB in the last 2 years.
- TB blood culture has a yield of 40%, but often takes weeks to become positive, so is seldom clinically useful. However, it can detect non-tuberculous mycobacteraemia and fungaemia, both of which can mimic TB.

Empiric anti-tuberculosis therapy should be commenced immediately in a patient with highly suggestive features on imaging or with no response to broad spectrum antibiotics (**see figure 5**). It is essential to wait for a response to empiric antituberculosis therapy to avoid missing alternative diagnoses.

Bacterial pneumonia

The incidence of bacterial pneumonia is increased about 100-fold in patients with AHD.

The clinical presentation is similar to community-acquired pneumonia in an HIV-uninfected patient, including respiratory symptoms <2 weeks duration with a compatible pulmonary infiltrate on CXR.

The aetiology is similar to community-acquired pneumonia in HIV-uninfected patients with co-morbidity:

Streptococcus pneumoniae
Haemophilus influenzae
Staphylococcus aureus
Moraxella catarrhalis
Klebsiella pneumoniae
"Atypical" bacteria

COMMON

↑

UNCOMMON

Microbiologic tests are of little value; although blood culture has a higher yield than in HIV-uninfected patients and should be done in a patient with features of severe pneumonia.

Empiric antibiotic therapy should include a broad spectrum β-lactam antibiotic (ceftriaxone or amoxicillin/clavulanate), and add a macrolide if the CURB-65 score is ≥3. An early switch to oral antibiotics is recommended. Antibiotic duration should be 5 days, or 10 days in severe pneumonia.

BOX 6: CURB-65 Score for Pneumonia Severity

Assess the following and add 1 point for each 'yes' answer:

1. Confusion?
2. Urea > 7 mmol/L?
3. Respiratory rate ≥30 bpm?
4. Systolic BP < 90 mmHg or Diastolic BP ≤ 60 mmHg?
5. Age ≥ 65 years?

Pneumocystis pneumonia

Pneumocystis jirovecii pneumonia (PJP) typically occurs in patients with CD4 counts <200 cells/mm^3. Most cases are diagnosed clinically. It usually presents sub-acutely with progressive dyspnea and a dry cough, and symptom duration is <12 weeks. Clinical features suggestive of PJP include tachypnoea without focal chest signs. A respiratory rate of >30 bpm or an O_2 saturation of <94% strongly support a diagnosis of PJP. If the resting O_2 saturation is above 94%, it is recommended to exercise the patient for up to 10 minutes. If the O_2 saturation drops to <90% this is suggestive of PJP.

CXR features that are strongly suggestive of the diagnosis include:

- A bilateral interstitial ("ground glass") infiltrate is characteristic.
- Small cystic lesions are not uncommon and may rupture, resulting in a pneumothorax, which is associated with a worse prognosis.

Diagnosis can be confirmed by identification of the fungus using special stains or immunofluorescent antibodies on a bronchoalveolar lavage or induced sputum specimen. PCR is increasingly being used but does not distinguish between colonisation and infection. Quantitative PCRs may be useful but clear cut-offs have not yet been established. An elevated serum β-d-glucan has a sensitivity of 92% and a specificity of 78% for diagnosing PJP in patients with HIV. However, this assay is expensive and therefore seldom used.

Recommended treatment of pneumocystis pneumonia includes high dose co-trimoxazole 480 mg (1 single strength tablet) per 4 kg body weight (maximum 16 single strength tablets/day) daily given in divided doses 6 – 8 hourly for 21 days. If the patient is hypoxic, add prednisone 40 mg twice daily for days 1–5, 40 mg daily for days 6–10 and 20 mg daily for days 11–21.

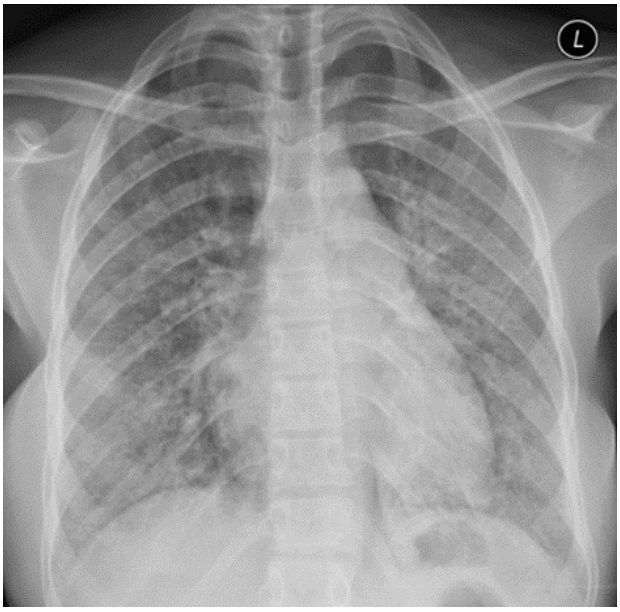


IMAGE 6: Typical bilateral interstitial infiltrate in a patient with pneumocystis pneumonia.

