

The hospitalised patient with HIV

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Programme

- What is AHD and why is a special approach needed?
- 5 clinical cases of patients with AHD needing inpatient care- management principles
- Keeping your patient out of hospital
- Time for questions

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Advanced HIV disease

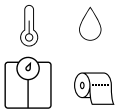
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AHD can be obvious

“Crash-landing”
Appear clinically unwell
WHO stage 3 or 4 conditions



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AHD can be hidden

CD4 count < 200 cells/uL
Patient might look well!
Careful clinical assessment may reveal
opportunistic infections
May deteriorate rapidly- high risk of death



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Don't forget the kiddies

All children living with HIV under age 5 years have AHD, unless stable on ART for at least 1 year



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Who to screen for AHD

Be on the lookout for concerning clinical features at every visit



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Why find these patients?

Increased risk of :

- opportunistic infections
- immune reconstitution inflammatory syndrome (IRIS)
- incomplete immune reconstitution
- AIDS-related and non-AIDS-related comorbidities
- **death**

- Causes of death in AHD:
- TB
 - Cryptococcal meningitis
 - Severe bacterial infections
 - PCP/PPV
 - Toxoplasmosis
 - Invasive fungal infections
 - Cancer

WHO recommends a package of care for all patients with AHD

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How to intervene

Patients with AHD should not remain in routine care
Require an intensified package of care:



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Clinical cases

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Case 1: Ms ML

38 year old woman, known with HIV for 6 years, on ART with good follow-up and adherence

Most recent CD4 count 28 cells/uL (> 1 year ago)

Brought by her sister today with cough and difficulty breathing- progressively worsening over the last 5 days

Vitals in triage:
BP = 104/72 mmHg
HR = 126 bpm
RR = 32 bpm
T = 36,8 C
Sats = 94%

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MCQ 1

- Choose the most correct statement about this case:
- A. Oxygen saturation = 94% excludes PCP/PJP in PLHIV
 - B. Cotrimoxazole prophylaxis for PLHIV is only effective at preventing PCP/PJP
 - C. Patients with AHD are at increased risk of severe bacterial pneumonia
 - D. Annual influenza vaccination is not indicated in AHD due to poor immune response

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MCQ 1

- Choose the most correct statement about this case:
- ~~x~~Oxygen saturation = 94% excludes PCP/PJP in PLHIV
 - ~~x~~Cotrimoxazole prophylaxis for PLHIV is only effective at preventing PCP/PJP
 - ✓Patients with AHD are at increased risk of severe bacterial pneumonia due to the same organisms affecting those without HIV
 - ~~x~~Annual influenza vaccination is not indicated in AHD due to poor immune response

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BP = 104/72 mmHg

HR = 126 bpm ▲

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Give urgent attention to the adult or adolescent with any of the following danger signs:

- Respiratory rate ≥ 30 breaths per minute
- Heart rate ≥ 120 beats per minute
- Unable to walk unaided
- Breathless at rest or while talking
- Coughs up ≥ 1 tablespoon of fresh blood
- Drowsy/confused/loss of consciousness
- Fitting/seizures
- Aggressive, confused or agitated
- Recent sudden onset weakness, numbness or visual disturbance

Source: Adult APC Guideline 2023

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Case 1: Ms ML

⚠ When speaking to Miss ML to get more history- very breathless, only able to say a few words

Peripheral sats decline to 82% with effort of speech, drop even lower when trying to move to examination couch

Normal oxygen saturation at rest does not exclude PCP!
Sats may drop precipitously with exertion- typical feature of PCP

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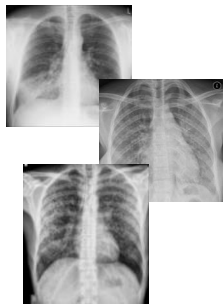
Respiratory presentation

Commonest reason for hospitalization in AHD
High mortality ⚠

Most patients will have one or more of the big 3:

- Bacterial pneumonia
 - Pneumocystis pneumonia
 - Pulmonary TB
- Co-infection is common!

Imaging is key to diagnosis!



