

Advanced disease – ambulatory patient



The package of care for a
primary care clinic

1. ART status
2. How stable they are clinically

In its 90:90:90 plan for 2020, WHO set the goal of 90% of all people with diagnosed HIV infection knowing their status, 90% of those patients being on antiretroviral therapy and 90% of those on this therapy achieving viral suppression. With the 90:90:90 goals, the global focus in HIV care is to reduce HIV infections and ensure that all PLHIV are on ART and are virally suppressed. However, people are still dying from advanced disease.

The focus here in addressing the care of the patient in primary care with advanced disease is to reduce mortality. With the rapid scale-up of ART globally from the early 2000s, the mortality rate from HIV dropped over the next 10 years by over 40%, but after this, the rate of this decline began to slow down. Studies have shown two new trends.

- A constant proportion of patients are still presenting with advanced immune suppression with CD4s <200 and many <100, despite the scale-up of ART.
- An increasing proportion of these people have previously been on ART, with one or more episodes of treatment interruption, or are currently on ART and failing their regimen.

This has given rise to a change in terminology, so that the previous term, 'the late presenter' has now been replaced by the term, 'patients presenting with advanced HIV disease'.

The 2017 **WHO definition** of the adolescent and adult presenting with advanced disease includes those with a CD4 count <200 or a new stage 3 or 4 disease.

Further evaluation of studies in many sub-Saharan countries showed that, in patients who presented to hospital with advanced disease, the mortality rate ranges from 25% to 50%, a third of which is in the first 48 hours of admission. A further 20% die after transfer back to primary care, and, on average, 30% are re-admitted to hospital within a short time of discharge.

The major causes of death are TB – the majority of which is disseminated – cryptococcal meningitis, pneumocystis pneumonia and severe bacterial infections. Other important contributors to mortality are toxoplasmosis, Kaposi's sarcoma, chronic diarrhoea and renal impairment.

A four-pronged approach is needed

All of this adds up to a serious problem that needs urgent attention, with the result that there is a large drive internationally to define and implement strategies to address the patient presenting with advanced disease. This challenge needs to be approached at four different levels:

1. **At community level**, especially targeting enhanced treatment literacy and educating people on the danger signs. The strategising around this falls outside the scope of this clinical guide.
2. **In primary health clinics**, through early identification of danger signs, focused screening and prophylaxis, early ART management, effective early treatment of OIs and timely referral. This is detailed in the rest of this chapter.
3. **In hospital**, by ensuring rapid investigation and management (e.g. by creating an HIV-focused rapid assessment unit within a hospital's emergency unit).



WHO guidelines

For a comprehensive guide for clinicians to manage patients in a hospital setting, see the **MSF HIV/TB Guide: Hospital Level**.

4. Post-discharge re-linkage to primary care within a public health strategy:

- Patients with advanced disease need to be seen for ongoing care by designated, experienced healthcare workers, as part of differentiated service delivery. Ensure your clinic has a plan for these patients. Stable patients can be followed up by an experienced nurse but unstable patients should be followed up by an experienced clinical officer or doctor.
- Patients with advanced HIV who have been discharged from hospital are at high risk of mortality. Together with your referral centre, develop a good system of two-way communication between the primary care site and the referral centre, to ensure optimal communication regarding diagnoses, management and clinic appointment dates.



Refer to the MSF HIV/TB Guide: Hospital Level

The package of care for a primary care clinic

The evaluation of the patient with advanced disease involves two important new clinical concepts:

1. ART status

With the ART public health programme growing older, an increasing proportion of patients are stopping or interrupting their treatment regimens, resulting in the development of ART resistance.

Unnecessary delay in switching to an effective regimen is resulting in steady worsening of immune status, the development of serious opportunistic infections and death. To address this, these guidelines therefore recommend strengthened VL monitoring and provide specific criteria for a rapid switch to a second line regimen on the assumption that treatment failure is highly likely. **The diagnosis of treatment failure in patients with advanced disease therefore does not always follow the standard criteria of 2 consecutive VL > 1 000 cp/ml, 3–6 months apart in the presence of good adherence.**

In order to make this important decision regarding a regimen switch, the ART status needs to be carefully evaluated, based on 4 key components:

- Is the patient ART-naïve or non-naïve?
- Have there been any treatment interruptions?
- Allowing for interruptions, has the total time on ART been > or < 6 months?
- What is the CD4 count?



ART-naïve refers to the patient who has never taken ART before. It is important to take a good history to clarify this, as patients have often been on ART many years previously and do not admit to this unless specifically asked. Any patient who has ever taken ART, however long ago, is considered to be **ART non-naïve**.

