ENGLISH

# MSF HIV/TB Guide

# HOSPITAL LEVEL

October 2021

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

# MSF HIV/TB Guide

# HOSPITAL LEVEL

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Our strategies and protocols in HIV/TB management could be disproved or confirmed when confronted with field experience. Keep it in mind when reading this.And please do refer to national protocols before prescribing any treatment.

**Please contact alexandra.meyer@joburg.msf.org if you happened to notice any abnormalities or mistakes.**


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# Advanced HIV – Seriously Ill Patients

SUMMARY

## Definition of 'seriously ill':

One or more danger signs

## Mortality is high:

Do not delay investigations and management

## DANGER SIGNS

- Respiratory rate > 30/min
- Temperature > 39°C
- Heart rate > 120/min
- Systolic BP < 90mm Hg
- Saturation < 90%
- Moderate/severe dehydration
- Unable to walk unaided
- Altered mental state: confusion, strange behaviour, reduced level of consciousness
- Any other neurological problem: headache, seizures, paralysis, difficulty talking, cranial nerve problems, rapid deterioration in vision

## Common causes of mortality: see box

Often there is more than one cause

- Take a good history
- Examine the patient
- Focus on respiratory & neurological systems and ARThistory

## Disseminated TB is the most common cause of mortality

**1. ART failure**

**2. Neurological disease – Big 3:**
- TB
- Cryptococcal meningitis
- Toxoplasmosis

**3. Respiratory Disease – Big 3:**
- Pneumocystis pneumonia
- Pulmonary TB
- Bacterial pneumonia

**4. Severe Diahorroea**

**5. Other bacterial infections**
- Bacterial meningitis
- Bacterial pneumonia
- Bloodstream infection
- Urinary tract infection

**6. Other non-infectious causes**
- Hypoglycaemia
- Renal failure
- Abnormal sodium, potassium
- Liver disease
- Drug side effects

## Investigations DO Immediately

**Basic package of point of care tests**
- HIV Testing
- CD4
- Serum CrAg
- TB LAM
- Rapid malaria test
- Glucose
- Haemoglobin
- Urine dipstick

## Additional investigations: Do what is available

**Basic TB investigations:**
- TB LAM (urine)
- GeneXpert (sputum)

**For either test: treat if positive, but a negative result does not exclude TB**

**Other TB Investigations::**
- Sputum Microscopy
- GeneXpert on non-sputum. Samples: urine, CSF, pus
- CXR
- Abdominal USS

**Lumbar puncture:**
- Necessary if there is any abnormal neurology
- Request: CrAg, cell count and differential, protein, glucose, gram stain, geneXpert
- If LP not possible or inevitable delay: serum CrAg, empiric treatment as indicated (see Management - Neurology)

**Blood tests:**
- Creatinine, sodium, potassium
- Full blood count
- VDRL
- Jaundice or hepatomegaly: bilirubin, ALT,
- Bacterial infection possible: blood/urine cultures

## Management

Initiate without delay

**Start empiric treatment** for diseases where clinical suspicion is high, but where there is no diagnostic test available or where diagnostic tests cannot exclude the disease. See section 'Drugs for treatment of common OIs' for drug doses and duration.

## Emergency Management

**Hypoglycaemia:**
- 50 mls of 50% dextrose

**Dehydration,Acute Kidney Injury:**
- See algorithm 'Kidney Disease in HIV positive hospitalized patients'

**Severe anaemia (Hb < 5g/dL):**
- Transfuse, oxygen
- See algorithm "anaemia'

**Start empiric antibiotics if bacterial infection likely:**
- Give first dose within 1 hour
- Blood cultures before antibiotics if available

## Respiratory Disease

**Respiratory Danger Signs: RR > 30 or saturation < 90%**
- Give oxygen

**Treat for Respiratory 'Big 3":**
- Pneumocystis pneumonia: treat if CD4 < 200 or unknown
- Bacterial pneumonia
- ***Pulmonary TB;*** *high clinical suspicion of pulmonary TB in all HIV positive patients with respiratory danger signs*

## Neurological Disease:

**Treat for Neurological 'Big 3':**

***Cryptococcal meningitis:***
- Treat if CSF CrAg positive, or serum CrAg positive and unable to perform LP immediately

***Toxoplasmosis:***
- CD4 < any abnormal neurology and CD4 < 200 or unknown

***Neurological TB:***
- High clinical suspicion of TB for all HIV positive patients with neurological symptoms or signs.

## Clinical indications for immediate empiric TB

- TB LAM negative and/or Xpert MTB/RIF negative cannot rule out TB if there is high clinical suspicion
- Start TB treatment on admission if high clinical suspicion

High clinical suspicion:
- Neurological symptoms/signs
- Respiratory danger signs
- Severe weight loss
- Clinical signs of TB: pleural effusion, pericardial effusion, ascites, lymphadenopathy

# ADVANCED HIV – SERIOUSLY ILL PATIENTS

DETAIL

## Definition of 'Seriously ill':

One or more danger signs

## Mortailty is high:

Do not delay investigations and management

## DANGER SIGNS

- Respiratory rate > 30/min
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- Moderate/severe dehydration

- Unable to walk unaided
- Altered mental state: confusion, strange behaviour, reduced level of consciousness
- Any other neurological problem: headache, seizures, paralysis, difficulty talking, cranial nerve problems, rapid deterioration in vision.

## Common causes of mortality: see box

Often there is more than one cause

**Investigations and management focus on these causes**

## Disseminated TB is the most common cause of mortality:

All patients need investigating for TB, and rapid initiation of treatment if indicated

**1. ART failure**

**2. Neurological disease – Big 3:**

- TB
- Cryptococcal meningitis
- Toxoplasmosis

**3. Respiratory Disease – Big 3:**

- Pneumocystis pneumonia
- Pulmonary TB
- Bacterial pneumonia

**4. Severe diarrhoea:**

- Renal failure and abnormal sodium and potassium levels are common, and are often asymptomatic

**5. Other bacterial infections:**

- 'Bloodstream' infections
- Meningitis
- Urinary tract infections

**6. Common non-infectious causes:**

- Hypoglycaemia
- Renal failure
- Sodium/potassium abnormalities
- Liver disease
- Drug side effects: find out all the medication the patient is taking

## Take a good history

- Start with the presenting complaint
- Always ask about neurological and respiratory symptoms, and diarrhea
- Ask the 2 key questions (see right)

## Examine the patient

- Reassess vital signs
- **Specifically assess neurological and respiratory systems, and assess for dehydration**
- Look for KS (skin, palate)
- Look for CMV retinitis if recent deterioration **in vision**

## Key question 1: is the patient on ART?

Patients on ART should be doing well, and not seriously ill: What has gone wrong?

- What is the regimen?
- How long is the patient on ART?
  < 3 months: TB is very common during this time - 'unmasking TB'
  >6 months: is there treatment failure?

The majority of seriously ill patients nowadays with advanced HIV are **failing first line and need rapid switch to second line**

- If this is not addressed, treating opportunistic infections alone will not save the patient's life
- Adherence issues must be addressed at the same time as changing regimen; staying on a failed regimen means the patient will die

## Key question 2: is the patient taking TB treatment?

Patients on TB treatment should be doing well, and not seriously ill: what has gone wrong?

**Questions to ask:**

- For how long is the patient on TB treatment?
- Was TB proven? Rifampicin sensitive?
- Is the admission due to drug adverse effects?
- Did the patient improve on TB treatment?
  If not – see algorithm 'Patients deteriorating or not improving on TB treatment'

# Investigations: Take sample immediately AND collect results within

**If the patient is to be referred to a higher level of care, do as many investigations as possible at the initial facility, and start management**

## Basic package of point of care tests:

**These should be available 24/7, and all clinical, nursing and lab staff trained in their use.**

- HIV Testing
- CD4
- Serum CrAg
- TB LAM
- Rapid malaria test
- Glucose
- Haemoglobin
- Urine dipstick

## Chest X Ray

**TB:**
- Miliary TB
- Pleural effusion, pericardial effusion
- Lymphadenopathy
- Pulmonary infiltrate

**Pneumocystis pneumonia:**
- Ground glass pulmonary infiltrate

**Bacterial pneumonia:**
- Consolidation, air bronchograms

## All patients need investigation for TB:

**TB LAM:**
- TB LAM positive: start TB treatment
- TB LAM negative: TB is not excluded! Continue investigations, start empiric TB treatment if indicated (see Management section)

**GeneXpert:**
- Sputum: spontaneous or induced
- Non-sputum samples: urine*, CSF*, ascites* pus

➔ **GeneXpert positive:** start TB treatment
➔ **GeneXpert negative:** TB is not excluded! Continue investigations, start empiric TB treatment if indicated (see Management section)

### Other investigations for TB:

**Sputum microscopy:**
- If geneXpert unavailable

**CXR: see left**

**Abdominal ultrasound:**
- Lymphadenopathy
- Ascites
- Hepatosplenomegaly

**Centrifuge urine, CFS, ascites, pus otherwise sensitivity is very low**

## Lumbar puncture

**Indications for LP:**
- Any neurological symptoms or signs
- Serum CrAg positive
- LP should be done before antibiotics are started unless this will delay the first dose; the sample can be stored in a fridge overnight

**Baseline investigations:**
- CrAg
- Cell count and differential (lymphocyte count, neutrophil count)
- Protein, glucose
- Gram stain for bacteria: Streptococcal pneumoniae: gram positive cocci in pairs/chains Neisseria meningitidis: gram negative diplococci
- GeneXpert*

➔ If unable to do an LP or if there is an inevitable delay (eg referral is necessary for LP), empiric treatment may be necessary
➔ See Management section: Neurological Disease

**REMEMBER:** All neurological signs are danger signs

## Blood Tests

- Creatinine, sodium, potassium
- Full blood count
- VDRL
- Jaundice or hepatomegaly: bilirubin, ALT, hepatitis B

## Does the patient have a bacterial infection?

**Look for any of the following:**
- Temp > 38 degrees or < 35 degrees
- HR > 120, or RR > 30
- White cell count <4 or > 12
- Other causes possible: Acute onset of symptoms suggests bacterial infection. In doubt, start antibiotics if seriously ill. Diagnosis can be reviewed upon further results
- Look for the source (pneumonia, meningitis , UTI): blood stream infections are also common
- Take blood culture*, using sterile technique; other relevant tests, e.g. urine dipstick, urine culture

**Take before antibiotics are started unless this will delay the first dose.**

# Management: Start without delay

**Start empiric treatment (highlighted text) for diseases where clinical suspicion is high, but there is no diagnostic test available, there is an unavoidabledelay with results, or if diagnostic test cannot exclude the disease.** See section 'drugs for treatment of common OIs for drug doses and duration

## General Management

**Hypoglycaemia:**

- Give 50mls of 50% dextrose, monitor PoC glucose 4 hourlyuntil hypoglycaemia has resolved for 24hours.

**Dehydration and/or Acute Kidney Injury:**

- See algorithm 'Kidney Disease in HIV positive hospitalized patients'

**Anaemia:**

- HB < 5g/dl: transfuse, give oxygen
- HB < 8g/dl and tachypnoea or active bleeding: transfuse
- Assess for likely cause: see anaemia algorithm

**Start empiric antibiotics if bacterial infection likely:**

- For example, lung crepitations, visible pus in the urine: Patients presenting with shock where septic shock is the likely cause
- ***Do not give antibiotics*** if urine dipsticks are positive for nitrates and/or leucocytes in an asymptomatic patients
- Give first dose within 1 hour: send blood cultures before antibiotics are given if feasible, and this does not delay antibiotics
- Use local guidelines for antibiotic prescription: see page 38 if you do not have local guidelines
- Review all antibiotic prescriptions every 48 hours to assess ifIV drugs can be changed to oral, or if antibiotics can be stopped

## Respiratory disease

**Respiratory 'Big 3' – start empiric treatment on admission for all patients with respiratory danger signs (RR > 30 or saturation < 90%)**

- Oxygen by nasal prongs and/or face mask

***Pneumocystis pneumonia:***

- Treat if CD4 < 200 or unknown
- High dose cotrimoxazole and prednisone: see page 35

***Bacterial pneumonia***:

- Use your local antibiotic guidelines or see page 38

***Pulmonary TB:***

- High clinical suspicion of pulmonary TB in all HIV positive patients with respiratory danger signs

## Clinical indications for immediateempiric TB treatment:

- TB LAM negative and/or Xpert MTB/RIF negative cannot rule out TB if there is high clinical suspicion
- Start TB treatment on admission if high clinical suspicion

**High clinical suspicion:**

- Neurological symptoms/signs
- Respiratory danger signs
- Severe weight loss
- Clinical signs of TB: pleural effusion, pericardial effusion, ascites, lymphadenopathy

## Neurological disease

**Neurological 'Big 3' – start empiric treatment on admission:**

***Cryptococcal meningitis:***

- Treat if CSF CrAg positive, or serum CrAg positive and unable to perform LP immediately
- Preferred regimen: liposomal amphotericin B plus flucytosine (page XX)
- Management of raised intracranial pressure: remember therapeutic LP reduces mortality by 70%
- Serum CrAg positive and CSF CrAg negative, or no neurological signs and unable to perform LP

***Toxoplasmosis:***

- CD4 < any abnormal neurology and CD4 < 200 or unknown
- Treatment: cotrimoxazole: see page xx for dosing and alternatives if cotrimoxazole hypersensitivity