Differentiating between tuberculosis, bacterial pneumonia, and pneumocystis pneumonia

Table 9 details symptom duration, imaging, and full blood count, which are helpful in differentiating these three major opportunistic infections. Co-infections are common, which makes differential diagnosis difficult. Pleural effusions occur commonly in TB and in bacterial pneumonia and if present, it is essential to do a diagnostic thoracentesis to exclude an empyema.

TABLE 9: Differing features between TB, bacterial pneumonia and PJP.

Feature	TB	Bacterial pneumonia	PJP
Symptom duration	Days to months	< 2 weeks	< 12 weeks
Hypoxia	Uncommon	Uncommon	Common
Haemoglobin	Decreased	Normal	Normal
White cell count	Normal or decreased	Increased	Normal
Chest x-ray	• Miliary • Nodules >3 mm • Hilar/mediastinal nodes	Consolidation	Interstitial infiltrate

Other respiratory infections

Other respiratory infections to consider include:

- Fungi
  Disseminated endemic mycoses (e.g. histoplasmosis, emergomycosis) mimic TB, but a pleural effusion and hilar/mediastinal nodes are less common. Mucutaneous papules or ulcers are often present, in which case a biopsy for fungal histology and culture should be done which is often diagnostic. Pulmonary cryptococcosis can also mimic TB and occasionally presents with a large cryptococcoma. Serum cryptococcal antigen (CrAg) or fungal culture of respiratory specimens is diagnostic in this case.
- Viruses
  Influenza is more severe in HIV-infected patients and oseltamivir should be given if it is influenza season and flu-like symptoms are present. CMV is often found on bronchoscopy in patients with PJP, but this typically resolves with PjP therapy without the need for specific anti-CMV therapy indicating that the CMV is seldom the cause of pneumonitis. The role of other respiratory viruses in the pathogenesis of lower respiratory tract infections in AHD is poorly characterised. COVID-19 pneumonitis closely resembles PJP – on CXR the infiltrates tend to be more peripheral than central and the duration of symptoms in COVID-19 is usually shorter but treatment for both conditions is warranted until a definitive diagnostic test result becomes available.
- Nocardia
  Nocardia infection can mimic TB but is rare.

Important non-infectious causes

The following are non-infectious causes that may have a respiratory presentation:

- Pulmonary Kaposi sarcoma
  The lungs are a common metastatic site in Kaposi sarcoma (KS). This can mimic TB. Mucocutaneous lesions are usually present in KS, and it is important to always examine the patient's palate. Pleural effusions occur commonly and are typically blood-stained.
- Lymphocytic interstitial pneumonitis
  Lymphocytic interstitial pneumonitis (LIP) can mimic miliary TB or PJP. Symptoms are typically slowly progressive, and bilateral parotidomegaly is commonly present as part of the diffuse infiltrative lymphocytic syndrome.
- Lymphoma
  The B symptoms of lymphoma can mimic TB but pulmonary presentations of lymphoma are uncommon.