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Management principles

Therapy should not be delayed by extensive diagnostics- prompt empiric treatment for multiple conditions may be life-saving

Inappropriate therapy can be discontinued once more info available

In the critically ill patient, empiric therapy will include:

- Broad spectrum antibiotic cover for bacterial pneumonia- ceftriaxone or co-amoxiclav +/- macrolide
- High dose cotrimoxazole + prednisone
- TB treatment

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Bacterial pneumonia

Incidence increased 100-fold in AHD

Same clinical picture, causative organisms, and treatment as community acquired pneumonia in those without HIV

Diagnostic clues:

- respiratory symptoms < 2 weeks
- consolidation on chest x-ray
- elevated WCC and preserved Hb
- hypoxia less common



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Pneumocystis pneumonia (PCP/PJP)

Typically affects patients with CD4 count < 200 cells/uL (but not always)

Subacute presentation- progressive dyspnoea and dry cough

May deteriorate suddenly with chest pain- pneumothorax

Diagnostic clues

- longer duration of symptoms
- dyspnoea out of proportion to auscultation findings
- hypoxaemia, may only be elicited by exercising patient
- bilateral interstitial infiltrates on chest x-ray
- normal WCC and Hb



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Pulmonary TB

May present with severe illness and sepsis like syndrome on background of more chronic symptoms

Ask about previous TB, treatment history, contacts

May need multiple tests to confirm diagnosis and susceptibility- consider empiric treatment while awaiting more information

Diagnostic clues

- symptoms > 2 weeks, productive cough
- prominent constitutional symptoms
- hilar adenopathy, nodular or miliary pattern on CXR
- normal WCC, low Hb



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Case 2: Mr PS

19 year old man, known with vertical transmission of HIV, on ART since early childhood

Adherence became patchy during adolescence- on and off treatment

Has now been off ART entirely for 2 years

Presents to the clinic weak and unable to walk or stand without assistance, reports diarrhoea with up to 10 watery stools per day

Vitals in triage:
 BP = 84/60 mmHg
 HR = 142 bpm
 RR = 22 bpm
 T = 37,2 C
 Sats = no tracing

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MCQ 2

- Choose the most correct statement:
- Chronic diarrhoea does not cause clinically significant dehydration
 - All patients with AHD who present with diarrhoea should receive empiric antibiotics for dysentery
 - Diarrhoea does not affect absorption of ART, provided the patient is not vomiting
 - All patients with diarrhoea should be assessed for risk factors for *Clostridioides difficile* diarrhoea

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MCQ 2

Choose the most correct statement:

- xChronic diarrhoea does not cause clinically significant dehydration
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Diarrhoea in AHD

3 or more loose stools per day
 Very common in AHD- acute and chronic
 Intermittent chronic diarrhoea may masquerade as acute episode
 Complications result in hospitalization - dehydration, electrolyte abnormalities, shock
 -may require aggressive resuscitation

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Management principles

Resuscitate with oral and/or IV fluids
 Correct electrolytes- hypokalaemia may be immediately life threatening
 Assess for features of dysentery- fever, blood or mucous in stool
 If present start empiric antibiotics:
 - Ciprofloxacin 500mg orally for 3 days or
 - Ceftriaxone 1g IVI twice daily for 5 days
 Assess for risk factors for *Clostridioides difficile* - older age, recent hospital admission, antibiotic exposure
No loperamide in dysentery or if any risk of *C. difficile*

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Recommended investigations

Electrolytes, urea and creatinine
 Full blood count
 Blood culture for dysentery
 Stool analysis
 Acute dysentery: MCS only
 Chronic/watery: MCS + "ova and parasites", 3 samples
 Test for *C. difficile* if at risk
 TB work-up
 Urine LF-LAM
 Chest x-ray
 Sputum TB-NAAT
 Abdominal ultrasound

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Chronic diarrhoea

Persistent for > 2 weeks
Usually related to opportunistic infections:

<i>Cryptosporidium parvum</i> and <i>Cystispora belli</i>	CMV	<i>Mycobacterium avium</i> complex (MAC)
<ul style="list-style-type: none"> • Cotrimoxazole treats <i>C. belli</i> • No specific Rx for <i>C. parvum</i> • Urgent immune reconstitution 	<ul style="list-style-type: none"> • CD4 < 50 cells/uL • Look for CMV disease at other sites- fundoscopy • Need endoscopy to confirm Dx 	<ul style="list-style-type: none"> • CD4 < 50 cells/uL • Triad of diarrhoea, anaemia and respiratory Sx • TB mimic

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Chronic diarrhoea

Consider TB abdomen, usually part of disseminated TB
Also consider non-infectious causes:
- medication (protease inhibitors)
- malabsorption (HIV enteropathy)
- malignancy (KS, lymphoma, other)