2. How stable they are clinically

Patients defined as clinically unstable are at higher risk of rapid deterioration and death, so warrant specific focused attention by a more experienced clinician.

The first step is the identification of the patient with danger signs and the commencement of emergency care and referral. Those without danger signs but who are clinically unstable require focused history, examination and rapid tests looking for specific illnesses identified as contributing to high morbidity and mortality in advanced disease (**especially pulmonary and disseminated TB, neurological and respiratory disease**).

By using the 2 key criteria of ART status and clinical stability to evaluate patients with advanced HIV disease, we are able to implement further diagnostic and management packages according to the patient's category. They are summarised in Figure 11.1, referencing the use of the 5 figures that follow.



The commonly held belief that all adherence problems must be sorted out before switching is not true! It is better to switch to an effective regimen, even if taking it inadequately, than to keep pushing for improved adherence in a patient who dies from an overwhelming opportunistic infection.



Refer to your national guidelines

Figures 11.1–6 will need to be used in the context of any **local guidelines** and constraints. We would encourage MSF to work with the Ministry of Health in their implementation. Due to the unnecessary delays caused by second line committees, these committees should ideally be abolished and replaced by more efficient means of decision-making.



samumsf.org/en/resources/msf-hivtb-clinical-guide-2018

Figures 11.1–6 can be downloaded from the additional resources folder on the **SAMU website** <https://samumsf.org/en/resources/msf-hivtb-clinical-guide-2018> (under resources/HIV/advanced disease) and printed in black and white or colour in whatever size and format they are needed for easy reference in clinicians' workplaces.

Figure 11.1 Overview of approach to the patient with advanced disease



Patients enter this algorithm if identified with new stage 3 or 4 disease or with a CD4 <200. Many patients with a CD4 <200 may be otherwise well but a triage system in a busy outpatient waiting room will identify the sicker patients with stage 3 or 4 disease and enable fast-tracking into the process outlined below.

First step for all patients with advanced disease is to check for danger signs.

If no danger signs, take fuller history, examination and do rapid diagnostic tests (Figure 11.2)

Patient is placed into one of 4 categories based on **clinical stability** and **ART status** (Figure 11.3)

ART-naïve or ART <6 months	STABLE and ART-naïve or on ART for <6 months	UNSTABLE and ART-naïve or on ART for <6 months
Total ART > 6 months (ongoing or interrupted)	STABLE and on ART for >6 months; ongoing or interrupted	UNSTABLE and on ART for >6 months; ongoing or interrupted

Packages of care defined by above 4 categories and detailed in figures 11.3, 11.4 and 11.5.

If danger signs present, (see Figure 11.2) provide urgent supportive management; eg, oxygen, IV fluids, and refer.

If transfer to referral site delayed provide whatever additional emergency management is possible (Figure 11.6)



Refer to hospital

Figure 11.2 Clinical approach to patients with advanced disease

Advanced HIV: CD4 <200 or new WHO stage 3 or 4

Clinical approach to patients: all patients



If there are any danger signs, refer to hospital immediately:



- Respiratory rate >30
 - Heart rate >120
 - Systolic BP <90
 - Temperature >39°C
 - Moderate/severe dehydration
 - Unable to walk unaided
 - Saturation <90%
 - Altered mental state: confusion, strange behaviour, reduced level of consciousness
 - Any other neurological problem: new onset severe headache, seizures, paralysis, difficulty talking, cranial nerve problems, rapid deterioration in vision
- While organising referral:**
- Point of care investigations
 - Urgent management, (e.g. IV fluids, oxygen)
 - Start urgent treatment: (e.g. pneumocystis treatment, antibiotics, TB treatment). If delay in referral, see Figure 11.6.

If NO danger signs: History and examination looking for ART status, OIs and co-morbidities:

TB assessment

Patients with advanced HIV are at high risk for TB.

Disseminated TB frequently does not present with respiratory symptoms.

Past history: Any previous TB?

Currently history: On treatment now? Not improving on treatment?

Symptom screening today: Loss of weight, fever, night sweats, cough?

Examination: Pleural effusion, nodes, tender or distended abdomen, ascites, hepatomegaly?

History and examination

ART history:

Which regimens and when? Previous CD4 and VLs: Is treatment failure suspected?

Co-morbidities: Diabetes, hypertension, epilepsy, kidney or liver disease.

Hospitalised recently: Within past 3 months? Include reason.

Neurological conditions: All are danger signs – refer.

Respiratory conditions: If danger signs – refer.

Kaposi's sarcoma: Palate, skin.

CMV retinopathy in high risk areas.

Chronic diarrhoea.

Assess for **dehydration**.