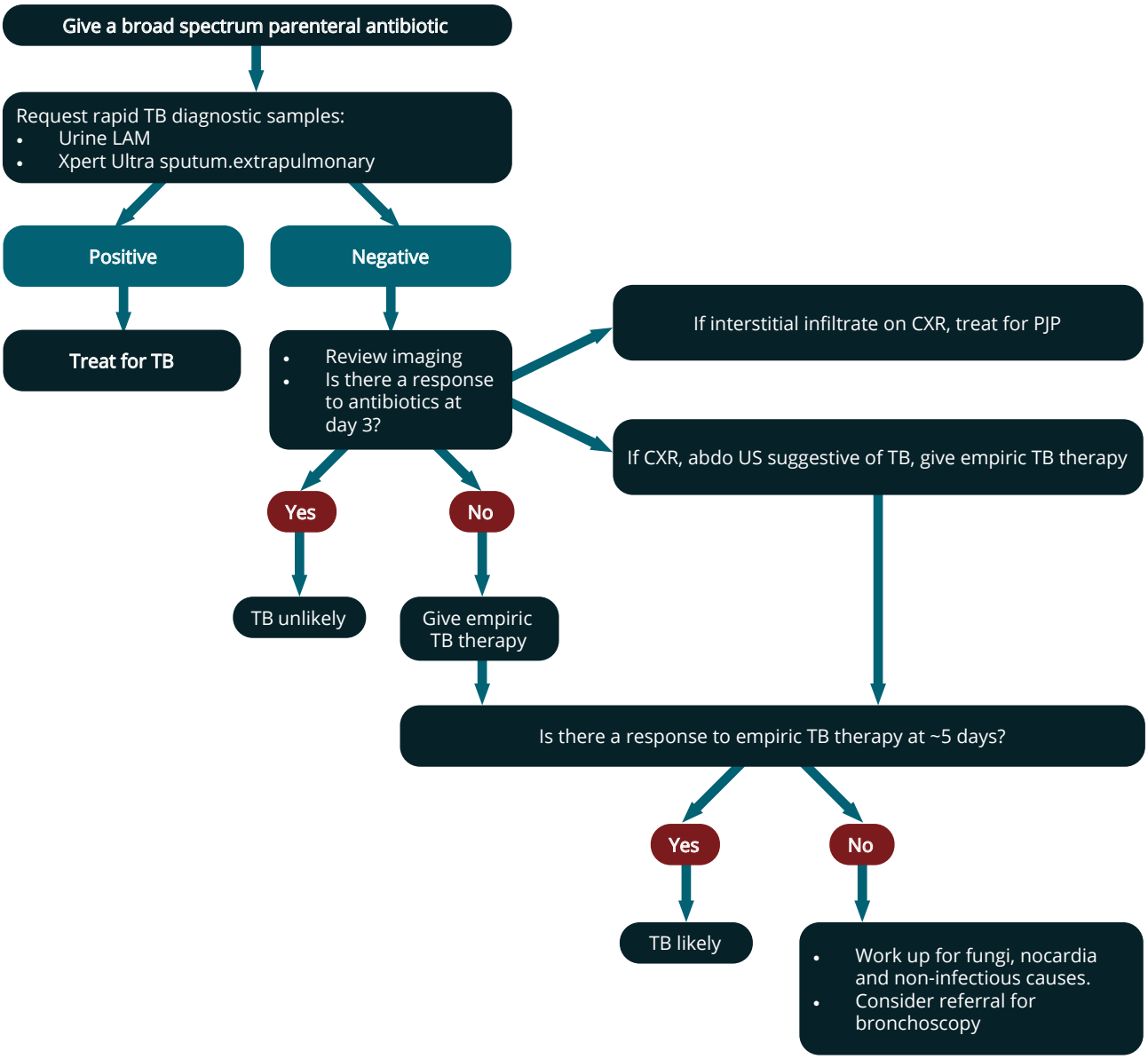
An algorithmic approach to an inpatient with AHD and a pulmonary presentation

Figure 5 is adapted from the WHO algorithm for seriously ill patients. Note that it is an over-simplification and is only intended as a guide. It cannot substitute for clinical judgement.

The management principles are straightforward:

- WHO recommends treating all seriously ill inpatients with AHD with parenteral broad spectrum antibiotics. This is reasonable as bacterial pneumonia is common, bacterial co-infections are common, and both TB and PJP can mimic bacterial infections.
- Rapid tests for TB should be done in all patients.
- Imaging should guide empiric therapy for TB and/or PJP.
- Patients not responding to antibiotics after about 3 days should be empirically treated for TB.
- Further diagnostic workup should be done in patients not responding to empiric TB therapy.

FIGURE 5: An approach to an inpatient with AHD and a pulmonary presentation



Recommended references

1. Dhana A, Hamada Y, Kengne AP, et al. Tuberculosis screening among HIV-positive inpatients: a systematic review and individual participant data meta-analysis. Lancet HIV 2022 in press.
2. Griesel R, Stewart A, van der Plas H, et al. Optimizing Tuberculosis Diagnosis in HIV-Infected Inpatients Meeting the Criteria of Seriously Ill in the WHO Algorithm. *Clin Infect Dis* 2018;66:1419-26.
3. Van Hoving DJ, Meintjes G, Takwoingi Y, et al. Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals. Cochrane Database Sys Rev 2019, Issue 9. Art. No.: CD012777.
4. Shah M, Hanrahan C, Wang ZY, et al. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in HIV-positive adults. Cochrane Database Syst Rev. 2016 May 10;2016(5):CD011420.
5. Antel K, Oosthuizen J, Malherbe F, et al. Diagnostic accuracy of the Xpert MTB/Rif Ultra for tuberculosis adenitis. *BMC Infectious Diseases* 2020;20:33.
6. Maartens G, Stewart A, Griesel R, et al. Development of a clinical prediction rule to diagnose *Pneumocystis jirovecii* pneumonia in the WHO's algorithm for seriously ill HIV-infected patients. Southern African Journal of HIV Medicine 2018;19:851.
7. Wasserman S, Engel ME, Griesel R, Mendelson M. Burden of pneumocystis pneumonia in HIV-infected adults in sub-Saharan Africa: a systematic review and meta-analysis. BMC Infect Dis 2016 Sep 9;16(1):482.
8. Feldman C, Anderson R. HIV-Associated Bacterial Pneumonia. Clin Chest Med 2013;34: 205–16.
9. Boyles TH, Brink A, Calligaro GL, et al. South African guideline for the management of community-acquired pneumonia in adults. Journal of Thoracic Disease 2017;9(6):1469-1502.