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Acute diarrhoea

Bacterial (dysentery) and viral causes, similar to patients without HIV
Any new medications?
Travel history?
Don't forget amoebic dysentery in endemic areas
Previous episodes- confirm this is not intermittent chronic diarrhoea

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Case 3: Mr NZ

45 year old man, living with HIV for 16 years

Re-engaged with care and reinitiated ART 1 month ago, after a treatment interruption of 2 years

Presents to his routine clinic visit complaining of a headache for the last week, his vision is not clear since yesterday and is getting worse

Reports good adherence to ART, except for the last 2 days when he experienced nausea and vomiting in the morning when he normally takes his tablets

Vitals:
BP = 126/84 mmHg
HR = 104 bpm
RR = 20 bpm
T = 37,1 C
Sats = 95%

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Choose the most correct statement:

- A. Cryptococcal meningitis does not occur in PLHIV with a CD4 count >200
- B. Lumbar puncture is recommended in asymptomatic PLHIV with a positive serum CrAg
- C. Lumbar puncture is recommended only in symptomatic PLHIV with a positive serum CrAg
- D. Antiretroviral therapy should be deferred for 4-6 weeks for all PLHIV with a positive serum CrAg

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Source: Adult APC Guideline 2023

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Case 3: Mr NZ

CD4 count = 98 cells/uL

Reflex CrAg positive

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Meningitis in AHD

Any 2 of:

- fever
- headache
- neck stiffness (often less prominent in subacute causes)
- confusion

High mortality and morbidity- urgent referral

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Meningitis in AHD

Can be acute (symptoms < 7 days)

- bacterial (hyperacute)
- viral

Can be subacute (symptoms > 7 days)

- TB meningitis
- cryptococcal meningitis

Don't forget neurosyphilis- acute or subacute

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Management principles

For all patients with confusion, reduced level of consciousness or new onset seizure- check serum glucose before anything else!

If acute meningitis is suspected, treat empirically for acute bacterial meningitis while awaiting transfer: **ceftriaxone 2g IVI 12 hourly**

If able to perform lumbar puncture and no contra-indications: do LP prior to initiating antibiotics

Antibiotics should never be delayed for LP

For subacute meningitis, investigation is urgent but treatment can usually be deferred until CSF results are available

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Contraindications to LP

- Reduced level of consciousness (GCS <10)
- New onset seizures or focal neurology
- Papilloedema on fundoscopy
- Haemodynamically unstable
- Bleeding from mucous membranes
- Local infection at lumbar site

Need a CT brain to exclude space occupying lesion/ raised intracranial pressure

Need resuscitation or further investigation incl. platelets and clotting profile

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Diagnostic tests

In both acute and subacute meningitis:

- opening pressure
- Gram stain and bacterial culture
- protein, cell count, glucose (with serum glucose)
- CrAg
- FTA-Abs and VDRL
- TB NAAT

Normal CSF results in PLHIV:
 Glucose > 3.5 mmol/dL
 Protein < 0.75
 1 polymorph
 5 lymphocytes
 CSF CrAg remains positive after treatment!

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TB meningitis

Common, high mortality, hard to confirm diagnosis

In a patient with AHD and lymphocytic CSF and no clear alternative explanation, start empiric TB treatment

Look for evidence of TB elsewhere:

- lymphadenopathy
- urine LF-LAM
- CXR
- sputum TB NAAT
- CSF and blood mycobacterial culture
- abdominal US

Typical CSF in TBM:
 - Lymphocyte predominant
 - Can be poly predominant in early disease
 - High protein
 - Low glucose
 - Sensitivity of TB NAAT on CSF is poor

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Cryptococcal meningitis

Usually affects those with CD4 count < 200 cells/ul, but can rarely affect more immune competent patients and also HIV negative patients

LP recommended in all PLHIV with a positive serum CrAg

Treatment for meningitis:

- therapeutic LP to manage raised ICP
 - induction phase with amphotericin B and flucytosine, then high dose fluconazole
 - consolidation phase of fluconazole
 - fluconazole prophylaxis until immune reconstitution
- ART should be deferred for 4 -6 weeks, only for patients with meningitis

Typical CSF in CCM:

- Elevated opening pressure
- Yeasts on Gram stain
- Lymphocyte predominant
- Protein and glucose may be normal
- CrAg positive
- *C. neoformans* on culture

CCM treatment induction update:

- Single dose of liposomal amphotericin B + 1 week flucytosine
- Still limited by availability

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Cryptococcal antigenaemia

Serum CrAg positive but no features of meningitis on LP

Still needs treatment:

- induction phase of fluconazole 1200mg dly for 2 weeks
- consolidation phase of fluconazole 800mg dly for 8 weeks
- prophylaxis with fluconazole 200mg dly until immune reconstitution

ART can be started immediately if meningitis has been excluded

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HSV or VZV meningitis

More commonly cause encephalitis, but clinical features overlap

Vesicular skin lesions may be present

Lymphocytic CSF, protein and glucose usually normal

Treatment with acyclovir is well tolerated

Proven HSV/VZV on CSF and good clinical response to acyclovir can inform a decision to discontinue TB treatment

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Case 4: Ms YG

A 36 year old woman attends her routine follow up appointment- she is known with HIV for 5 years and has been very adherent to her ART
 Her last CD4 count was 240 cells/uL
 She has been losing weight for the last month and also reports sweating at night
 A sputum TB NAAT done 2 weeks ago during a TB screening initiative at her employer was negative
 Today, she is very weak and collapses in the waiting room
 A urine pregnancy test and urine LF-LAM are both positive

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MCQ 4

- Choose the most correct statement
- A. Urine LF-LAM should not be used in PLHIV with a CD4 count > 200
 - B. A negative urine LF-LAM test excludes TB
 - C. A definitive bacteriological diagnosis of TB should be made prior to initiating TB treatment in patients with AHD
 - D. LF-LAM can be positive in patients without TB

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MCQ 4

- Choose the most correct statement
- ~~x~~Urine LF-LAM should not be used in PLHIV with a CD4 count > 200
 - ~~x~~A negative urine LF-LAM test excludes TB
 - ~~x~~A definitive bacteriological diagnosis of TB should be made prior to initiating TB treatment in patients with AHD
 - ✓LF-LAM can be positive in patients without TB

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Case 4: Ms YG

A 36 year old woman attends her routine follow up appointment- she is known with HIV for 5 years and has been very adherent to her ART
 Her last CD4 count was 240 cells/uL (more than a year ago)
 She has been losing weight for the last month and also reports sweating at night
 Today, she is very weak and collapses in the waiting room ▲
 A sputum TB NAAT done 1 week ago during a TB screening initiative at her employer was negative
 ▲ A urine pregnancy test and urine LF-LAM are both positive today

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Give urgent attention to the adult or adolescent with any of the following danger signs:

• Respiratory rate ≥ 30 breaths per minute	• Drowsy/confused/loss of consciousness
• Heart rate ≥ 120 beats per minute	• Fitting/seizures
• Unable to walk unaided	• Aggressive, confused or agitated
• Breathless at rest or while talking	• Recent sudden onset weakness, numbness or visual disturbance
• Coughs up ≥ 1 tablespoon of fresh blood	

Source: Adult APC Guideline 2023

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TB in AHD

Confirming diagnosis can be challenging
 Greater risk of extra-pulmonary and disseminated TB
 Greater risk of TB-IRIS
 Vulnerable to drug-drug interactions and adverse effects (polypharmacy)

TB outcomes in pregnancy- bad for the mother and the baby

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Systematic screening for TB

Who?	How?
<ul style="list-style-type: none"> - at HIV diagnosis/first evaluation for ART - past history of TB - confirmed/presumed AHD - new TB exposure - clients on ART attending annual clinical review - PLHIV who become pregnant 	<ul style="list-style-type: none"> - symptom screen - clinical examination - chest x-ray - sputum TB-NAAT - urine LF-LAM - other relevant specimens for NAAT or culture

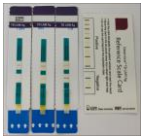
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Urine LF-LAM

Indicated in all PLHIV admitted to hospital
 In outpatient setting:

- symptomatic PLHIV with CD4 <200 or AHD by clinical criteria
- current serious illness warranting admission

A positive test confirms TB (or MAC) but does not give any indication of drug-susceptibility
 Start treatment for DS-TB unless the patient has a personal history of DR-TB or a known DR-TB contact
 Follow up with TB-NAAT on sputum or other specimens
 Always perform on a clean-catch specimen, not urine from a collection bag (false positives)
 Always adhere to time limit for reading (25 minutes) and use the reference card in the pack