Investigations for ALL patients

CD4:

- <200: do serum CrAg.
- <100: do TB LAM.
- 100–200: do TB LAM if TB symptoms.
- Collect sputum if productive cough.

Haemoglobin.

Urine dipstick: If proteinuria, do serum creatinine.

Routine viral load if not done within past 6 months.

Targeted viral load if not done within past 3 months, or if stage 4 condition, or last VL >1 000.

Malaria rapid test if endemic.

Hepatitis B if available and not yet done.

Management is now based on two key criteria:

1. Is the patient clinically STABLE or UNSTABLE?
2. Is the patient ART-naïve (or on ART for <6 months) or on ART >6 months?

Communication with hospital:

- Patients, apart from those with danger signs, may need referral – if appropriate investigation or management is not available at primary care, or if rapid decision-making for regimen switch for treatment failure is necessary at referral level.
- Establish a 'hotline' with hospital clinicians for clinical advice, case discussion, referral and back-referral – particularly when transfer is difficult.



Figure 11.3 Management plans based on clinical stability and ART status

Definition of an UNSTABLE patient:

- One or more danger signs
- Clinical suspicion of any new stage 4 disease or any TB (including PTB)
- IRIS; commonest is TB or cryptococcosis
- Serum CrAg positive
- Adverse drug reaction, requiring ongoing management
- Discharged from hospital within past 3 months
- Pregnant
- Mental health or substance abuse problems
- Co-morbid conditions requiring frequent follow-up (for example: diabetes, unstable hypertension, epilepsy, renal or liver impairment)

Definition of a STABLE patient: CD4 <200 but otherwise well

	STABLE	UNSTABLE
ART-naïve or ART <6 months	<p>STABLE and ART-naïve or ART <6 months</p> <p>Package of care:</p> <ul style="list-style-type: none"> • ART management: <ul style="list-style-type: none"> • If no prior ART start immediately (see point 7 on page 225). • If defaulted, start first line ART. • Check VL after 6 months of continuous ART. <p>Follow-up:</p> <ul style="list-style-type: none"> • After 2 weeks, then monthly. • Care to be provided by experienced nurse. 	<p>UNSTABLE and ART-naïve or ART <6 months</p> <p>Package of care:</p> <ul style="list-style-type: none"> • Care package for unstable patient. See Figure 11.5. • ART management: <ul style="list-style-type: none"> • If no prior ART start immediately (see point 7 on page 225). • If defaulted, start first line ART. • Check VL after 6 months' continuous ART. <p>Follow-up:</p> <ul style="list-style-type: none"> • After 1–2 weeks then 2–4 weekly. • Care to be provided by experienced clinical officer/doctor.
ART >6 months (ongoing or interrupted)	<p>STABLE and total ART >6 months</p> <p>Package of care:</p> <ul style="list-style-type: none"> • ART management: see Figure 11.4. <p>Follow-up:</p> <ul style="list-style-type: none"> • After 2 weeks, then monthly. • Care to be provided by experienced nurse. • VL and ART management according to Figure 11.4. 	<p>UNSTABLE and total ART >6 months</p> <p>Package of care:</p> <ul style="list-style-type: none"> • Care package for unstable patient. See Figure 11.5. • ART management: see Figure 11.4. <p>Follow-up:</p> <ul style="list-style-type: none"> • After 1–2 weeks, then 2–4 weekly. • Care by experienced clinical officer/doctor. • VL and ART management according to Figure 11.4.

All patients need the following prophylaxis and patient and community support packages:**Prophylaxis package**

- Cotrimoxazole.
- Isoniazid/B6, if not on TB treatment; if on TB treatment, start after completion. Duration, 36 months or longer (WHO).
- Fluconazole, if serum CrAg positive, CrAg unavailable; and secondary prophylaxis for patients with cryptococcal meningitis.