7. ALTERED MENTAL STATE

Primary Author: Tom Boyles

Background

Altered mental states are common in patients with AHD. The list of possible causes is vast and so it is vital to have an approach to such patients. This chapter begins with a description of the 3 cardinal syndromes (delirium, dementia, and psychosis) and then provides a practical approach to diagnosis and treatment.

Presentations of altered mental state

A definition of each of the 3 cardinal symptoms is given below:

Delirium

A serious disturbance in mental abilities that results in confused thinking and reduced awareness of the environment. Poor thinking skills (cognitive impairment), behaviour changes and emotional disturbance may be present.

Dementia

A group of symptoms that together affect the memory, normal thinking, communicating, reasoning ability and social abilities severely enough to interfere with daily life.

Psychosis

Gross impairment in reality testing, presence of hallucinations and/or delusions, marked disturbance in personality, with impairment in social, interpersonal, and occupational functioning. There is marked impairment in judgment and absence of understanding of presenting/current symptoms and behaviour (lack of insight).

Table 10 gives features that can help differentiate between the 3 syndromes. It is important to realise that the causes are overlapping, and more than one syndrome may be present. For example, delirium is common in patients with dementia, and delirium can present with features of psychosis. As a result, it may not be possible to immediately fit the patient into a single category.

A suggested approach to a patient with HIV who presents with an altered mental state is provided below:

Emergency assessment (within the first hour)

Measure and correct any of the following if present:

- Hypoglycaemia
- Hypotension
- Hypoxia

Take a rapid focused history and examination to determine if the patient fits the case definition of **meningitis** and if so, refer to meningitis sections.

TABLE 10: Differentiation in symptoms between delirium, psychosis and dementia

Symptom	Delirium	Psychosis	Dementia
General presentation	**Sick (abnormal vital signs, sweaty, look sick)**	**Not sick**	**Not sick**
Onset	Sudden onset (was OK yesterday)	No sudden onset	No sudden onset but may have stepwise deterioration
Course	Fluctuating course	Non-fluctuating	Non-fluctuating
	Forgetfulness	Preserved memory	Forgetfulness
Attention	Inattention or distraction	Attention often preserved	Attention often preserved (unless delirium co-existing) or advanced disease
Level of consciousness	Altered level of consciousness	Normal level of consciousness	Normal level of consciousness
Orientation	Disoriented (time, place, person)	Oriented	Disoriented
Hallucinations	Visual hallucinations	Hallucinations more likely to be auditory	Hallucinations less common

Begin a full assessment (within the first day)

It is likely that the problem is acute or sub-acute in a patient presenting to hospital. Think first about delirium but it is important to remember that delirium is common in patients with dementia and can present with psychotic features, so unless the diagnosis is already clear at this point it will be necessary to consider all causes of delirium. There are a vast number of causes of delirium. Table 11 provides a non-exhaustive list.

Assess the following:

- History
  This is often difficult to obtain from the patient but any collateral history from relatives or previous clinical notes can be helpful, particularly the duration of symptoms. A medication history is important, including all prescribed, over the counter, traditional medications, and consumption of alcohol and/or illicit drugs.Past psychiatric history is very important.

- Physical examination
  Thorough examination of all systems is vital. In particular, neurological signs that may suggest a space occupying lesion.

- Mental state examination
  Focus specifically on behaviour and appearance of the patient. Speech and speed of thoughts should be assessed, and mood, affect, suicidality and neuro-vegetative symptoms evaluated. Perceptual disturbances, thought form, thought content, and insight and judgement also needs to be assessed.

- Chest X-ray

- Blood tests
  Request FBC, U and E, LFTs, TSH, Calcium, CRP, CD4 count with reflex CrAg (if not done recently), and HIV viral load (if on ART for ≥4 months)

TABLE 11: Possible causes to consider in a patient presenting with delirium

Infectious	Non-infectious
Primary brain disease • HSV • VZV • CMV • TB • HIV • JCvirus (PML) • Cryptococcosis **Secondary brain disease** • Disseminated TB • Sepsis syndrome due to bacterial infection	**Drugs and toxins** • Efavirenz • Isoniazid • Steroids • Alcohol • Illicit drugs • Traditional meds • Withdrawal • Unknown toxin **Metabolic** • Hypoglycaemia • Hyponatraemia • Hypernatraemia • Hypercalcaemia • Uraemia • Liver failure • Wernicke's **CVS/respiratory** • Hypotension • Hypoxia

Urgent actions (before full assessment is complete if suspicion high)

Consider serious bacterial infection as a cause, take a blood culture, urine culture and give a broad-spectrum antibiotic, typically ceftriaxone 2g IV stat.