***Neurological TB:***

- Occurs at all CD4 counts. High clinical suspicion of TB for all HIV positive patients with neurological symptoms and signs. Start empiric TB treatment and steroids on admission
- Note a normal LP does not rule out TB meningitis or tuberculomas; neutrophils in CSF occur in early TB meningitis, in severe TB meningitis, and in TB meningitis IRIS
- See page 34 for TB treatment regimen, steroid dosing and when to start/switch ART

**Bacterial Meningitis:**

- Do not routinely treat all patients with neurological problems for bacterial meningitis
- Suspect if there is an acute onset of symptoms of meningitis: headache, neck stiffness, photophobia or reduced consiousness
- CSF: high protein and neutrophil predominance, however neutrophils may also be found in TB meningitis

# Respiratory Problems

* = in red, the "big 3" respiratory diseases! They may co-exist, always look for all 3

**Clinical presentation**

- Dyspnoea
- Cough; productivw or dry?
- Fever

**Respiratory danger signs:**

- Respiratory rate > 30
- Hypoxia: oxygen saturation < 90%
- Haemoptysis

**Initial assessment**

**History**

- Duration of onset, additional symptoms

**Examination**: look for

- lymph nodes
- pleural effusion
- wasting
- skin lesions

**Investigations:**

- All patients are TB suspects!
- Investigate for TB
- CXR for all patients as soon as possible
- Pleural effusion: diagnostic tap, therapeutic tap if large and causing respiratory distress

**Emergency management**

- Oxygen via face mask or nasal prongs if RR > 30 or hypoxia
- Initiate antibiotics immediately if bacterial pneumonia suspected
- Look for pneumothorax

**Haemoptysis**

- Codeine or other opiate for cough suppression (do not ask patient to give sputum samples)
- Start empiric TB treatment
- Check Hb stays > 8 (or > 10 if haemoptysis > 250ml/day

## All patients are TB suspects

## *Tuberculosis: investigations

- Pulmonary TB; any CD4 count
- Sputum for geneXpert (microscopy if not available)
- TB LAM if CD4 known or considered < 100
- Other investigations as indicated: eg pleural tap, LN FNAB

**Infection control:**

- surgical mask for patients not needing oxygen; move to TB isolation area)
- Open windows!

## Chronic lung disease

- All CD4 counts
- Chronic dyspnoea, chronic cough, chronic hypoxia
- CXR: post TB destructive lung disease – fibrosis, cavities, bronchiectasis on CXR
- Comparison with previous CXRs shows this is chronic: treat TB if proven, avoid empiric treatment on the basis of CXR alone

## Look for alternative/additional causes

### Acute onset: days

## *Bacterial pneumonia

- Occurs with any CD4 count
- Auscultation: Bronchial breathing and crepitations
- CXR: Pulmonary infiltrate or consolidation; empyema may occur (purulent pleural effusion, mostly neutrophils)

**Treatment:**

- Antibiotics
- Ceftriaxone 1g: change to oral antibiotics (co-amoxyclav) after 1-2 days, when clinical improvement shown
- Duration of antibiotics: 5-7 days

### Subacute onset: up to 2 weeks

## *Pneumocystis pneumonia

- CD4 count generally < 200
- Progressive dyspnoea: often dry cough
- Very high respiratory rate (> 40) and hypoxia are common
- Sudden deterioration: pneumothorax is common and life-threatening
- Auscultation: crepitations or may be normal
- CXR: 'ground glass' infiltrate; look for pneumothorax

**Treatment:**

- Cotrimoxazole 480mg 1 tablet for each 4kg of body weight, in 3-4 divided doses (if 48 kg, 4 tablets 3 x day)
- Hypoxia: prednisone
  - 40mg twice daily x 5 days – then:
  - 40mg once daily x 5 days – then:
  - 20mg once daily x 11 days

## Look for Kaposi's Sarcoma

- CD4 often < 200, often higher
- Look for KS lesions on skin, palate
- CXR: 'lines and nodules' – reticulonodular pattern, radiating from the hilar regions
  May be bloody pleural effusion

**Treatment:**

- Fast track for ART, chemotherapy

## Don't Forget – Respiratory Emergencies:

- Pulmonary embolism
- Pneumothorax (common complication of pneumocystis pneumonia)
- Haemoptysis
- Empyema

# Neurological Disease in HIV positive patients

## How does neurological disease present?

*Any combination* of the following:

| ***Altered mental state - including:*** | ***Focal abnormal neurology – including:*** | ***Meningism:*** |
|---|---|---|
| • confusion<br>• reduced consciousness<br>• strange behaviour<br>• headache | • cranial nerve problems<br>• visual problems<br>• hemiplegia<br>• paraplegia<br>• abnormal movements<br>• ataxia | • headache<br>• photophobia<br>• neck stiffness<br><br>Note: TBM and cryptococcal meningitis are often atypical, with additional or alternative neurological abnormalities |

***Convulsions*** can occur alone or with any combination of neurological abnormalities: even 1 convulsion in an HIV patient needs investigation and treatment

## what are the common causes?

### Neurological causes

#### 'Big 3' HIV related diseases

- Cryptococcal meningitis
- CNS TB: TB meningitis, tuberculomas
- Toxoplasmosis

Remember paradoxical IRIS - neurological IRIS has a high mortality

#### Other common neurological infections:

- Cerebral malaria
- Bacterial meningitis
- Neurosyphilis

#### Rarer HIV related diseases:

- CMV encephalitis: more likely in regions with high prevalence of CMV retinitis
- Progressive Multifocal Leucoencephalopathy (PML)*
- Primary CNS lymphoma*

*no diagnostics and no effective treatment in MSF settings

### Medical causes: these can all cause altered mental state

#### Bacterial sepsis:

- Look for the source of the sepsis

#### Metabolic abnormalities – look for the underlying cause:

- Hypoglycaemia
- Hypotension
- Hypoxia
- Abnormal sodium: too high or too low
- Renal impairment
- Liver impairment

#### Medication – most commonly:

- Efavirenz: psychosis, dizziness
- Isoniazid: psychosis
- Cycloserine/Terizidone (DRTB): psychosis
- Alcohol, methamphetamines, other substance abuse

### Which neurological diseases cause which of the 3 clinical presentations?

- All of the neurological causes can cause altered mental state
- Typical meningitis symptoms can be caused by any type of infection (Cryptococcal disease, TB, bacterial meningitis): but cryptococcal disease and TB often do not present with all of the typical symptoms
- Focal neurology is common in the following:
  - TB meningitis
  - Toxoplasmosis
  - Neurosypilis
  - PML
  - Cryptococcal disease: cranial nerves 3,4 and 6 (which control eye movements) and loss of vision

note: psychiatric disease is a diagnosis of exclusion: for patients with 'strange behavior', hallucinations and other psychotic symptoms. Always investigate and treat for likely organic causes, *particularly* at low CD4 counts

## Danger signs

All neurological abnormalities are danger signs

**note** - peripheral neuropathy is an exception :lower limbs, symmetrical, loss of sensation or pain; no motor loss; if you are certain about this diagnosis, this is not a danger sign and can be managed in primary care

**Other danger signs may be found, particularly:**

- Temperature > 39°C
- Heart rate > 120/min
- Systolic BP < 90mm Hg
- Unable to walk unaided

## Emergency management

## What to do

- ABC: hypoxia and hypotension cause altered mental state!
- Point of care glucose: 50 ml of 50% dextrose if glucose < 72 mg/dl (4mmol/L): repeatt glucose in 1 hour
- Place patient in recovery position: keep airway open, prevent aspiration

*Convulsions*:

Stop convulsions:

- Diazepam 5-10 mg IV, repeat as needed

Prevent further convulsions:

- IV valproate first choice: loading dose 17mg/kg
- if unavailable: IV phenytoin 20mg/kg (give slowly) phenobarbitone 10mg/kg

## Investigations:

begin PoC investigations in parallel with history and examination

do not delay specific treatment while waiting for results

***Point of care (PoC):***

- glucose: *emergency investigation for all pts with abnormal neurology*
- Rapid malaria test
- Haemoglobin
- creatinine (if PoC)
- CD4
- TB LAM
- Serum CrAg
- Syphilis

***Laboratory investigations:***

- creatinine (if no rapid test)
- Sodium and potassium
- FBC
- Bilirubin and ALT if concerns about liver impairment

TB Investigations – all pts:

- Xpert on sputum, urine or other body fluids
- Imaging: focused abdominal ultrasound, CXR

***Lumbar Puncture (indications according to your local guidelines):***

- aspect (bloody, pus, straw-coloured
- biochemistry: glucose, protein (Pandy)
- cells: cell count and differential
- special investigations: Xpert, CrAg, gram stain

If CSF CrAg positive – do opening pressure (pt in lateral position) and drain up to 30ml CSF if pressure ≥ 25mmHg: repeat at least daily (see CCM guidelines)

**History and examination**

***Important points on history:***

- Timecourse: acute onset (a few days) or subacute (1-3 weeks)
- Symptoms outside the CNS: is there evidence of disseminated TB?
- ART regimen failure?
- Already on TB treatment? think about poor adherence, DR TB, paradoxical IRIS

***Important points on examination:***

- Level of consciousness: AVPU for initial assessment, then Glasgow Coma Scale

See neurological examination guide:

- Remember neck stiffness
- Look for focal neurology – including cranial nerves
- Unconscious patients – assess tone, reflexes, is patient moving all limbs?
- Fundoscopy for CMV retinitis (CD4 < 100)

**Treat *all likely causes*:**

ensure first dose of all medications given within one hour

***'Big 3' diseases:***

***Cryptococcal meningitis* ( see CCM guidelines):**

- Treat if CSF CrAg positive or serum CrAg positive and neurological symptoms and unable to do immediate LP. *Remember therapeutic LPs reduce mortality by 70%.*

***Toxoplasmosis:***

CD4 ***CNS TB:***

- < 200 or unknown and focal neurology or abnormal mental state
- Cotrimoxazole 1 x 480mg tablet for each 8kg of body weight daily, 2 divided doses

***CNS TB:***

- Note a normal LP does not rule out TB meningitis or tuberculomas. Start treatment for CNS TB for all patients unless there is a specific reason not to do so
- RHEZ 9-12 months (use local guidelines): IV rifampicin while hospitalized if availalble

***Additional diagnoses:***

- *Bacterial meningitis*: treat if LP suggestive or clinical presentation compatible. If in doubt, start treatment and review with senior clinician the following day
- *Malaria*: start artesunate; however do not assume this is the only problem particularly in advanced HIV, continue all investigations and treat for all likely causes
- CMV: treat if retinitis on fundoscopy: valganciclovir 900mg 12 hourly for 21 days
- Metabolic and other medical causes: treat as indicated, and ensure follow up

**Ongoing care**

**All pts with reduced consciousness need ICU admission**

- Vital signs and GCS: document frequency in pt notes
- PoC glucose if reduced consciousness, or any documented hypoglycaemia
- Nurse head up and in recovery position, regular turning to prevent bedsores
- Maintenance fluids and input/output monitoring; creatinine and electrolytes 2-3 x weekly
- Enteral feeding by NGT

**If no response to treatment**

***Repeated reassessment for reversible causes:***

- Look for common causes of deterioration:
  hospital acquired sepsis, PE, drug adverse effects, AKI and electrolyte abnormalities due to inadequate fluids,

***Palliative care:***

- some causes of neurological problems cannot be treated (PML, CNS lymphoma)
- If patient does not improve or deteriorates and no additional intervention or investigations are available, discuss with family regarding palliative care

# Neurological problems:
# Interpretation of lumbar puncture results

| | Normal | Viral | Bacterial | TB | Cryptococcal |
|---|---|---|---|---|---|
| **CD4 count** | | Any | Any | Any – often low | Low, usually < 100 |
| **Onset** | | acute | acute | Sub-acute | Sub-acute |
| **appearance** | Clear | Clear | Often turbid | Clear | Clear |
| **Cells** | < 5 lymphocytes no neutrophils<br><br>See note* | Lymphocytes Usually < 100<br><br>*See note below: lymphocytes In advanced HIV mean TB, not viral meningitis* | Cell count high, mostly **neutrophils**<br>*However:*<br>• *If antibiotics are given before LP is done, cell count may fall, and bacteria are unlikely to be seen* | Lymphocytes Variable, may be several hundreds<br>*However:*<br>• *Cell count may also be normal*<br>• *In early TBM, neutrophils can predominate* | Very variable, may be raised with mostly lymphocytes, often normal |
| **Protein** (High = Pandy +ve) | Normal | Normal | Usually high | Usually high | Normal or high |
| **Glucose** | Normal | Normal | **Usually Low** | **Usually Low** | Normal or slightly low |
| **Special tests** | | | Microscopy to look for bacteria: low sensitivity, but gives definitive diagnosis | GeneXpert on centrifuged CSF (note: negative GeneXpert does not rule out TB) | **CrAg: sensitivity and specificity very high** |

As can be seen, there is a lot of overlap between findings in different types of meningitis

***Viral meningitis:**

- Most viral meningitis is self-limiting and is caused by viruses such as enterovirus
- This causes a rapid onset meningitis, with rapid recovery - most patients are not admitted to hospital because they recover rapidly at home
- **As a general rule: a lymphocytic CSF in hospitalised HIV positive patients is TB meningitis and not "viral meningitis"**

# Diarrhoea in HIV positive patients

## What is diarrhoea?

- > 3 stools per day
- Decreased consistency: 'takes the shape of the container'
- Associated symptoms: fever, abdominal pain, vomiting

## Complications:

- Dehydration, hypovolemic shock
- Acute kidney injury
- Electrolyte abnormalities
- Bacteraemia, septic shock

## Causes:

**Infectious:**

- Viral
- Bacterial
- Parasites
- Mycobacteria: disseminated TB

## 3 questions

**Acute vs Chronic:**

- Acute - < 2 weeks
- Chronic - > 2 weeks

**Inflammatory vs Non-inflammatory:**

Small bowel - non-inflammatory:

- Large volume watery diarrhoea: no blood or mucous

Large bowel – inflammatory:

- Frequent small volume stools, with blood and mucous ( WBC on microscopy)

**Does the patient have advanced HIV: is CD4 < 200?**

- Chronic watery diarrhoea is common - caused by parasite opportunistic infections: Isospora belli, Cryptosporidium
- Dehydration, renal impairment and severe hypokalaemia are common
- **WHO stage 4: need effective ART – change to second line if suspect first line failure**

## Acute diarrhoea

### Non-inflammatory:

- Viruses: norovirus, rotavirus
- Bacterial: toxin secreting – be alert for cholera (large volume of rice water stools)
- Nausea and vomiting, abdominal cramps

### Inflammatory:

- Bacteria: Salmonella, shigella, Campylobacter, E coli, C difficile
- Parasites: amoebic dysentery
- Fever, abdominal cramps common
- More severe illness: gut mucosa damaged

### Investigations:

- Creatinine and electrolytes
- Stool microscopy if available: bacteria or parasites found?