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Case 5: Ms YG is back

Miss YG was transferred to hospital and was diagnosed with disseminated TB (urine LF-LAM, abdominal ultrasound)
 TB NAAT was negative on a poor-quality sputum specimen- had difficulty expectorating
 Mycobacterial blood culture sent and still incubating
 Discharged from hospital on DS-TB treatment, cotrimoxazole and TLD 2 weeks ago
 Now returned with extensive skin rash, as well as blistering in the mouth making it difficult to eat, drink, and swallow tablets



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MCQ 5

- Choose the most correct statement:
- A. Severe cutaneous adverse reactions (SCAR) can occur with any medication
 - B. Medications should be introduced one at a time when rechallenging drugs in a patient with SCAR
 - C. Cotrimoxazole is a rare cause of SCAR and should always be rechallenged in patients with AHD as benefit outweighs risk
 - D. SCAR can usually be managed with topical treatment as an outpatient

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MCQ 5

- Choose the most correct statement:
- ✓ Severe cutaneous adverse reactions (SCAR) can occur with any medication
 - ~~x Medications should be introduced one at a time when rechallenging drugs in a patient with SCAR~~
 - ~~x Cotrimoxazole is a rare cause of SCAR and should always be rechallenged in patients with AHD as benefit outweighs risk~~
 - ~~x SCAR can usually be managed with topical treatment as an outpatient~~

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Adverse drug effects in AHD

At greater risk due to polypharmacy- exposed to more drugs
 Treatment interruption may be very problematic for life-threatening OIs
 Delayed immune reconstitution if ART interrupted
 Vulnerable to complications:
 - secondary bacterial infections of skin lesions
 - hospital acquired infections

Painful and frightening- affects trust and adherence

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Management principles

Always take a skin rash seriously, especially if medication added or changed recently
 Refer immediately if any mucosal involvement, or if systemically ill
 Stop all medication for severe cutaneous adverse reactions- may need to make substitutions for critical medications (ask for help)
 Not always the antimicrobial agents, don't forget anticonvulsants, allopurinol- take a comprehensive drug history

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Management principles

SCAR requires inpatient management with intensive supportive care
 Ideally, medications should not be rechallenged after SCAR- not always possible
 If clear temporal association with cotrimoxazole, can consider careful inpatient rechallenge of other agents
 Never rechallenge cotrimoxazole, can substitute with dapsone

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The ambulant patient with AHD
 How to keep your patient out of hospital

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Screening, treatment and prophylaxis for major OIs

Cotrimoxazole prophylaxis

- HIV positive infants under 1 year
- CD4 < 200 cell/uL or < 25 %
- WHO stage 3 or 4
- after treatment for PCP/PJP

Cotrimoxazole prevents:

- PCP/PJP
- toxoplasmosis
- *Cystispora belli*
- bacterial pneumonia
- other severe bacterial infections
- mortality

TB preventive therapy

- at HIV Dx/starting ART
- at new diagnosis of AHD
- after significant TB exposure

Always ensure active TB has been excluded as best possible

Fluconazole for cryptococcal antigenaemia

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Rapid initiation of (effective) ART

If ART naïve or interrupted ART:

- careful clinical assessment and CD4 count to screen for AHD
- rapid ART initiation on a DTG containing regimen unless medical contraindications to starting ART

Currently on ART but not virally suppressed:

- follow VL monitoring and management algorithm
- intensified adherence support and follow-up
- discuss with HIV expert if unsure or repeated high viral load with good adherence

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Intensified adherence support

Harder for patients with AHD to adhere:

- clinically unwell and weak, including vomiting and diarrhoea
- pill burden and adverse effects
- depression and anxiety
- existing barriers to engaging meaningfully with care may have resulted in AHD
- unable to work- financial constraints

Patient centred care using their preferred support modalities

Treatment supporters, telehealth/whatsapp and tracing and recall for missed appointments
Mental health assessment and referral

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Integrate "other" care

- Address non-communicable diseases
- Sexual and reproductive health services
- Mental health services
- Immunisations including annual influenza vaccination
- Routine childhood and maternal care
- Palliative care when indicated

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Take home points

- Patients with AHD are at increased risk of death- risk can be mitigated
- Empiric treatment may be life-saving, start and get more information
- Empiric treatment can be stopped
- Polypharmacy is common in AHD- think of adverse effects, interactions, and pill burden
- Mental health concerns are common, and affect adherence
- Patients with AHD move between different levels of care frequently- communication and teamwork is essential
- Complex patients- ask for help

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