Consider a CNS infection if the cause is unclear, particularly if there is a fever. If suspicious, do the following:

- Lumber puncture (unless contra-indicated): (see **Chapter 5: meningitis**).
  - Measure opening pressure
  - Gram stain and bacterial culture
  - CSF protein, cell count, glucose (send
  - Serum glucose
  - CrAg
  - Syphilis
  - Store 10mls of CSF for possible future tests
- CT brain

Normal CSF findings (see box 7) suggests that CNS infection is unlikely and further tests on the stored CSF are unlikely to be helpful. However, herpes simplex virus (HSV) encephalitis can occur with normal CSF findings and PCR can be negative in early disease (< 3 days), so acyclovir may be necessary even when CSF is normal, if the symptom duration is short. In this case, the LP should be repeated when at least 3 days have elapsed since the onset of symptoms. Acyclovir can safely be stopped if an alternative cause is found, or if the clinical or radiological picture is no longer suggestive of HSV and the herpes simplex virus PCR on ≥ 0.5ml of CSF remains negative.

BOX 7: CSF results that are typically considered normal in HIV patients, although exceptions occur

- Glucose >3.5
- Protein <0.75
- 1 polymorph
- 5 lymphocytes

Abnormal CSF findings strongly suggest brain infection (encephalitis). The common and treatable causes include HSV, VZV and TB in which case empiric therapy (acyclovir and RHZE) can be considered. Confirmatory testing with Ultra, mycobacterial culture and viral PCR should be done. CMV is less common but a potential cause. However, there is no need to request a serum CMV viral load. If the CrAg is positive, treat as for cryptococcal meningitis. If the VDRL or FTA-Abs are positive with abnormal cells present and no other clear cause, treat for neurosyphilis.

Reassess the situation based on results received (from day 1 post admission)

If the cause is clear, it can be treated and, if possible, withdraw potentially responsible drugs (see box 8 if on efavirenz). Consider other drugs (not just INH related if they are on it), substance abuse and withdrawal.

BOX 8: Efavirenz toxicity

Efavirenz toxicity is more likely if the any of the following are present: short history of efavirenz exposure, psychomotor retardation, cerebellar signs, female sex, low BMI or recently initiated isoniazid therapy.

If efavirenz toxicity is a consideration, send a random serum efavirenz level (if available), change to an alternative agent (e.g., dolutegravir) and monitor for symptom improvement. Improvement in symptoms may take many weeks if the level was high, as efavirenz has a half-life of around 2 weeks.

If may be necessary to continue the work up for other causes at the same time.

If the cause is unclear but there are significant abnormalities, ensure they are monitored (e.g., liver or renal impairment) Always consider looking for TB in the usual way.

If the cause is not clear at this point - are the symptoms primarily psychotic?

The pathophysiology of psychosis and other forms of severe mental illness in HIV infection is complex, and multifactorial causation is likely in most instances. Severe mental illness has been identified as a risk factor for the acquisition of HIV infection and occurs as both a manifestation of an opportunistic infection and a result of the neurotropic effects of the virus. In this case, seek specialist psychiatric advice as drugs, infections and delirium are unlikely.

While primary psychiatric disease is a possibility, HIV associated neurocognitive disorders (HAND) can also present with features of psychosis and this remains high on the differential diagnosis. If the viral load is high, start suppressive ART.

If psychiatry referral is not possible, start antipsychotic medication according to national guidelines. Typical agents include haloperidol 0.5 mg - 2.5 mg p.o. nocte and/or lorazepam 1 - 2 mg p.o. q 8 h. If extrapyramidal side-effects occur, change to an atypical agent such as risperidone 1 - 2 mg p.o. nocte or in divided doses (1 mg p.o. b.d.)

If manic symptoms are a prominent feature, consider using valproate 300 mg twice daily, increasing to 600 mg twice daily. If liver function is impaired, use lower doses and monitor liver function tests.

If causes of delirium have been excluded or treated some patients may continue to have features of dementia

HIV associated neurocognitive disorders (HAND) are a group of disorders with high prevalence in South Africa. HIV-dementia (HIV-D) is the most severe form of HAND. A validated screening tool is the CAT-rapid which can be accessed here: **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5771655/#APP1**

A score above 10 on CAT-rapid screening suggests that HIV-D is not present. A score below 10 suggests that it may be a cause for the patient's symptoms.

It is important to rule out other causes as best you can before settling on a diagnosis of HIV-D.

If the HIV viral load is high, start suppressive ART.

If available, refer for neuropsychiatric assessment. Consider a social grant and supportive management such as a treatment buddy.

Treatment of a behaviourally disturbed patient with HIV

While searching for and treating the underlying cause, it may be necessary to treat behavioural symptoms.

Haloperidol (0.5 mg - 2.5 mg p.o daily) is safe to use in this case, however; there is a high potential for

extrapyramidal side-effects. If available, atypical antipsychotics, such as risperidone 0.5 - 2 mg twice daily or quetiapine 50 - 200 mg twice daily, may be better.