### Treatment:

- Fluid and electrolyte replacement
- Most acute diarrhoea is non-inflammatory and self-limiting, antibiotics not needed

**Antibiotics if bacterial cause or amoebic dysentery:**

- Fever > 38 degrees
- Severe dehydration
- Bloody diarrhoea
- Mucous, or WBC on microscopy

**Which antibiotics:**

- Ciprofloxacin 500mg x 12 hourly for 3 days
- Add metronidazole for 10 days if bloody diarrhoea or amoebae seen

## Chronic diarrhoea

### Non-inflammatory:

- CD4 < 200: isospora belli, cryptosporidium are common WHO stage 4 diseases
- Giardia Lamblia
- Vomiting, weight loss, malnutrition common

### Inflammatory:

- Parasites: amoebic dysentery, strongyloides, Giardia lamblia
- CD4 < 100: CMV (rare) – look in eyes to see if there is CMV retinopathy

### Investigations:

- Creatinine and electrolytes – renal impairment and hypokalaemia common
- Stool microscopy if available: parasites found?
- 2 or more stool samples may be necessary: parasites are shed intermittently; negative stool does not rule out parasite causes

### Treatment:

- Fluid and electrolyte replacement

### Anti-parasite treatment:

**Inflammatory:**

- metronidazole for amoebiasis (7 days) or strongyloides (10 days)

**Non-inflammatory:**

- Giardiasis is common, treat with metronidazole for 3 days, or single dose tinidazole (2g)
- Empiric treatment for Isospora belli: cotrimoxazole 480mg dose: 1 tablet for each 8kg of body weight per day in divided doses – for 10 days
- Followed by prophylaxis 480mg x 2 tablets per day
- Cotrimoxazole hypersensitivity: ciprofloxacin, 500mg bd for 10 days

Some patients have recurrent episodes, despite immune restoration: treat with cotrimoxazole plus ciprofloxacin for 10 days, then maintenance cotrimoxazole 480mg 2 tablets bd

# Liver Disease in HIV positive patients

**Are there Liver Danger signs?**

## Jaundice is a liver danger sign:

- **Refer all patients with jaundice to Hospital**

Confusion or reduced consciousness: these are signs of severe liver disease, due to:

- hypoglycaemia
- Hepatic encephalopathy
- sepsis

Other danger signs commonly co-exist:

- Temperature > 39°C
- Heart rate > 120/min
- Systolic BP < 90mm Hg
- Unable to walk unaided

**Clinical presentation**

- Jaundice
- Incidental finding if ALT checked
- Hepatomegaly
- Nausea/ vomiting

**Common causes**

**There may be more than one cause**

**Most common:**

- Drug induced liver injury (DILI)
- Viral hepatitis:
  - acute (A,B)
  - chronic (B,C)
  - hepatitis B IRIS
- Toxins: traditional medications, alcohol
- Bacterial sepsis (jaundice +/- raised hepatocellular or cholestatic enzymes)
- Malaria
- TB and TB IRIS: often tender hepatomegaly

Others:

- Right heart failure: tender hepatomegaly +/- raised bilirubin and transaminases
- Schistosomiasis chronic liver disease

**Common causes of DILI:**

**Prophylaxis or treatment doses of:**

- Cotrimoxazole
- Fluconazole (less common)

**TB medication:**

- Rifampicin, isoniazid, pyrazinamide

**ART:**

- Nevirapine, Efavirenz: Usually within first 2-8 weeks, ***Efavirenz can also cause late DILI - after many months***
- Lopinavir, ritonavir, atazanavir*

*note: Atazanavir commonly causes ***benign*** jaundice (high unconjugated bilirubin with normal liver enzymes): bilirubin transport problem: it is not pathological

**What do the liver tests show?**

Normal values – minor variations between laboratories:

- ALT ≤ 40 IU/L
- bilirubin ≤ 17 µmol/l (<1.0mg/dl)
- GGT ≤ 40 IU/L

Transaminases (ALT and AST):

- markers of hepatocyte damage
- raised in DILI, viral hepatitis
- ALT is most important marker for DILI

Cholestatic enzymes (GGT and ALP):

- markers of obstruction
- sometimes raised in DILI
- raised in TB, TB IRIS
- do not show liver damage Bilirubin:
- raised in liver disease, other systemic diseases and systemic sepsis
- detectable clinically when > 50 µmol/l (> 3mg/dl)

The most important widely available test of liver function is ***blood glucose:***

- The liver regulates blood glucose levels, and makes glucose
- Hypoglycaemia is common in liver disease, and is rapidly fatal
- Check at least 2 x daily if liver disease not resolving: give 50% or 10% glucose if hypoglycaemia, and check at least 4 times daily
- INR is also a test for liver disease: request if available: if > 1.2, give vitamin K 10mg IV daily, repeat after 3 days

## History and examination

Important points on history:
Drugs:
- TB treatment
- Cotrimoxazole
- ART – especially EFV
- Fluconazole
- Traditional medicines

Other:
- History of viral hepatitis
- Alcohol history

Important points on examination:
- Jaundice
- Confusion, reduced consciousness
- Liver flap
- Hepatomegaly; is liver tender?
- splenomegaly
- Ascites

Signs of chronic liver disease:
- Spider naevi, gynaecomastia, palmar erythema

## Investigations

Point of care investigations:
- **glucose – urgent!!**
- CD4
- Hepatitis B (A, C if available)
- Malaria
- Haemoglobin
- Creatinine

Other investigations:
- Bilirubin, ALT
- GGT if available
- Note: AST and ALP give no additional information
- Ascites present: ascitic tap for cell count, protein, glucose, Xpert MTB/RIF, gram stain
- Creatinine, sodium, potassium
- Full blood count
- TB investigations
- Abdominal ultrasound: look for evidence of TB, liver masses (eg malignancy) liver abscess

## Management

**All patients:**
- Avoid alcohol
- Avoid liver toxic drugs; NSAIDS, paracetamol,traditional medicines

**Treat other causes:**
- Treat TB; steroids for IRIS
- Treat schistosomiasis:praziquantel 40mg/kg single dose

**Hepatitis B:**
- TDF and 3TC reduce replication of hepatitis B virus
- Continue TDF if switch to second line ART: standard second line regimen becomes AZT/TDF/3TC plus DTG or PI

**Hepatitis C:**
- Use local protocols

## Management of DILI

**DILI: definition - *one or more* of the following:**
- ALT more than **3 times** upper limit of normal if the patient has symptoms (nausea/vomiting, abdominal pain)
- ALT more than **5 times** upper limit of normal if the patient is asymptomatic
- Bilirubin more than 40 µmol/l (more than 2.3 mg/dl)
- *Note: GGT and ALP are not part of the definition of DILI*

**If ALT or bilirubin are raised *before* starting TB treatment:**
- Start RHZE as normal and repeat ALT and bilirubin every 3 days
- If ALT or bilirubin increase by more than 50% when TB treatment started, change to alternative regimen
- Giving Rifampicin/Isoniazid/Ethambutol without Pyrazinamide is also an option if severe (presence of symptoms, ALT more than 10 times upper limit of normal or bilirubin more than 80 µmol/l (more than 4.6 mg/dl)
- If there is liver failure – recurrent hypoglycaemia, raised INR or hepatic encephalopathy – start alternative regimen

***See next algorithm* for the management of DILI:**

**If criteria for DILI are met – stop all drugs that may cause DILI**

- If ALT and/or bilirubin are raised but the criteria for DILI are not met, continue all drugs and repeat ALT/bilirubin after 3 days **+**

# Drug Induced Liver Injury (DILI): How to do a TB drug rechallenge

## Check TB Diagnosis:

- TB proven? Rifampicin sensitivity proven? If not, request Xpert/LAM - sputum/non-sputum samples
- If TB not proven, but there is clinical response to TB treatment (weight gain, symptoms resolving, anaemia improving, CXR improving) then TB diagnosis can be assumed to be correct

**Normal values (minor variations between labs):**

- ALT ≤ 40 IU/L
- bilirubin ≤ 17 µmol/l (1.0mg/dl)

***When is rechallenge contraindicated?***

- clinical evidence of fulminant liver failure – new onset of coma (GCS ≤ 8, persistent severe hypoglycaemia, clinical concern of coagulopathy (bleeding from gums, puncture sites)
- Always discuss (contact SAMU): if rechallenge is considered contraindicated, the patient will need a regimen consisting of DRTB drugs – longer, more expensive, and drugs can be difficult to obtain

## Diagnosis of DILI: See 'Definition of DILI'

***Patient severely ill with TB***: CNS TB, respiratory symptoms, severe wasting, bedbound

- start alternative TB treatment with a '***backbone***' of TB drugs that are safer for the liver

***Patient is not severely ill with TB,*** and TB does not involve CNS

- stop all TB treatment, do not give the backbone drugs
- **Review the decision not to give backbone at least weekly; start backbone if TB symptoms recur, or if time taken to start or complete rechallenge is prolonged**

### 'Backbone' drugs

- Ethambutol
- Levofloxacin*

**3rd drug – depends on availability and contraindications**

- **Amikacin: if CrCl > 50**
  **Linezolid: Hb > 9, contraindicated if peripherhal neuropathy**
  **Cycloserine: contraindicated if psychotic symptoms**
  **Clofazamine: however slow onsent of action, not good for CNS TB**

**TB treatment stopped**

Check ALT/bilirubin every 3 days* – start rechallenge when:

- ALT < 100 IU/L ***with no symptoms of liver disease***
- ***and*** biluribin is normal

Is it always essential to wait for ALT/bilirubin to decrease to these levels?
**See *Questions* section below**

***if only ALT raised initially and bilirubin normal, follow ALT alone**

**Day 1 of rechallenge – pt taking backbone drugs:**

- add isoniazid
- continue ethambutol
- continue levofloxacin
- stop 3rd drug

**Day 1 of rechallenge – pt without backbone drugs – start both of these drugs:**

- isoniazid
- ethambutol

**Day 3:** Check ALT/bilirubin

**Day 4:** if ALT /bilirubin unchanged

- Add rifampicin
- continue isoniazid
- continue ethambutol
- stop levofloxacin for pts on backbone regimen

Give as RH plus E

**ALT and or bilirubin are increased: See box below**

**Day 7:** Check ALT/bilirubin

**Day 8 –** If ALT/bilirubin unchanged:

- Add PZA*
- continue rifampicin
- continue isoniazid
- continue ethambutol

Give as RHZE

**ALT and or bilirubin increased: See box below**

**Day 11:** Check ALT (and bilirubin if initially raised)

**Day 12** – ALT/bilirubin unchanged:

- ***Congratulations, all TB drugs are rechallenged!***
- ***However there is still a risk of recurrence of DILI check ALT (and bilirubin if initially raised) at least weekly for the next 4 weeks***
- Restart ART 1-2 weeks after all TB drugs rechallenged
- Ensure patient has **correct duration of TB treatment**: ie **total** 2 months RHZE and 4 months of RH: this includes time on TB treatment prior to DILI, but not time taken to rechallenge
- If longer duration required (eg CNS TB) adjust accordingly

**ALT and or bilirubin increased: See box below**

***PZA rechallenge:**

- not needed if patient is already on continuation phase !
- if prolonged or very severe DILI or further relapse, avoid PZA
- Without PZA, 9 months of TB treatment is necessary rather than 6 months

**ART rechallenge:**

- Never rechallenge with nevirapine: change to dolutegravir or PI (avoid EFV)
- Rechallenge with efavirenz only if there is a more likely cause of DILI (eg recent start of TB treatment), and if mild DILI; otherwise change to DTG or PI
- If late EFV DILI suspected, never rechallenge, change to protease dolutegravir or PI

**Cotrimoxazole:**

- Do not rechallenge cotrimoxazole. Do not change to dapsone (can also cause DILI)

## What to do if ALT or bilirubin increases during rechallenge:

### What level of increase is a concern?

- Generally, if ALT increases to > 120 IU/L ***or*** bilirubin increases to > 40 µmol/l (> 2.3 mg/dl)

### Is the last drug added the cause?

- Not always, but a good first step
- Stop the drug added last
- For patients taking backbone drugs, keep 3 drugs in regimen – may need to add back the last backbone drug that was stopped
- For patients not taking backbone drugs, keep at least 2 drugs in the regimen – stop all drugs rather than continue with one drug
- Repeat ALT/bilirubin after 3 days

### If ALT/ bilirubin decrease when last drug is stopped:

- When ALT/bilirubin have returned to levels before the rechallenge, continue with the next drug in the rechallenge regimen
- If ALT/bilirubin remain unchanged after 3 days, continue with rechallenge of any remaining drugs
- If ALT/bilirubin remain unchanged when all other drugs are rechallenged, try a further rechallenge with the drug which failed the rechallenge

### If ALT/ bilirubin have not decreased:

- Repeat ALT/bilirubin after a further 3 days

### If ALT/bilirubin increase further despite stopping last drug? It may not be the last drug that is the cause

- stop the next most recent drug that was rechallenged – and follow steps above
- Follow 1 or 2 above depending on ALT and bilirubin levels

### Important notes:

- if at any time during the rechallenge, patient develops symptoms of liver disease (nausea, vomiting, right upper quadrant pain) stop all rechallenged drugs, and return to backbone regimen or no backbone

## Questions:

### Is it always necessary to wait for ALT < 100 and bilirubin to be normal before starting rechallenge?

- This is a general rule, but not absolute. For example, if it is taking a long time for these to settle, rechallenge can be started earlier, with close monitoring. Seek advice.