If needed, lorazepam 2 - 4 mg 8-hourly (or oxazepam if liver function is impaired) may be used for sedation in the short term.

If manic symptoms are a prominent feature, consider using valproate 300 mg twice daily, increasing to 600 mg twice daily. If liver function is impaired, use lower doses and monitor liver function tests.

Recommended references

1. Ho EL, Jay CA. Altered mental status in HIV-infected patients. Emerg Med Clin North Am. 2010 May;28(2):311-23, Table of Contents. doi: 10.1016/j.emc.2010.01.012. PMID: 20413014.
2. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. Lancet Infect Dis. 2013 Nov;13(11):976-86. doi: 10.1016/S1473-3099(13)70269-X. PMID: 24156898; PMCID: PMC4108270.
3. Joska JA, Westgarth-Taylor J, Hoare J, et al. Validity of the International HIV Dementia Scale in South Africa. AIDS Patient Care STDS. 2011 Feb;25(2):95-101. doi: 10.1089/apc.2010.0292. Epub 2011 Jan 7. PMID: 21214343.
4. Boyles TH, Bamford C, Bateman K, et al. Guidelines for the management of acute meningitis in children and adults in South Africa. South Afr J Epidemiol Infect 2013;28(1):5-16.
5. Boyles TH, Joska J. The HIV positive patient with behavioural disturbance Southern African Journal of HIV Medicine 2009;10(3):28-29.

8. AN APPROACH TO A PATIENT WITH AHD THAT IS DETERIORATING DESPITE TREATMENT FOR AN OPPORTUNISTIC INFECTION

Primary Author: Tom Boyles

Background

It is common for patients to be initiated on treatment for an opportunistic infection but not improve as expected. When this happens, there are several possibilities, and a systematic approach is required. An approach is given below. Note that the information is not ordered by incidence but rather is a systematic way of thinking through the problem of a patient deteriorating despite treatment.

Drug not getting to 'bug'

No medication will work if it cannot get to the site of infection in adequate concentrations. Think through all the reasons why this might happen-

- Medication not being given appropriately
  - For inpatients, always check the prescription chart to ensure that medications are being given appropriately.
  - For outpatients, check that there was no stock-out, and that the medication was properly dispensed, and the patient knows how to take it correctly.
- Non-adherence
  - Self-report is a poor measure of adherence unless the patient says they are not taking the medication at all. Attendance at clinic visits and pharmacy pick-ups are an indication of adherence but are not definitive. Inpatients are sometimes non-adherent and hide medications that they don't swallow.
  - It is important to explore reasons for nonadherence including side-effects, disclosure, and financial stress.
  - Occasionally random drug levels may be used to assess adherence.
  - Ultimately it may be difficult to know if the patient has been adherent and it is best to continue with the evaluation on the assumption that they are adherent.
- Malabsorption
  - Swallowed medication must be absorbed to be effective. Patients with persistent vomiting and/or diarrhoea may not fully absorb medications given. Drug levels may occasionally assist in this scenario.
- Drug-drug interactions
  - Even when absorbed, medication effects can be limited by drug-drug interactions. For interactions between ARVs and other medications see **www.hiv-druginteractions.org/checker**, or contact the National HIV/TB Hotline on 0800 212 506 or check the App **(http://www.mic.uct.ac.za/MIC/HotlineApp)**
- Difficult to reach site
  - Even when a medication makes it into the bloodstream, it may not reach adequate levels at the site of infection e.g., anti-tuberculous medications do not always penetrate TB cavities in the lung or abscesses well. In these circumstances surgery is sometimes necessary.
- Medication being under-dosed for patient weight
  - Check the dose is correct for the patient's weight and is increased if needed if they gain weight on treatment.

'Bug' resistant to drug

Once you are satisfied that the drug is most likely getting it to the 'bug', consider whether the 'bug' might be resistant. This is less likely if there is confirmed sensitivity (e.g., Xpert Ultra with rifampicin sensitivity) and more likely when treatment was either empiric or based on a test that does not identify resistance (e.g., treatment for TB with RHZE based on urine LAM or abdominal ultrasound findings could be DR-TB.) In this case, it is necessary to seek microbiological confirmation and drug sensitivities.

Incorrect diagnosis

When empiric therapy (i.e., without microbiological confirmation) has been initiated, it may be that the diagnosis is incorrect. Always revisit and question the basis for the original diagnosis. Common pitfalls include prescribing RHZE to patients with positive urine LAM, but this can also be indicative of disseminated

non-tuberculous mycobacterial infections. Similarly, non-infectious conditions such as malignancies, especially lymphomas and Kaposi sarcoma can mimic infections in AHD.

Additional diagnosis

If you remain unsure at this stage, consider that there might be a second or even third diagnosis. Patients with AHD often have more than one opportunistic infection, or concurrent malignancy. Review the history, examinations and test results including radiology to search for another diagnosis.