### What happens if rechallenge fails with a particular drug? Can a second rechallenge be done?

- Yes, a further rechallenge can be tried; for example if ALT increases significantly with rifampicin, and falls when it is stopped. If rechallenge has been successful with INH and PZA, a second rechallenge with rifampicin can be tried - with close follow up

### If the bilirubin only is raised, should all TB drugs be stopped?

- No, rifampicin is the most common cause and therefore this should be stopped, and HZE continued
- Levofloxacin should be added if the patient is severely ill with TB, or has CNS TB
- Stop cotrimoxazole if GGT or ALP are also elevated, or not available
- Check bilirubin every 3 days: rechallenge rifampicin when bilirubin is normal

### Does the duration of TB treatment need to be prolonged?

- Yes, the total duration of normal TB treatment should stay the same, but the time between stopping TB treatment and starting again on a normal regimen needs to be added to the total duration of treatment; respecting the normal duration of intensive phase and continuation phase for the pt (ie total of 6 months, 12 months if CNS TB)

## What if the rechallenge with one or more drugs has been unsuccessful?

Seek advice if uncertain – the following is a guide:

| Drug omitted | Regimen |
|---|---|
| **Isoniazid** | 6 RZE plus levofloxacin |
| **Pyrazinamide** | 2RHE + 4RH |
| **Rifampicin** | As for rifampicin resistant TB:<br>if the correct drugs cannot be accessed, use 6 months of HEZ plus levofloxacin can be used |
| **Rechallenge contraindicated:**<br>clinical evidence of fulminant liver failure – new onset of coma (GCS ≤ 8, persistent severe hypoglycaemia, clinical concern of coagulopathy (bleeding from gums, puncture sites) | As for DRTB: omit RHZ and use at least 4-5 available alternative drugs; duration of regimen as for DRTB, for example:<br>Levofloxacin/linezolid/cycloserine/clofazamine/ethambutol<br>Contact SAMU if medication access a problem |
| **Chronic liver disease** (for example, cirrhosis due to alcoholic liver disease | • If prolonged and difficult rechallenge – aim for rifampicin rechallenge only:<br>Rifampicin, ethambutol, levofloxacin or cycloserine for 12-18 months |

# Patients deteriorating or not improving on TB treatment

- This is a common reason for admission
- Patients on TB treatment should be improving, and not need hospital admission
- It is important to find the reason patients are not doing well, and correct the cause
- Many of these patients have disseminated TB, and non-specific symptoms It always important to review the initial diagnosis, as per algorithm

## 1. Essential background information

**1. Evolution of illness:**
- Pattern of improvement/deterioration

→
- Initial improvement on TB treatment?
- No improvement at all?
- Improved with TB treatment, deteriorated when ART started?

**2. Was TB proven?**
- How?
- When?
- Drug sensitive?

→ **If not proven or no sensitivity testing**
- Send all possible samples
- GeneXpert very helpful: sputum, CSF, urine

**3. TB medication history:**
- When started? Regimen?
- Detailed adherence history: from folder, patient family

→ **Poor adherence is a common cause:**
- Poor adherence - why?

**4. ART history:**
- On HAART?
- When started, which regimen
- Detailed adherence history: from folder, patient, family
- CD4 and VL history

→ **Timeline always important**: when started, when stopped, when restarted:
- Poor adherence: virological failure?
- Recently started ART: IRIS
- Not taking ART prior to admission, but prescribed because history of non-adherence not known: IRIS
- If poor adherence – why?

## 2. Consider specific causes

**Drug sensitive Tb proven, therapeutic level of drugs too low:**
- Dose too low
- Malabsorption: Chronic diarrhoea, vomiting
- Rifampicin levels sub therapeutic

**Not drug sensitive TB:**
- DR TB
- MAC

**Adverse drug effects:**
- TB meds
- ART
- Cotrimoxazole
- Efavirenz
- Others

**Additional diagnosis:**
- Original TB diagnosis correct, but now something extra

**Alternative diagnosis:**
- Original diagnosis of TB not correct

- **New OI**: eg pneumocystis, cryptococcal disease
- Other HIV related problem
- HIV unrelated problem

**If cause cannot be found:**
- Retake history… anything missed?
- Re-examine patient– again and again

←
- **Infection:** viral, bacterial, parasite, fungal Infections may be acute or chronic
- **Malignancy:** for example KS, lymphoma, lung cancer
- **Organ failure:** cardiac, renal, liver, blood, chronic lung disease … and look for the cause
- **Other chronic disease:** eg diabetes,
- Drugs, alcohol, smoking, traditional medication

# Kidney Disease in HIV positive hospitalized patients

**There are 3 main types of kidney disease in HIV positive patients**

**Acute Kidney Injury: (AKI)**

- Very common
- Reversible if detected early and managed optimally

AKI is a medical emergency

**Common causes – often there is more than one cause:**

- Hypovolaemia
- Sepsis
- Nephrotoxic drugs

**HIV associated nephropathy: (HIVAN)**

- Very common
- Reversible if detected early and managed optimally

**Low CD4 count and unsuppressed VL are most common risk factors:** however HIVAN occurs at all CD4 counts

- Patients with AKI or CKD may also have HIVAN

**Chronic kidney disease: (CKD)**

- CKD is irreversible
- Early diagnosis and optimal management can slow down the progress to end-stage kidney disease

**Common causes:**

- AKI or HIVAN that have been diagnosed late or poorly managed
- Hypertension, diabetes

**AKI is the most common type of kidney disease in hospitalized patients**

**Definition**: Sudden deterioration in kidney function

**Presentation**:

- Elevated creatinine on admission
- Patients with dehydration, shock or sepsis are at very high risk of AKI
- Creatinine is an emergency investigation and should be available 24/7, and is necessary for all patients needing hospital admission
- Urine dipsticks for protein are also an essential investigation: Detecting proteinuria is the reason for performing urine dipsticks

**AKI is very common in acutely ill patients:**

- Unless a patient has already been diagnosed with CKD, manage all patients with abnormal creatinine for AKI
- Mortality is high for severe AKI and around 60% of survivors of AKI have a high risk of CKD and shortened lifespan
- **For all patients with AKI or at risk of AKI – look for and correct the underlying cause. If AKI is not well managed immediately, it will be irreversible**

**Diagnosis: one or both of the following**

Rise in creatinine:

- Either relative rise compared to baseline, or high absolute level
- Creatinine clearance is not part of the definition: all formulae for creatinine clearance are not validated for AKI and cannot be used

Decreased urine output:

- Monitoring fluid input and urine output is difficult in under-resourced settings
- aim to monitor urine output at least for patients with severe AKI (see below)

**Definition and staging of AKI:**

KDIGO 2012

(Kidney Disease Improving Global Outcomes)

These criteria are agreed internationally, including low resource settings: before this, there were 30+ definitions of AKI

| KDIGO stage | Urine output | Relative creatinine rise *from baseline* | Absolute creatinine rise |
|---|---|---|---|
| **1 early** | less than 0.5mg/kg/hr for 6-12 hours | 1.5 – 2 fold rise within 7 days | increase in creatinine *by* > 26umol/L or 0.3mg/dL within 48 hours |
| **2 moderate** | less than 0.5mg/kg/hr for ≥ 12 hours | 2-3 fold rise within 7 days | |
| **3 severe** | less than 0.3mg/kg/hr for ≥ 24 hours or anuria for 12 hours | > 3 fold rise within 7 days | Increase in creatinine level *to* > 350 umol/L or > 4mg/dL |

**However, in many MSF HIV sites these criteria are difficult to implement:**

- Lack of HR to monitor urine output
- Lack of previous creatinine levels, so unable to assess if there is an increase from baseline

**A pragmatic interpretation of KDIGO guidelines**

**Document 'AKI' or 'severe AKI' in the patient's folder, on prescription sheet and on input-output chart**

Severe AKI:

This includes any of the following:

- Creatinine > 350 umol/L or > 4mg/dL: on admission or developing during admission
- Increase in creatinine by 2 fold or more within 7 days
- Oliguria: < 400mls in 24 hours – this is a useful general guideline
  More accurately – if urine output <0.3ml/kg/hr for 24 hours or more (for 50kg patient, this is <15mls/hr or < 360 mls of urine in 24 hrs)
- Anuria for > 12 hours
- Patients with severe AKI need the highest level of care available: assessment by a senior clinician, and high care/ICU as available
- For ongoing management and monitoring: see 'severe AKI package of care' page 24

AKI other than severe AKI:

- Patients with AKI that does not meet the criteria for severe AKI, or those at high risk of AKI

This includes:

- Creatinine above upper limit of normal, or 1.5 fold risk from previous creatinine if known
- Normal creatinine: Females < 90 µmol/L or < 1.0 mg/dL
  Males < 110 µmol/L or < 1.2 mg/dL

There is some variation between laboratories; use your own laboratory levels

- Patients who are dehydrated, with shock or with severe diarrhoea and vomiting with normal creatinine – these patients are at high risk of AKI, which may develop in hospital without optimal management of rehydration
- For ongoing management and monitoring: see 'AKI package of care'

**Approach to the management of patients with AKI**

Emergency management: ABCDE approach

Look for and treat the underlying causes

**A** – Airway

**B** – Breathing

**C** – Circulation

**D** – Disability – particularly reduced consciousness

**E** – Exposure – examine the patient

For AKI – circulation is frequently abnormal: assess fluid status rapidly.

However always correct A and B if necessary before moving to C

## Hypovolaemia

**Causes of hypovolaemia:**

- Shock – inadequate blood flow to organs and tissues:
  - Most commonly hypovolaemic shock, septic shock
- **Dehydration:**
  - Diarrhoea, vomiting
  - Poor fluid intake – AKI can develop in hospitalized pts who are confused or weak and are not drinking enough water

**Assess fluid status:**

Document your findings well to enable response to treatment to be assessed

**Hypovolaemia: clinical signs**

- Systolic BP < 90mmHg
- RR > 20 breaths per minute
- HR > 90 bpm
- Pulse volume: weak, thread pulse
- Capillary return > 3s
- Hands and/or feet cold to touch; upper limb is warmern
- Dehydration: dry mucous membranes, decreased skin turgor, sunken eyes
- Urine output < 0.5ml/kg/min

- Passive leg raising suggests fluid responsiveness: HCW to raise both of patient's legs from the hips to 45 degrees, which causes a fluid bolus of 300ml of blood into the right ventricle. Immediately measure SBP (within 30-90s). If SBP has increased by ≥ 10mmHg, this shows fluids are needed

**Fluid resuscitation and Replacement**

**Input-output monitoring**

**Daily prescription of fluids**

**3 indications for fluids:**

**Resuscitation if hypovolaemic/septic shock:**

- 500-1000ml of crystalloid as a bolus over 15 mins
- Re-evaluate: further fluid boluses as necessary, if poor response and more than 2000L in total in boluses, re-evaluate with a senior doctor

**Fluid replacement:**

- Estimate fluid losses, including ongoing loss eg diarrhoea/vomiting and replace with IV crystalloid

**Maintenance:**

- At least 30ml/kg/day in addition to fluid replacement: many patients with AKI need 3L of IV fluid per day, and tolerate this well. Ensure the patient has water available to drink

Assess fluid status frequently: every 1-2 hours if shocked, at least daily if haemo-dynamically stable

**Ensure fluid overload is detected early:**

- Shortness of breath
- HR > 90 bpm
- RR > 20 breaths per minute
- Elevated JVP
- Peripheral oedema
- Fine basal crepitations

Treatment of fluid overload:

- Restrict fluids: monitor input and output
- Diuretics: furosemide IV 40-80mg immediately and twice daily

**Treat the underlying cause of hypovolaemia**

- If diarrhoea, vomiting – treat the likely causes
- Septic shock – treat for sepsis (see below)

## Sepsis

**Definition:**

- Suspected infection with organ dysfunction
- Organ dysfunction: RR >22, altered mental state, systolic BP < 100mmHg
- Septic shock may be present
- Causes: bacterial infection, TB also causes the same clinical picture, both may occur together

**Treat septic shock if present**

**Look for and treat the underlying cause**

**Look for the likely source of infection – for example respiratory tract, urinary tract. A source is not always obvious in advanced HIV**

- Bacterial infection suspected: blood cultures, antibiotics according to local protocols – first dose to be given within 1 hour (do blood cultures first if this does not delay antibiotics)
- Clinical suspicion of TB: TB investigations as for all patients with advanced HIV, empiric treatment – first dose to be given within one hour

## Nephrotoxic drugs

**Nephrotoxic drugs – most commonly:**

- Tenofovir
- Aminoglycosides: gentamicin, amikacin
- Ask the patient to show you all the medicine they are taking: Specifically ask about non-prescribed medication, including NSAIDS, aspirin and traditional medication
- Drugs that rarely cause AKI: rifampicin and cotrimoxazole: see below

**Stop nephrotoxic drugs immediately: ensure the patient and family are informed**

- Change tenfovir to ABC immediately
- Stop NSAIDS and aspirin
- Aminoglycosides – review ongoing need for antibiotics. If there is no alternative, for example aminoglycosides are essential for treatment of resistant bacterial infection:
    - discuss with a senior doctor
    - ensure good IV and oral hydration
    - monitor creatinine every 2 days or more frequently
    - give for as short a duration as possible

**Drugs that rarely cause AKI:**

**Rifampicin and cotrimoxazole**

Note that cotrimoxazole is not contraindicated in AKI

- Mechanism of AKI: hypersensitivity reaction, rather than direct nephrotoxicity: causing Acute Interstitial Nephritis (AIN)
- These are rare but serious causes of AKI: ***most*** patients with advanced HIV and AKI are taking both of these medications, but ***very rarely*** are they the cause of AKI
- Think of these only if there is no other more common cause, and AKI occurred after starting either drug

AIN caused by rifampicin:

- AKI typically occurs if rifampicin is restarted, for example after treatment interruption or if there has been a previous course of TB treatment
- Stop rifampicin: use DILI algorithm for alternative TB drugs
- Start prednisone 1.5mg/kg/day for 2-4 weeks
- Rechallenge only if creatinine rapidly normalises, there is no available alternative to rifampicin and the patient can be closely monitored in hospital

AIN caused by cotrimoxazole:

- If there is strong clinical suspicion that cotrimoxazole is the cause of AKI, stop the drug, do not rechallenge and avoid in the future: ensure the patient and family are informed

## Monitoring and ongoing management of AKI
## If not improving or deteriorating, look again for the underlying causes

AKI package of care:

- IV and oral fluids for rehydration, fluid replacement and maintenance
- Monitoring urine output:
    - Ask the patient/family how often they are passing urine, expect at least 4 times a day
    - Patients with shock on admission or developing during admission should have a urinary catheter to measure urine output for 24-48 hours
    - If concern there is olguria (< 0.5ml/kg/hr – for 50kg patient this is < 25mls/hour, and < 600mls in 24 hours) then insert a urinary catheter and ensure adequate rehydration: remove catheter after 24-48 hours if urine output is good

Repeat creatinine and electrolytes every 3 days

- If creatinine increases more than 2-fold within a week, or if absolute creatinine > 350umol/L: move to 'Severe AKI care' package (below)

Severe AKI package of care:

- Patients with severe AKI need the highest level of care available: assessment by a senior clinician, and high care/ICU as available
- Ensure all underlying causes have been identified and managed
- IV and oral fluids for rehydration, replacement and maintenance
- Monitor urine output using urinary catheter: document output every 6 hours: fluid input should also be documented
- Request electrolytes: sodium and potassium
- Repeat creatinine and electrolytes every 2 days
- Update senior doctor at least every 2 days

**Note**: it is not necessary to immediately adjust doses of drugs excreted by the kidneys for patients with AKI

Most AKI is reversible if treated promptly: do not adjust drug doses in the first 5 days of admission – and only after this if creatinine is not improving or is deteriorating

AKI package of care:

- Ensure all underlying causes have been identified and managed
- IV and oral fluids for rehydration, fluid replacement and maintenance

Monitoring urine output:

- Ask the patient/family how often they are passing urine, expect at least 4 times a day. If the patient is capable of urinating into a jug/bottle, urine output can be documented over 24 hours: aim for > 0.5ml/kg/hr
- If concern there is olguria (< 0.5ml/kg/hr – for 50kg patient this is < 25mls/hour, and < 600mls in 24 hours) then insert a urinary catheter and ensure adequate rehydration: remove catheter after 24-48 hours if urine output is good
- Patients with shock on admission or developing during admission should have a urinary catheter to measure urine output for 24-48 hours

Repeat creatinine and electrolytes every 3 days

- If creatinine increases more than 2-fold within a week, or if absolute creatinine > 350umol/L: move to 'Severe AKI care' package of care, as above

## The 2 other common causes of kidney disease in advanced HIV

### HIV Associated Nephropathy: HIVAN

- Common in HIV patients with unsuppressed viral load
- Effective ART prevents HIVAN: incidence and mortality were high in the pre-ART era
- Most common at low CD4 counts; however occurs at all CD4 counts: WHO stage 4 irrespective of CD4 count

### Clinical presentation and diagnostic criteria

- Abnormal creatinine (but not always, HIVAN may cause proteinuria with a normal creatinine)
- There must be proteinuria for a diagnosis of HIVAN; therefore dipstick essential
- Usually large echogenic kidneys on ultrasound

### Management

- Efficient ART: start ART if naïve, change regimen if failure; avoid tenofovir
- Enalapril to reduce proteinuria: proteinuria damages kidney tubules which worsens AKI
- Start at 2.5mg orally twice daily: increase weekly as tolerated. Hypotension is rare when starting with low dose enalapril and slowly increasing.
- Avoid nephrotoxic drugs. Rapid and optimal management of AKI if coexists
- 'General kidney care package' as for chronic kidney disease (see below)

### Chronic Kidney Disease

**Definition:**

- eGFR < 60ml/min for 3 months or more
- use CKD-EPI formula to calculate (widely available in several medical calculation apps)

**Most common causes:**

- Delayed and poorly treated AKI and HIVAN
- Diabetes, hypertension

**Chronic kidney disease is irreversible:**

- Progresses to end-stage renal failure and death but progress can be slowed by optimised management

**Clinical presentation:**

- Usually asymptomatic, found incidentally when creatinine is requested or proteinuria is found on dipsticks
- There may be superimposed AKI: patients with CKD have kidneys that are vulnerable to hypovolaemia, sepsis and nephrotoxic drugs
- Diabetes and hypertension: may be undiagnosed or already known – there may be other target organ damage such as peripheral neuropathy or diabetic retinopathy in diabetes or cardiac failure in hypertension

**End-stage renal failure:**

- Small kidneys on ultrasound (<9cm)
- Severe anaemia, often < 5g/dL. This is caused by lack of erythropoietin, which is made by the kidneys. AKI and mild/moderate CKD do not cause anaemia.
- Fluid overload may be the presenting complaint, and most severe problem for the patient. Fluid restrict and give IV diuretics

## Assessment

**Look for and treat reversible causes:**

- Look for diabetes and hypertension; if previously diagnosed, has there been optimal management of these conditions
- Identify and treat hypokalaemia and hyperkalaemia
- Patients with CKD may also develop AKI: if creatinine has increased in a patient known with CKD, also look for AKI – identify and treat the causes of AKI
- Virological suppression: HIVAN may worsen CKD if there is a high viral load

## Management

**Optimal management will slow the progression to end stage kidney disease**

- Treat any reversible causes identified in history, examination and blood tests above
- General kidney care package:
    - Optimal treatment of diabetes
    - Optimal treatment of hypertension: aim for BP 130-140/90
    - If obese, weight loss and exercise will improve both diabetes and hypertension
    - Stop smoking
    - Avoid nephrotoxic drugs: ensure the patient knows to avoid NSAIDS and aspirin, and traditional medication
- Ensure effective ART regimen and regular viral load testing
- Women of reproductive age: CKD has major risks for both mother and fetus. Ensure women have access to counselling and contraception.
- Dose adjustment of drugs that are excreted by the kidneys; use CKD-EPI to calculate creatinine clearance, and adjust doses accordingly
- If end-stage kidney disease develops with fluid overload, restrict fluids, optimize comfort, discuss situation with the patient and family. The patient now needs palliative care.

# Ascites in HIV positive patients

**Ascites – fluid in the abdominal cavity**

- Ascites is always abnormal, and a sign of severe underlying disease
- The most important issue is to look for and treat the underlying cause

**Clinical presentation:**

- Abdominal swelling, distension of flanks
- Symptoms and signs of the underlying disease

**How much ascites is present?**

- Detectable with ultrasound: 10-20ml
- Detectable clinically: 1000ml
- Massive, tense ascites: 12 litres or more

**Common causes of ascites in advanced HIV**

## Infection/inflammation of peritoneal cavity:

- **TB and TB IRIS**– the most common cause in advanced HIV
- **Malignancy:**
  - Kaposi's sarcoma
  - Lymphoma
  - Other abdominal malignancy; ovarian, gastrointestinal, pancreas: not common in hepatocellular carcinoma
- **Rare in advanced HIV:**
  - Other inflammatory causes:
    - Pancreatitis
    - Autoimmune disease, for example Systemic Lupus Erythematosis
  - Other infections:
    - Filiariasis

## Fluid shifts – water and sodium:

**Mechanisms:**

- Low albumin causing low oncotic pressure
- Liver disease or fluid overload causing high pressure in portal vein, and loss of water and sodium into abdomen

Note: There may be other signs of low oncotic pressure or fluid overload, for example limb oedema

**Specific causes:**

- Liver disease:
  - Cirrhosis – most often due to alcohol, hepatitis B
- Cardiac disease:
  - cardiac failure
  - constrictive pericarditis
- Renal:
  - nephrotic syndrome
  - end stage renal disease
- Protein losing states:
  - gastrointestinal pathology

**Approach to the patient with advanced HIV and ascites**

History:

- New presentation or previously diagnosed?
- Duration
- Severity
- Symptoms relating to ascites
- Symptoms of the underlying cause

**Symptoms of ascites:**

- Abdominal pain and distension
- Shortness of breath – splinting of diaphragm due to massive ascites

**Symptoms of the underlying cause:**

Symptoms of TB, malignancy and other causes of ascites are often non-specific and overlap:

- Loss of weight and fatigue are common in disseminated TB, malignancy, chronic liver disease, cardiac failure
- shortness of breath may occur in TB (pulmonary TB) and malignancy (pulmonary metastases) and cardiac failure
- Confusion may occur with neurological TB, malignancy (primary or secondary brain cancer), hepatic encephalopathy, end-stage renal failure

**Patients with ascites often have pleural effusions:**

- Most causes of ascites also cause pleural effusions

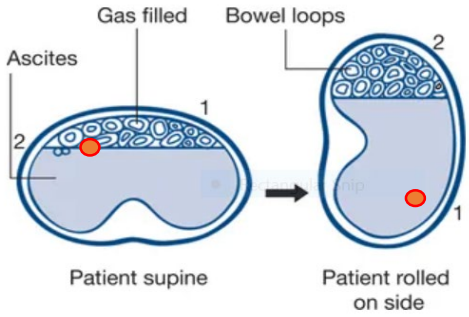
**Clinical Examination**

- Clinical diagnosis of ascites
- signs of the underlying cause

**Note:** there may be more than one cause of ascites in patients with advanced HIV, For example TB and heart failure may co-exist

**Clinical diagnosis of ascites – 'shifting dullness':**

- When a patient with ascites is supine, the intestines float in the midline
- on percussion: the midline is tympanic (like a hollow drum due to gas in the intestines), and there is dullness in the flanks (fluid)
- Turn the patient to the right side and wait 30 seconds; the fluid shifts within the abdomen due to gravity
- Dullness shifts to the dependent part of the abdomen, and tympany shifts to the highest part: the umbilical area is now dull to percussion, and the left flank is tympanic




Area 1 is tympanic when supine and dull in lateral position

Area 2 is dull when supine and tympanic in lateral position

● umbilicus

**General and abdominal examination; look for:**

- Wasting
- Lymphadenopathy
- Fluid overload: elevated jugular venous pressure, periorbital oedema, anasarca (general swelling of the whole body), pitting oedema of lower limbs
- Hepatosplenomegaly: (TB, malignancy, cardiac failure - pulsatile hepatomegaly)
  With cirrhosis, liver may be small

**Other organ systems:**

- Clinical evidence of TB: respiratory, neurological systems
- Heart: signs of heart failure
- Liver: signs of chronic liver disease

See summary on page 4 on ascites in 'TB and TB IRIS'

**Investigations:**

Diagnostic ascitic tap

Lower left lateral flank: at least 20ml of fluid required

If ultrasound available, use this to visualize ascites and mark site for tap

**Contraindications:** clinically a safe procedure, contraindicated only if platelets < 20 x $10^9$/L or clinical evidence of coagulopathy