Adverse drug reaction

The patient may be responding to appropriate treatment but have developed an adverse drug reaction (ADR). Examples include neurological efavirenz toxicity or drug-induced liver injury. Remember to report ADRs.

Inappropriate expectations

Some opportunistic infections (OIs) take longer to improve than others, and a patient can deteriorate despite appropriate therapy, so it is important to have appropriate expectations. For example, the mortality rate from treated TB meningitis is at least 25% so one can expect some patients to deteriorate despite treatment. The mortality rate from treated PJP is similar to that of treated TB meningitis.

IRIS

Immune reconstitution inflammatory syndrome (IRIS) is the last consideration. This is not because it is uncommon but because it is necessary to consider all the other possibilities listed above before making the diagnosis of IRIS.

IRIS represents an exaggerated inflammatory response to an antigen when there is immune recovery due to ART. It is divided into 'unmasking IRIS' when the diagnosis of an OI is only made when the patient deteriorates after starting ART, and 'paradoxical IRIS' when the patient initially responds to treatment for an OI but then deteriorates after initiating ART.

IRIS is common and has been described with multiple antigens. The commonest form is papular pruritic eruption (PPE) but more serious forms include TB and cryptococcal meningitis IRIS. Risk factors for IRIS include a low CD4 count, and shorter duration between initiating treatment for an OI and ART. There is no evidence that a particular ARV increases or decreases the risk of IRIS.

Paradoxical TB IRIS occurs in approximately 18% of patients when initiating ART while taking antituberculous therapy. The most frequent features are pulmonary and lymph node involvement.

There is no specific test for IRIS, but it is rather a diagnosis of exclusion when all of the above have been excluded.

There is only one randomised controlled trial (RTC) evaluating TB IRIS treatment. This study showed that prednisone 1.5mg/kg given for 2 weeks followed by 0.75mg/kg given for 2 weeks reduced morbidity in patients with non-neurological paradoxical TB IRIS. There is limited evidence for the use of steroids in other forms of IRIS and they should therefore generally be avoided. The dose and duration of prednisone should be individualised (e.g., patients with extensive lymph node IRIS commonly require a longer courses of steroids).

Recommended references

1. Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment adherence. *Med Pharm Rep.* 2019;92(2):117-122. doi:10.15386/mpr-1201
2. Nel JS, Lippincott CK, Berhanu R, et al. Does Disseminated Nontuberculous Mycobacterial Disease Cause False-Positive Determine TB-LAM Lateral Flow Assay Results? A Retrospective Review. Clin Infect Dis. 2017 Oct 1;65(7):1226-1228. doi: 10.1093/cid/cix513. PMID: 28575238.
3. Wilkinson RJ, Rohlwink U, Misra UK, et al. Tuberculous Meningitis International Research Consortium. Tuberculous meningitis. Nat Rev Neurol. 2017 Oct;13(10):581-598. doi: 10.1038/nrneurol.2017.120. Epub 2017 Sep 8. PMID: 28884751.
4. Chiliza N, Du Toit M, Wasserman S. Outcomes of HIV-associated pneumocystis pneumonia at a South African referral hospital. PLoS One. 2018 Aug 2;13(8):e0201733. doi: 10.1371/journal.pone.0201733. PMID: 30071089; PMCID: PMC6072084.
5. Namale PE, Abdullahi LH, Fine S, et al. Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. Future Microbiol. 2015;10(6):1077-99. doi: 10.2217/fmb.15.9. PMID: 26059627.
6. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS. 2010 Sep 24;24(15):2381-90. doi: 10.1097/QAD.0b013e32833dfc68. PMID: 20808204; PMCID: PMC2940061.

9. USE OF STEROIDS IN AHD

Primary Author: Tom Boyles

Background

Systemic corticosteroids are powerful medications with important side-effects, and it is important to avoid overprescribing. Unlike many areas of AHD medicine, there have been several high quality randomised controlled trials (RCTs) to guide the use of steroids. This chapter describes the effects of steroids and summarises the evidence base for their use.

Effects of corticosteroids

Corticosteroids mimic the effects of hormones produced naturally in the adrenal glands. When prescribed in doses that exceed the body's usual levels, corticosteroids suppress inflammation and immunity. These properties are advantageous in some inflammatory and autoimmune conditions.

Patients with advanced HIV have, by definition, severely impaired immunity; therefore the autoimmune properties of corticosteroids are more likely to be deleterious. Possible reasons for prescribing corticosteroids in AHD include maintenance of physiological steroid levels in the context of adrenal insufficiency, and to suppress inflammation.

Steroids to maintain physiological steroid levels in the context of adrenal insufficiency

Reports of the prevalence of adrenal insufficiency in patients with HIV vary considerably. Patients with advanced HIV tend to have higher cortisol levels with less adrenocorticotropic hormone (ACTH), suggesting reduced reserves. There are no RCTs evaluating steroid replacement for adrenal insufficiency in patients with AHD.