**Tests for ascitic fluid – do all that are available:**

- Colour ('aspect') – document in patient folder:
  - Clear (usually transudate), cloudy (exudate or infection), straw coloured or lemon yellow (TB), bloody (KS, other malignancy, trauma, ruptured ectopic pregnancy), milky (chylous ascites – see summary page 4)
- **Cell count and differential - Lymphocyte and neutrophil numbers and percentage:**
  - Lymphocyte predominant: TB or malignancy; however, zero lymphocytes do not exclude
  - Neutrophils > 250/$mm^3$ – Spontaneous Bacterial Peritonitis (SBP – see summary page 4): if high, also request gram stain and bacterial culture and sensitivity of ascitic fluid
- **Albumin or protein:**
  - Albumin level is best
  - Protein if albumin not available
  - If neither available: Rivalta test (positive Rivalta test in ascites = protein ≥ 30g/L)
- **Investigations for TB:**
  - Adenosine deaminase (ADA): produced by activated lymphocytes, level > 30 IU/L is typical of TB (may also be raised in malignancy)_
  - Xpert MTB/RIF: sensitivity 30-60%, **negative Xpert MTB/RIF cannot rule out TB**
- **Other investigations for specific causes:**
  - Cytology – if malignancy suspected, if available
  - Amylase – if pancreatitis suspected, request for both ascitic fluid and serum: amylase is higher in ascitic fluid than serum
  - Nephrotic syndrome: dipstick for proteinuria

**Additional investigations Of the underlying cause**

**As for all patients with advanced HIV:**

- Point of care tests: CD4, Serum CrAg, TB LAM, glucose
- TB investigations

**Other laboratory investigations:**

- creatinine, electrolytes. Do ALT and bilirubin if jaundice, hepatomegaly, or clinical concern regarding liver disease
- Serum Albumin: normal is > 30g/L, some variation between laboratories
- Request serum protein if albumin is not available: normal is > 60g/L, some variation between laboratories
- Hepatitis B; Hepatitis C depending on setting

**Imaging**:

- CXR for all patients:
  - Look for TB, metastatic disease, pulmonary oedema, pleural effusion
- Abdominal ultrasound:
  - confirm ascites, hepatosplenomegaly, abdominal TB or malignancy (lymph nodes, splenic micro-abscesses)
  - 'stranding' on ultrasound: fibrous strands shows it is an exudate, and typical of TB

**Note**: blood in the abdominal cavity may be bloody ascites (KS or other malignancy) or frank blood due to trauma or ruptured ectopic pregnancy

**Exudate or transudate?**

**What does this mean?**

- Exudate: an inflammatory fluid, with a high albumin and total protein content
- Transudate: results from shift of fluid and sodium into the abdominal cavity from blood and lymphatic vessels. Albumin and protein do not shift, so their levels are low in transudates

**How is this information useful?**

- This is important for the diagnosis of the underlying cause

**Exudates:**

- All causes of infection/inflammation of peritoneal cavity – see 'causes of ascites'
- Nephrotic syndrome

**Transudates:**

- All causes due to fluid shifts, except nephrotic syndrome
- Nephrotic syndrome: clues to diagnosis are heavy proteinuria, low serum albumin and periorbital/peripheral oedema

Diagnosis of exudate vs transudate:

**The most accurate method is to work out the Serum Albumin Ascites Gradient (SAAG):**

- Definition: Serum albumin level in g/L *minus* ascites albumin level in g/L
- SAAG < 11g/L (1.1g/dL) : albumin in ascitic fluid is high relative to serum, so the difference between these values is low: this is an exudate
- SAAG > 11g/L (1.1g/dL): albumin in ascitic fluid is low compared to serum, so the difference between these 2 values is high: this is a transudate

**If albumin is not available but protein level is available:**

- Exudate: Total protein > 30g/L – if the serum protein is normal (> 60g/L)
- Transudate: Total protein < 30g/L – if the serum protein is normal (> 60g/L)
- There is no 'gradient formula' for protein, analogous to SAAG

**If the serum protein is low (common in patients with TB, malignancy or malnutrition), ascitic fluid protein < 30g/L cannot exclude an exudate**

**If both albumin and protein are not available:**

- Rivalta test on ascitic fluid: positive if protein > 30g/L (note Rivalta test is used for ascites and for pleural effusions)
- A positive Rivalta test confirms an exudate
- A negative RIvalta shows ascitic fluid protein is < 30g/L: this shows that the ascitic fluid is a transudate, *assuming that the serum protein level is normal*

**If the serum protein is low, a negative Rivalta test cannot exclude an exudate: a negative Rivalta test does not exclude TB**

- If albumin is available for selected patients only due to cost, serum/ascitic fluid albumin levels can be reserved for patients with suspected TB with a negative Rivalta test

**Management:**

Therapeutic ascitic tap

**Indications:**

- Relieve pain and discomfort
- Relieve dyspnea due to splinting of diaphragm

A therapeutic tap temporarily relieves symptoms, it is not a 'cure' for ascites

**Procedure:**

- Lower left flank, using intravenous cannula or needle and IV tubing. (remove at end of procedure)

**How much ascites can be removed safely?**

- Up to 4L can safely be removed in a single episode (albumin infusion is not required)
- Removing more than this can cause haemodynamic shifts
- Can be repeated as needed for symptom relief

**Definitive management:**

Treat the underlying cause

Regular therapeutic taps may be necessary if the cause is not reversible (for example, cirrhosis)

**Exudates:**

- Manage the underlying cause
- Spironolactone and furosemide have no role in treatment of exudates

**Transudates:**

- Manage the underlying cause
- Remove sodium and water:
  - Spironolactone: start at 100mg orally daily; increase by 50-100mg weekly
  - Furosemide: start at 40mg IV or orally daily; increase as necessary
  - Monitor potassium levels (spironolactone increases $K^+$; furosemide decreases $K^+$)

**Monitoring resolution of ascites**:

- Abdominal girth measurement at the level of the umbilicus
- Monitor loss of weight for causes due to fluid shifts

**Notes on specific conditions**

**TB/TB IRIS – the most common cause in patients with advanced HIV:**

Ascitic fluid:

- Usually straw coloured or lemon yellow
- Exudate – however a negative Rivalta test does not exclude TB, as noted above
- Lymphocytes may be present or may be normal; ADA usually raised (however, poorly available), Xpert MTB/RIF may be positive; negative does not exclude TB
- May be other manifestations of abdominal TB:
  - Hepatomegaly, splenomegaly with splenic micro-abscesses (TB granulomas visible on ultrasound), lymphadenopathy – often painful
- May be symptoms/signs of TB in other organ systems

Start empiric treatment of TB if high clinical suspicion

- Paradoxical TB IRIS: prednisone 1.5mg/kg as single daily dose for 2 weeks; reduce to half this dose for 2 further weeks if good resolution of symptoms: if not, continue higher dose and review with senior doctor

**Malignancy:**

- If definitive diagnosis/treatment not possible, and TB either ruled out or already on treatment – relieve symptoms with regular therapeutic taps, analgesia including opioids, discuss with patient and family

**Notes on specific conditions**

**Chylous ascites:**

- Milky ascites – due to high triglyceride content ( >110 mg/dL or (1.24 mmol/L)
- Cause – blockage o rupture of lymphatic drainage
- Causes: TB/TB IRIS (most common cause in advanced HIV), can occur with malignancy (rarer); XpertMTB RIF may be positive; negative Xpert does not rule out TB
- May occur with chylothorax (chylous pleural effusion)
- Management:
    - TB treatment
    - High protein, low fat diet
    - Therapeutic ascitic tap(s) according to need for symptom relief

**Spontaneous Bacterial Peritonitis:**

- Infection of ascites – due to translocation of organisms across the bowel wall
- Most common: E coli, Klebsiella, Enterococci
- Most commonly occurs in ascites due to cirrhosis, may occur in ascites due to other causes
- Symptoms: fever, abdominal tenderness, confusion – however may be none
- Diagnosis: neutrophils > 250/$mm^3$ on ascitic tap: request gram stain and bacterial culture/sensitivity
- Urine dipstix are a rapid method of diagnosis; if ascitic fluid is positive for leucocytes, this suggests SBP
- Treatment: ceftriaxone 2g daily plus ciprofloxacin 400mg IV every 12 hours (change to 500mg orally every 12 hours after 2 days if improving). Duration 5 days: continue if neutrophils remain > 250/$mm^3$ on repeat ascitic tap on day 4
- Mortality 25% or more: there is a high risk of recurrence

# Anaemia in HIV positive patients: look for and treat the *underlying cause*

## Causes of anaemia

**Definition:**
- Clinically important anaemia: Hb < 8
- Severe anaemia: HB < 5

### Blood loss

**Clinically obvious:**
- Haemoptysis
- Haematemesis
- Malaena

**Easily missed:**
- Kaposi's sarcoma: gastro-intestinal bleeding is common – look for KS on the skin and palate
- Kaposi's sarcoma also causes bloody pleural/pericardial effusions/ascites
- Ectopic pregnancy, miscarriage
- Cervical cancer

Note: hookworm – common, but rarely the only cause; treat all patients with albendazole 400mg single dose and continue to look for other causes

****Note****

The same principles can be used to find the cause of anaemia in HIV negative patients: always look for and treat the cause

### Decreased production of red cells

**Bone marrow not working:**

TB is the most common cause of anaemia in HIV patients:
- All patients with anaemia need TB LAM, Xpert on urine, sputum or other samples; start empiric treatment if high clinical suspicion of TB, particularly for patients with advanced HIV
- Advanced HIV also contributes to bone marrow suppression

Drugs:
- AZT: most common in first 6 months of treatment, and with low CD4 counts
- Cotrimoxazole

**Lack of raw materials:**
- Iron deficiency
- Folate deficiency

Note: these are rarely the only cause; treat all patients with iron and folate, and continue to look for other causes
- Severe chronic renal failure: lack of erythropoietin

### Increased destruction of red cells

**Bone marrow is making red cells: but they are destroyed rapidly**

Most common cause:
- Malaria

Drugs:
- Cotrimoxazole
- Rifampicin

Other causes:
- Splenomegaly from any cause
- Sickle cell disease; prevalence 1-3% in Malawi

Transfusion is not a cure for anaemia: find and treat the underlying cause

# Anaemia: investigations and management

## History and examination:

### Important points on history:

- Is this a new diagnosis of anaemia?
  - It is common that patients have had previous transfusions without investigation and treatment of the cause
- ART history: is your patient taking AZT?
- Other drugs: cotrimoxazole, rifampicin
- **TB history: are there symptoms of TB?**
  - wasting
  - fever
  - night sweats
  - cough
  - general body weakness
  - and many others (see 'clinical presentation of TB in HIV' poster)

### Important points on examination:

- Look for KS
- Look for PR bleeding
- Look for PV bleeding; pregnancy, examine for cervical cancer
- Look for splenomegaly
- **Look for TB:**
  - Pulmonary
  - Extrapulmonary is common: lymph nodes, pleural effusion, ascites

## Investigations:

- Full blood count
- CD4 count
- Other HIV point of care tests (CrAg if CD4 < 200)
- Malaria rapid test
- Creatinine; electrolytes if abnormal
- (reticulocyte count may be part of automated FBC: if high shows RBC destruction; low shows problem with RBC production

**TB Investigations:**

- TB LAM, Xpert on urine, sputum or any other body fluid samples, or pus from cold abscesses
- CXR, abdominal ultrasound\
- linical suspicion high: start TB treatment while awaiting results, or if results negative

**ART failure?**

- VL if on ART for more than 3 months

## Cause not found?

- If not on TB treatment, start empiric treatment unless clinical decision is that TB is excluded

**Taking TB treatment:**

- Is patient otherwise improving? See 'TB not improving on TB treatment' algorithm
- Rifampicin? see box on right

**Rare causes include:**

- Lymphoma
- 3TC/FTC
- In some countries: sickle cell disease, thalassaemia
- Parvovirus B19: takes several months to recover with effective ART and repeated transfusions
- Autoimmune haemolysis: steroids (note Coomb's test is commonly positive in HIV, so cannot be used as a diagnostic test for haemolysis

## Management:

### 1. General management:

**When to transfuse – most anaemia in HIV pts is chronic, and does not need correcting to the normal range:**

***Remember!!!***
***Transfusion gives a temporary rise in Hb: it is not a 'cure' for anaemia***

- Hb < 5.5
- HB > 5.5 and:
  - Active bleeding, eg haemoptysis
  - Pregnant
  - Respiratory distress: respiratory rate > 30 or saturation < 90%
  - Hypotension
- If blood is readily and continuously available, some units may be able to use a higher threshold for transfusion

**All patients:**

- Albendazole 400mg single dose for hookworm
- Iron and folate to treat nutritional deficiency
- **Remember: both are common but rarely the only causes: continue to look for other causes**

### 2. Specific management:

- Cotrimoxazole: stop if Hb < 6; this is rarely the only cause, restart when other causes identified and treated
- AZT: change to ABC or TDF (seek advice if unsure which drug): check VL result to see if regimen switch is needed rather than single drug change
- Rifampicin: stop if severe anaemia (Hb < 5). Rifampicin is a rare cause of anaemia; and TB treatment without rifampicin is prolonged and needs alternative drugs. Always seek advice.
- Start TB treatment if high clinical suspicion: remember negative TB investigations do not exclude TB

# Treatment of common Opportunistic Infections

## Treatment of TB

**Note: Empiric TB treatment is often necessary for patients who are seriously ill with high clinical suspicion of TB, particularly neurological TB. Proof of TB (LAM or XPert) is not a pre-condition for treatment in PLHIV; delay in starting treatment increases the risk of dying from TB. Treatment should be started within one hour for seriously ill patients. LAM, Xpert MTB/RIF and Xray thorax should still be requested to provide evidence for TB and rifampicin sensitivity; however testing must not delay treatment initiation when urgent.**

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| **Drugs for drug sensitive TB:**<br>**RHEZ** | R – Rifampicin<br>H – Isoniazid<br>E – Ethambutol<br>Z – Pyrazinamide<br><br>See local TB protocols for dosing of Fixed Dose Combination tablets<br><br>Isoniazid induced peripheral neuropathy (PN):<br>• Prevention – for all pts: Vitamin B6 (pyridoxine) 25 mg daily<br>• Treatment – if symptoms/signs of PN: 50-200mg daily |
| **Pulmonary TB**<br>**Disseminated TB**<br>**Most Extrapulmonary TB:** ***for exceptions see below*** | • 2RHEZ plus 4 RH (2 months of RHEX plus 4 months of RH) |
| **TB Pericarditis** | • 2RHEZ plus 4 RH<br>• Prednisone: same protocol as for neurological TB (see below) |
| **Bone TB**<br>**Orally tt's disease (vertebral TB) or any other bone involvement** | • 2RHEZ plus 10 RH |
| **Timing of ART initiation or switch from first line to second line for patients** who do not have neurological TB | • Within 2 weeks of initiating TB treatment<br>• For hospitalized patients, this should be done before the patient is discharge |
| **Neurological TB:**<br>• TB meningitis<br>• Suspected tuberculomas<br>• TB affecting spinal cord<br><br>Start treatment immediately based on clinical suspicion | • 2RHEZ plus 10RH<br><br>Plus Prednisone:<br>• 1.5mg/kg/day orally as a single daily dose for 6 weeks<br>• Followed by half this dose – 0.75mg/kg/day orally as a single daily dose for 2 weeks<br>• For patients with reduced consciousness or otherwise unable to swallow: dexamethasone 8mg IV 3 times a day until able to take oral medication<br>• Omeprazole 20mg orally daily for the duration of prednisione treatment is recommended |
| **Timing of ART initiation or switch to second line for patients** with neurological TB | • Start or switch ART 4 weeks after initiation of TB treatment<br>• Do not start or switch ART at the same time as stopping prednisone -<br>  ○ prednisone 1.5mg/kg/day orally should be continued for a further 2 weeks as above<br>  ○ Followed by 0.75 mg/kg/day orally for 2 weeks |
| **If drugs for drug sensitive TB are contraindicated:**<br>• Drug Induced Liver Injury (DILI)<br>• Skin hypersensitivity | • See MSF DILI algorithm for protocol and doses<br>• If an alternative regimen is needed – give 3 drugs:<br>  ○ Ethambutol<br>  ○ Quinolone: Levofloxacin first choice, Moxifloxacin second choice<br>  ○ Linezolid or Clofazamine or Cycloserine or Amikacin (see DILI algorithm) |
| **Rifampicin resistant TB** | • Use your national protocols |
| **TB IRIS** | • Prednisone 1.5mg/kg/day orally as a single dose for 2 weeks<br>• Reduce to 0.75mg/kg/day orally for a further 2 weeks<br>• Omeprazole 20mg orally daily for duration of prednisione treatment is recommended<br>• Procedures: repeated aspiration of lymph nodes, pleural effusion, ascites to reduce symptoms |

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| **TB IRIS**<br>*(Cont.)* | If symptoms/signs of IRIS have significantly improved or resolved after 4 weeks of prednisone:<br>• Stop prednisone<br>**If symptoms/signs do not improve or worsen at any stage:**<br>• Continue high dose prednisone for a further 2 weeks, then reduce dose slowly – for example by 10mg every 7 days<br>• Some patients need prednisone treatment for IRIS for many months |
| **Cotrimoxazole for prophylaxis and treatment of Opportunistic infections**<br>For treatment doses: add folic acid 5mg orally daily | |
| **Cotrimoxazole preparations** | • Available in 960mg tablets (800mg sulfamethoxazole 800mg and trimethoprim 160mg) and 480mg tablets (sulphamethoxazole 400mg and trimethoprim 80mg). Which is used differs between countries: ensure you know which dose you have available<br>• Oral cotrimoxazole has excellent absorption; if patient is unable to swallow or is acutely and severely ill, IV cotrimoxazole can be used for treatment if available.<br>• IV cotrimoxazole is available in 480mg vials: 1x 480mg vial is equivalent to 1 x 480mg tablet for dosing calculations |
| **Cotrimoxazole prophylaxis:**<br><br>Lifelong, irrespective of CD4 count for countries with high incidence of malaria and bacterial infections | Prevention of PJP, toxoplasmosis, Isosopora belli, bacterial pneumonia<br>• 1 tablet of 960mg orally daily<br>***Or:***<br>• 2 tablets of 480mg orally daily<br><br>Dapsone 100mg daily orally is an alternative if previous mild hypersensitivity reaction to cotrimoxazole (maculpapular skin rash, no mucous membrane lesions, no systemic symptoms for example fever or hepatitis, no anaphylaxis). However dapsone is also a sulfonamide and cross-reactivity is common; it is ineffective prophylaxis for toxoplasmosis and bacterial infection. For mild hypersensitivity cotrimoxazole can often be rechallenged or desensitization performed. Dapsone is also very expensive, and long-term treatment is not possible in most countries.<br><br>For more severe hypersensitivity or DILI, do not rechallenge with cotrimoxazole or give dapsone: prevention of OIs relies on ART increasing the CD4 count. |
| **Pneumocystis jirovecii pneumonia (PJP)**<br><br>Indication for treatment:<br>RR> 30 or saturation < 90%, with CD4 < 200 or unknown | **Cotrimoxazole – duration 21 days:**<br>•Total daily dose is 1 tablet of 960mg orally for every 8kg of body weight; divide total dose into 3-4 individual doses. Maximum 8 tablets per day<br>***Or:***<br>• Total daily dose is 1 tablet of 480mg orally for every 4kg of body weight; divide total dose into 3-4 individual doses. Maximum 16 tablets per day<br><br>**Plus Prednisone orally – duration 21 days**<br>• Day 1-5: 40mg 2 times a day<br>• Day 6-10: 40mg daily<br>• Day 11-21: 20mg daily<br>• Omeprazole 20mg orally daily for duration of prednisione treatment is recommended<br>• Follow above schedule to decrease prednisone only if there is a good clinical response: if the patient is not responding well, continue the highest dose of prednisone<br>• If prednisone is also indicated for treatment of TB (neurological TB, pericardial TB, TB IRIS) – look at both PJP and TB protocols for steroid dosing, and use the highest dose with duration according to TB protocol<br><br>**Alternative treatment if cotromoxazole is contraindicated (hypersensitivity, hepatotoxicity):**<br><br>**Give both for 21 days:**<br>• Primaquine 15mg orally daily<br>Plus:<br>• Clindamycin 600mg 3 times a day orally. If the patient is severely unwell or unable to swallow and IV formulation is available, give 600mg IV 3 times daily for the first 3-5 days<br>If gastrointestinal side effects (nausea, epigastric pain, abdominal pain – can occur with high dose oral treatment) reduce oral dose to 450mg 3 times daily<br><br>• **Give steroids as above** |

| | |
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| **Toxoplasmosis**<br><br>Indication for treatment:<br>Neurological symptoms/signs and CD4 < 200 or unknown | **Cotrimoxazole – duration 6 weeks:**<br>• Total daily dose is 1 tablet of 960mg orally for every 16kg of body weight; divide total dose into 2-3 individual doses. Maximum 4 tablets per day<br>***Or:***<br>• Total daily dose is 1 tablet of 480mg orally for every 8kg of body weight; divide total dose into 2-3 individual doses. Maximum 8 tablets per day<br>**Alternative treatment if cotromoxazole is contraindicated (hypersensitivity, hepatotoxicity):**<br>**Give all 3 drugs for 6 weeks:**<br>• Pyrimethamine 200mg orally as loading dose, then 50mg orally daily if weight less than 60kg, or 75mg orally daily if weight 60kg or above<br>Plus:<br>• ***Folinic*** acid 15mg orally daily<br>Plus:<br>• Clindamycin 600mg 3 times a day orally.<br>• If the patient is severely unwell or unable to swallow and IV formulation is available, give 600mg IV 3 times daily for the first 3-5 days<br>• If gastrointestinal side effects (nausea, epigastric pain, abdominal pain – can occur with high dose oral treatment) reduce oral dose to 450mg 3 times daily |
| **Isosorally ra belli**<br><br>Chronic watery diarrhoea (> 2 weeks or previous episodes); CD4 < 200 or unknown | **Cotrimoxazole – duration 10 days:**<br>• Total daily dose is 1 tablet of 960mg orally for every 16kg of body weight; divide total dose into 2-3 individual doses. Maximum 4 tablets per day<br>***Or:***<br>• Total daily dose is 1 tablet of 480mg orally for every 8kg of body weight; divide total dose into 2-3 individual doses. Maximum 8 tablets per day<br>• If severe watery diarrhea or severe nausea/vomiting, oral absorption may be impaired. IV cotrimoxazole is indicated if available ( each vial is 480 ml vial; use same dosing as for480mg tablets)<br>**Alternative treatment if cotrimoxazole is contraindicated (hypersensitivity, hepatotoxicity):**<br>**Give either regimen for 10 days:**<br>**First choice if pyrimethamine is available:**<br>• Pyrimethamine 75mg orally daily<br>Plus:<br>• ***Folinic*** acid 15mg orally daily<br>**Second choice - if pyrimethamine is not available:**<br>• Ciprofloxacin 500mg orally 2 times a day<br>• If severe watery diarrhea or severe nausea/vomiting, oral absorption may be impaired. IV ciprofloxacin is indicated if available: 400mg orally 2 times a day<br>**Recurrent Isospora belli:**<br>• Cotrimoxazole plus ciprofloxacin for 10 days – doses as above.<br>• **Do not use cotrimoxazole and pyrimethamine together.**<br>• After 10 days, stop ciprofloxacin and continue half the treatment dose of cotrimoxazole for long term maintenance: 1 tablet of 960mg 2 times orally daily, or 2 tablets of 480mg 2 times orally daily<br>• Avoid long term use of ciprofloxacin due to concerns this will cause bacterial infections to become quinolone resistant |
| **Cryptococcal Disease:**<br>**Cryptococcal meningitis and management of positive serum CrAg** | |
| **Cryptococcal meningitis**<br><br>Remember: management of raised intracranial pressure reduces mortality by 70%<br><br>• Measure opening pressure for all patients at diagnosis | • **Pre-medication :** 1L normal saline plus 20mmol potassium chloride by IV infusion over 2 hours<br>**Prevention of electrolyte deficiency:**<br>• Potassium chloride: 2 tablets of 600mg orally daily<br>• Magnesium: slow Mg 2 tablets orally daily, or Aluminium magnesium hydroxide 2 tablets orally daily<br>**Induction Phase (14 days in total – *note differing duration for different medications*):** |

- Perform Therapeutic LP and drainage of CSF if pressure is greater than 25mmHg or if there are neurological symptoms/signs

Repeat LP and CSF drainage after 24 hours:

- If pressure is greater than 25mmHg
- If there are ongoing or new neurological symptoms/signs – repeat more than once daily if symptoms/signs are severe or rapidy reappear

Continue to repeat LP and CSF drainage daily until both opening pressure is normal and all neurological abnormalities have resolved

Option 1 - current preferred option in most settings:

- amphotericin B 3mg/kg IV daily, or amphotericin B deoxycholate 1mg/kg IV daily: duration ***7*** Liposomal days

***Plus:***

- Flucytosine total daily dose 100mg/kg/day orally; divide into 4 individual doses: duration ***7*** days

***Followed by:***

- Fluconazole 1200mg orally daily : duration ***7*** days

Option 2 – only use if this is agreed by your project:

- Liposomal amphotericin B 10mg/kg IV ***single dose***

***Plus both:***

- Flucytosine total daily dose 100mg/kg/day orally; divide into 4 individual doses: duration ***14*** days
- Fluconazole 1200mg orally daily: duration ***14*** days

Option 3 – only use if flucytosine is not available:

- Liposomal amphotericin B 3mg/kg IV daily or amphotericin B deoxycholate 1mg/kg IV daily: duration ***14*** days

***Plus:***

- Fluconazole 1200mg orally daily: duration ***14*** days

Option 4 – only use if amphotericin B is not available or a fully oral regimen is essential:

- Flucytosine total daily dose 100mg/kg/day orally; divide into 4 individual doses: duration ***14*** days

**Plus:**

- Fluconazole 1200mg orally daily: duration ***14*** days

***Following the Induction Phase, all of the above options use the same Maintenance Phase::***

- Fluconazole 800mg orally daily : duration ***8*** weeks

***Followed by:***

- Fluconazole 200mg orally daily

**Duration of fluconazole:**

- Stop fluconazole only after maintenance phase treatment has been given ***for at least 1 year***, and the patient is stable on ART, clinically well, has completed treatment for any previously diagnosed stage 3 or 4 OIs, and there is no evidence suggesting new stage 3 or 4 OIs
- In addition, if the ART monitoring is available:
    - If both CD4 and VL are available: stop after 1 year if both CD4 > 200 and VL undetectable
    - If CD4 is available and VL is not available: stop after 1 year if CD4 > 200
- Restart fluconazole 200mg daily if CD4 is known to fall below 200 at any time in the future

**Treatment interruptions of fluconazole during the maintenance phase:**

- Most common cause – stock out of fluconazole
- If the patient remains clinically well without neurological symptoms, restart fluconazole 200mg orally daily, and continue for at least one year total satisfying the criteria above to stop

**If the patient has neurological symptoms/signs and was previously treated for cryptococcal meningitis:**

- Note that CSF CrAg may stay positive for several months after initial treatment due to detection of dead antigen
- A positive CSF CrAg cannot distinguish between previously treated cryptococcal meningitis and recurrent Cryptococcal meningitis; if CSF CrAg is positive and there are neurological symptoms, restart treatment for cryptococcal meningitis
- If CSF CrAg is negative, treat for other causes of neurological disease, and restart fluconazole 200mg orally daily for prophylaxis.