Empiric corticosteroids in AHD should be avoided as there is a lack of evidence of the potential benefit/s and a significantly increased risk of increased immunosuppression. If a patient presents with symptoms and signs suggestive of steroid deficiency (e.g., sodium < 120 mEq/L, potassium > 5mmol/L, hypotension and hypoglycaemia) it is imperative to send a sample for a random cortisol level before administering exogenous steroids. If the random cortisol level is normal steroids should be avoided.

Steroids to suppress inflammation

Unlike adrenal insufficiency, there are several well conducted RCTs to inform the use of corticosteroids to reduce inflammation in patients with AHD and OIs, including:

- TB pericarditis- risks outweighed benefits, driven by increases risk of Kaposi sarcoma – avoid routine use.
- Cryptococcal meningitis- steroids increase mortality- avoid.
- *Pneumocystis jirovecii* pneumonia (PJP)- hypoxic patients benefit from oral prednisone 40mg twice daily.
- Thrombotic Thrombocytopaenic Purpura (TTP)- steroids are indicated in confirmed cases.
- TB meningitis- studies include small numbers of patients therefore wide confidence intervals, and small (not statistically significant) benefit. Ongoing RCTs are required to answer this question definitively – avoid routine use.
- Treatment of paradoxical TB IRIS- reduced morbidity in patients with non-neurological IRIS - give 1.5mg /kg daily for 2 weeks followed by 0.75 mg/kg daily for 2 weeks.
- Prevention of paradoxical TB-IRIS- reduced IRIS events in patients with CD4<100 who started ART within 2 weeks of TB treatment- give prednisone 40 mg daily for 2 weeks followed by 20mg daily for 2 weeks.
- Septic shock- evidence for use of steroids suggests an overall benefit. However, very few patients with AHD were included in these studies and the results should therefore be treated with caution. Steroid use in a patient with AHD and in septic shock should be considered only within an ICU setting and prescribed by experienced ICU consultants.
- COVID-19 - RTCs have shown a benefit of corticosteroids in patients with COVID-19 pneumonia who require oxygen therapy to maintain adequate saturations. While these studies included very few patients with AHD expert opinion is that an AHD patient with COVID-19 should receive corticosteroids.

The use of corticosteroids to suppress inflammation outside of these conditions should be considered on

a case-by-case basis but, in general, they should not be used. Examine all patients for Kaposi sarcoma and, if present, avoid steroids.

Recommended references

1. Mayosi BM, Ntsekhe M, Bosch J, et al. IMPI Trial Investigators. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014 Sep 18;371(12):1121-30. doi: 10.1056/NEJMoa1407380. Epub 2014 Sep 1. PMID: 25178809; PMCID: PMC4912834.
2. Beardsley J, Wolbers M, Kibengo FM, et al. CryptoDex Investigators. Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. N Engl J Med. 2016 Feb 11;374(6):542-54. doi: 10.1056/NEJMoa1509024. PMID: 26863355; PMCID: PMC4778268.
3. Gagnon S, Boota AM, Fischl MA, et al. Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. N Engl J Med. 1990 Nov 22;323(21):1444-50. doi: 10.1056/NEJM199011223232103. PMID: 2233916.
4. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020 Oct;18(10):2496-2502. doi: 10.1111/jth.15010. Epub 2020 Sep 11. PMID: 32914526; PMCID: PMC8091490.
5. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004 Oct 21;351(17):1741-51. doi: 10.1056/NEJMoa040573. PMID: 15496623.
6. Donovan J, Phu NH, Mai NTH, et al. Adjunctive dexamethasone for the treatment of HIV-infected adults with tuberculous meningitis (ACT HIV): Study protocol for a randomised controlled trial. Wellcome Open Res. 2018 Jun 20;3:31. doi: 10.12688/wellcomeopenres.14006.2. PMID: 30320225; PMCID: PMC6143919.
7. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS. 2010 Sep 24;24(15):2381-90. doi: 10.1097/QAD.0b013e32833dfc68. PMID: 20808204; PMCID: PMC2940061.
8. Meintjes G, Stek C, Blumenthal L, et al. PredART Trial Team. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. N Engl J Med. 2018 Nov 15;379(20):1915-1925. doi: 10.1056/NEJMoa1800762. PMID: 30428290.
9. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. Cochrane Database Syst Rev. 2019 Dec 6;12(12):CD002243. doi: 10.1002/14651858.CD002243.pub4. PMID: 31808551; PMCID: PMC6953403.
10. RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021 Feb 25;384(8):693-704. doi: 10.1056/NEJMoa2021436. Epub 2020 Jul 17. PMID: 32678530; PMCID: PMC7383595.

Website: www.sahivsoc.org

Telephone: +27 (0) 11 728 7365

Email: sahivcs@sahivcs.org