**If the patient was previously treated only for positive serum CrAg:**

- Treat for cryptococcal meningitis if CSF CrAg positive; if negative restart prophylaxis with fluconazole

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| **sCrAg positive and CSF CrAg negative, or no neurological symptoms and LP cannot be performed** | • Fluconazole 800mg/day; duration ***10*** weeks<br>Followed by:<br>• Fluconazole 200mg/day; stop only after treatment has been given for at least 1 year, and both CD4 > 100 and VL undetectable |
| **sCrAg positive , with any neurological symptoms and LP cannot be performed** | • Treat for cryptococcal meningitis.<br>• Transfer the patient to a centre able to perform LP to measure opening pressure and provide therapeutic CSF drainage |
| **Other Opportunistic Infections** | |
| **Herpes simplex:**<br>• Oral herpes<br>• Genital herpes | • Aciclovir 400mg orally 3 times a day for 5-10 days<br>• If severe or recurrent, increase to 800mg 3 -5 times a day for 5-10 days depending on response<br>• For 5 times daily dosing: start at 6.00hrs and give every 4 hours, with last dose at 22.00hrs<br>• Note: topical acyclovir is ineffective<br>• If frequent recurrences: start chronic suppressive therapy – acyclovir 400mg orally 2 times a day: review need for treatment at least annually |
| **Herpes zoster:**<br>• Chickenpox<br>• Shingles | • Aciclovir 800mg orally 5 times a day: duration 7 days<br>• For 5 times daily dosing: start at 6.00hrs and give every 4 hours, with last dose at 22.00hrs<br>• Zoster ophthalmicus: oral aciclovir as above. If IV acyclovir is available, start treatment with Aciclovir IV 10mg/kg x 3 per day until there is clinical improvement, then continue with oral treatment for total of 7-14 days. |
| **CMV retinitis** | • Valganciclovir 900mg orally 2 times a day: duration 21 days<br>• Continue valganciclovir 900mg orally daily until CD4 > 100 and patient stable on ART. If CD4 is unavailable, continue for at least 6 months. |
| **Common bacterial infections: use your local guidelines for antibiotic prescribing based on antibiotic stewardship priniciples. If your project does not have local guidelines, use the regimens below** | |
| **Antibiotic stewardship:**<br>• Prescribe antibiotics only if needed – if strong clinical suspicion of bacterial infection<br>• Review the need for antibiotics after 2-3 days<br>•Perform blood cultures before first dose of antibiotics is given if there is access to microbiology<br>•Give the correct dose<br>• Give by the correct route – change to oral antibiotics after 2-3 days if good clinical response and oral regimen is available<br>• Correct duration – write duration or stop date on prescription | |
| **Bacterial meninigitis** | • Ceftriaxone 2g IV 2 times a day for 10 - 14 days, depending on response to treatment. There is no oral alternative; continue IV treatment for the duration.<br>• Meningococcal meningitis (diagnosis confirmed by CSF gram stain): treat for 7 days |
| **Neurosyphilis** | • Benzylpenicillin 4MU IV every 4 hours for 14 days.<br>• Due to global stockouts, and the difficulty in many settings of ensuring 4 hourly IV medication is given correctly, alternative treatment:<br>ceftriaxone 2g IV daily for 10 days |
| **Bacterial pneumonia**<br>**And**<br>**Bacterial sepsis, source undetermined** | • Ceftriaxone 2g IV daily; if there is a good clinical response after 2-3 days, change to amoxycillin-clavulinic acid orally 2 tablets of 500/62.5 mg 3 times daily . Total duration of antibiotics: 5-7 days |
| **Pyelonephritis** | • As for bacterial pneumonia: however duration of treatment is longer - 10-14 days<br>• Alternative: Ciprofloxacin 400mg IV 3 times a day; change to ciprofloxacin 500mg orally 2 times daily after 2-3 days if good clinical response. Total duration of treatment reduced to 7 days. |
| **Suspected hospital acquired infection** | • If no local guidelines, discuss each case with your senior clinician.<br>• Blood cultures are essential, if available; adjust antibiotic treatment according to results<br>• If the absence of local guidelines and no access to microbiology results: the following empiric regimen will cover some resistant gram positive and gram negative organisms:<br>○ clindamycin 600mg IV 3 times a day (or same dose orally if IV is not available) |

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| | ***plus:***<br>○ amikacin 15mg/kg IV once daily; gentamicin 6mg/kg IV once daily if amikacin not available<br>○ Duration of treatment: 5-7 days, depending on response; 14 days if suspected pyelonephritis |
| **Kaposi's Sarcoma** | |
| **Conditions for giving chemotherapy:**<br>• Trained clinicians and nurses<br>• Complete protocol available and understood<br>• Training in safe handling, reconstitution and administration of chemotherapy<br><br>**Indication for chemotherapy:**<br>• Stage T1:<br>Oral lesions<br>Nodular lesions<br>Visceral involvement<br>Oedema | Full protocol must be followed exactly; this is a guide to the medication that should be ordered<br>Note:<br>• Ensure patient is on effective ART: if naïve, start ART immediately, if suspicion of first line ART failure start second line ART without waiting for VL if not available within 48 hours.<br>• Investigate and manage other IOs: if chemotherapy is urgent, make a rapid decision whether treatment for TB or other OIs is needed.<br><br>• Timing of ART and chemotherapy depends on clinical urgency.<br>• Chemotherapy can be started before starting/switching ART if treatment is an emergency (for example pulmonary or laryngeal KS, or GIT with haemorrhage).<br>• If ART is started/switched first, there is no required waiting time before starting chemotherapy: if the patient is not needing hospital admission, chemotherapy can be started 2 weeks after starting/switching ART, however for patients needing hospitalization, clinical urgency means starting much sooner.<br>• If a new diagnosis of TB is made at the time of KS diagnosis, ART can be started/switched within 3-14 days depending on clinical urgency.<br><br>Which chemotherapy?<br>• **Paclitaxel is first line for all patients – except the following:**<br>○ Hospitalised patient with poor general condition and/or multiple pathologies<br>○ Haematological disease:<br>baseline neutrophils < 1500/$mm^3$ or platelets < 75 x $10^9$/L (< 75000/$mm^3$)<br>• **Liposomal Doxorubicin should be given if any of the following:**<br>○ Paclitaxel contraindicated or not tolerated<br>○ Failure of Paclitaxel regimen<br>○ Hospitalised patients with poor general condition and/or multiple pathologies. If Liposomal doxorubicin is not available, low dose paclitaxel is an option for these patients (see paclitaxel regimen 2 below)<br>• **If neither of the above are available: Bleomycin and Vincristine** |
| **Paclitaxel**<br><br>Dosing is based on Body Surface Area (BSA) in $m^2$<br><br>**See protocol for the following:**<br>• chart showing calculation of BSA<br>• dose adjustments for liver impairment; no dose adjustment needed for renal impairment<br>• toxicities and their management<br>• drug interactions | **Available as 100mg vials (100mg/16.7ml: 6mg/ml)**<br>• Regimen 1: 100mg/$m^2$ given over 3 hours every 2 weeks, usually 6-8 cycles<br>• Regimen 2: 25mg/$m^2$ given over 1 hour every week for 8 weeks. This regimen is for patients in poor condition or patients who do not tolerate regimen 1 if liposomal doxorubicin is not available<br>• Regimen 3: 135mg/$m^3$given over 3 hours every 3 weeks, usually 6-8 cycles<br><br>**Premedication before first dose:**<br>• Dexamethasone 10mg orally for 2 doses – given 12 hours and 6 hours before the first dose (or 60mg prednisone orally ?)<br>• Loratidine 10mg orally single dose 6 hours before the first dose |
| **Pegylated Liposomal Doxorubicin (PLD)** | **Available as 10ml vials (2mg/ml)**<br>• Dose: 20mg/$m^2$ every 21 days, until clinical resolution, usually 6-8 cycles<br>• Maximum cumulative dose 550mg/$m^2$<br>**Premedication :**<br>• Nausea/vomiting is common: metoclopramide 10mg orally 3 times a day can be given before the first dose and continue for 3 days according to symptoms |

<table>
<tr><td>Bleomycin</td><td>Available as 15000 IU vials ; 1mg = approximately 1500IU, so 1 vial is approximately 10mg<br>• Dose: 15mg every 21 to 30 days<br>• Maximum cumulative dose 330mg/m$^2$</td></tr>
<tr><td>Vincristine</td><td>Available as 1mg/ml vials<br>• Dose : 2mg/ml every 21-30 days</td></tr>
<tr><td colspan="2">Other Essential Medications</td></tr>
<tr><td>Stop convulsions</td><td>Diazepam :<br>• 5-10mg IV orally or rectally. Do not give IM : very poor absorption .<br>• Repeat if necessary</td></tr>
<tr><td>Anticonvulsants : prevent further convulsions</td><td>Sodium Valproate - no interaction with ART; contraindicated in pregnancy unless no alternative; contraindicated in women of childbearing age as ongoing treatment unless no alternative<br>• Loading dose: 17mg/kg IV or oral as single dose<br>• Followed by 300mg orally 2 times daily for 3 days; continue with 300mg IV 2 times daily if patient unable to swallow<br>• After 3 days, increase both doses by 200mg every 3 days, until no breakthrough seizures. Maximum dose 2500mg (2.5g) daily dose<br>Phenobarbital:<br>• Loading dose: 10mg/kg IV (usually 400-600mg)<br>• Regular dose: 2mg/kg daily at night (maximum 100mg daily); increase gradually if necessary to 3mg/kg every 12 hours<br>Phenytoin:<br>• Loading dose: 20mg/kg IV slowly (not exceeding 3mg/kg/minute – approx. 7 mins)<br>• Regular dose: 150-300mg orally once daily<br>Levetiracetam:<br>• No interaction with ART, now available within MSF<br>• 250mg orally 2 times daily; increase after 1-2 weeks to 500mg orally twice daily.<br>• Increase by 500mg orally 2 times daily if breakthrough seizures every 2-4 weeks, maximum dose 1500mg orally 2 times daily.</td></tr>
<tr><td>Low Molecular Weight Heparin for treatment of Deep Vein Thrombosis and Pulmonary Embolism<br><br>See algorithm for the following:<br>• Indications for prophylaxis<br>• Diagnosis of DVT/PE<br>• Contraindications<br>• Dose adjustment for renal impairment<br>• Avoid NSAIDS<br>• Give together with Omeprazole 20mg orally (treatment doses)</td><td>Nadroparine (Fraxiparine):<br>• Prefilled syringes of different volumes are often available (0.3ml, 0.4ml, 0.6ml, 0.8ml).<br>Prophylaxis:<br>• Nadroparine (Fraxiparine) 0.3ml subcutaneous daily<br>Treatment:<br>Indications:<br>• Suspected or confirmed deep vein thrombosis or pulmonary embolism<br>• Dose: 0.1mg/kg subcutaneously every 12 hours. It is not possibleto give a fraction of a prefilled syringe. Give the nearest possibledose using combination of available syringes.<br><table><tr><th>Bodyweight</th><th>Fraxiparine volume every 12 hours</th></tr><tr><td>≤ 39kg<br>40-49kg<br>50-59kg<br>60-69kg<br>70-79kg<br>80-89kg<br>90-99kg<br>≥ 100kg</td><td>0.3ml<br>0.4ml<br>0.5ml<br>0,6ml<br>0.7ml<br>0,8ml<br>0.9ml<br>1.0ml</td></tr></table></td></tr>
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| | • Duration: Ideally, anticoagulation treatment is needed for 3 months. Warfarin and direct anticoagulants are not widely available. Discuss with senior doctor regarding duration of treatment, and whether it is possibleto give fraxiparine for home administration on discharge. |

**Notes:**

Dosing intervals:

- 2 x a day is every 12 hours
- 3 x a day is every 8 hours (oral medication can be given at more convenient times eg 8.00hrs, 14.00hrs, 22.00hrs)
- 4 x a day is every 6 hours

Weight-based dosing:

- If the patient is unable to stand or a scale is unavailable, measure mid-upper arm circumference (MUAC) in cm to estimate weight:

$$\text{Weight (kg)} = (\text{MUAC} \times 4) - 50$$

# NOTES

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October, 2021
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