Patient and community support package

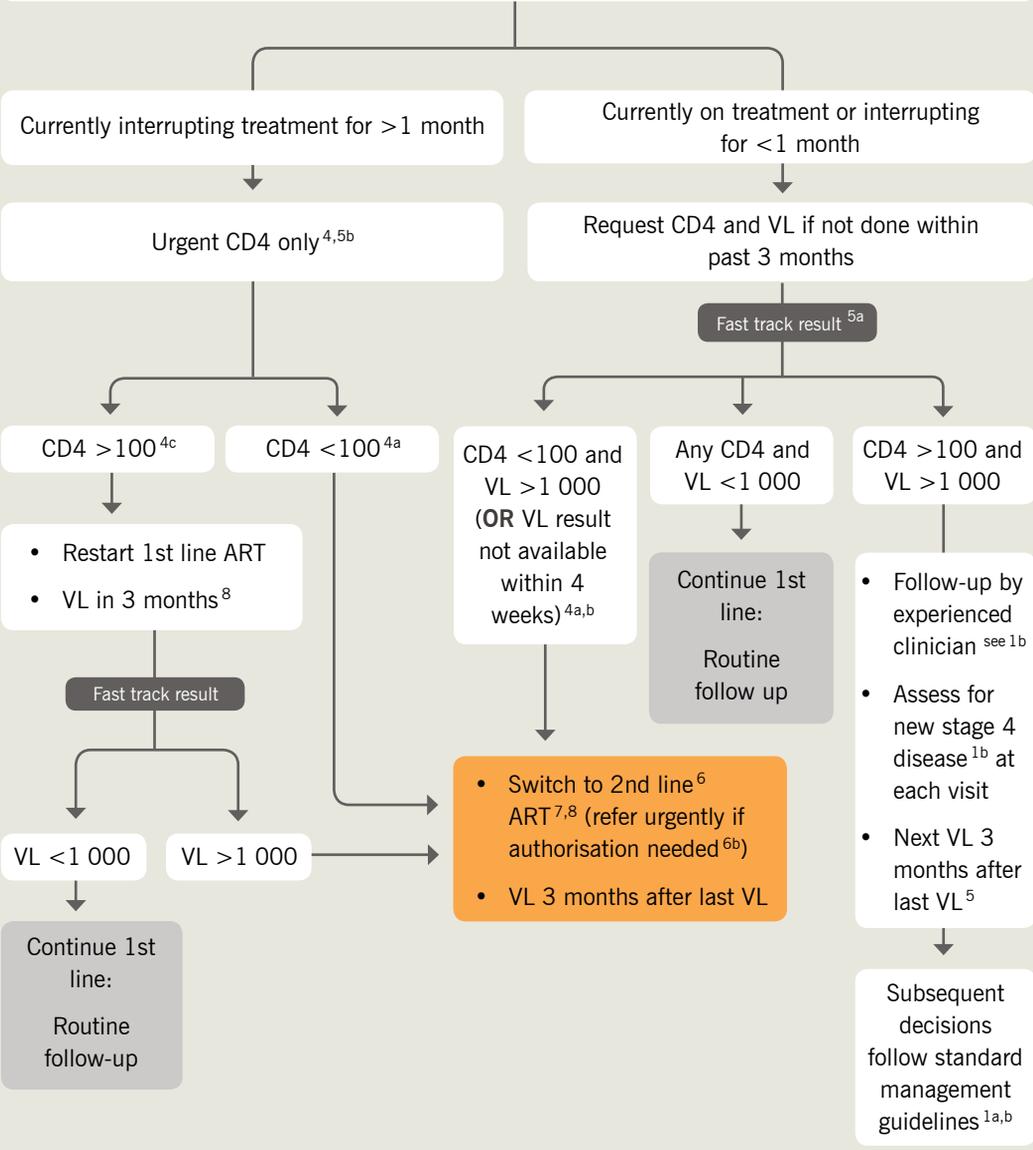
- Adherence support.
- Community worker tracing if appointments defaulted.
- Teach danger signs to patients and family, and when/how to access health care, if concerns.

Figure 11.4 Advanced HIV ART management diagram

Management of patients with advanced HIV¹, total ART >6 months², NO new stage 4 illness

If WHO criteria are already met for treatment failure switch to 2nd line ART immediately.^{1b}
(see Chapter 6, Table 6.1)

First line ART currently, or at the time of treatment interruption.
(The decision regarding whether to switch to a new regimen is based on CD4, viral load (VL) and the ART history regarding treatment interruptions^{1a,b,3})



Notes for Figure 11.4

1. **Patients presenting with advanced disease are at high risk of mortality and morbidity.**
 - a. A decision may need to be made to switch to second line ART outside standard guidelines. This will be guided by:
 - Whether the patient is currently on ART or has interrupted (see also note 3);
 - CD4 <100 indicates high risk of developing a fatal OI; requires an urgent decision;
 - The timeous availability of VL for confirming treatment failure.
 - b. If there is already a clear basis for diagnosing treatment failure (**Chapter 6**, sections 3–5) according to WHO criteria (virological, clinical or immunological) the ART regimen must be switched immediately. Note that a new stage 4 disease qualifies for clinical failure.
2. The total time on ART. The longer one is on an NNRTI-based regimen, the greater the opportunity for errors leading to the development of resistance. Conversely, it is very unlikely that resistance will develop in less than 6 months of total ART exposure.
3. ART-naïve or prior ART. As it is being increasingly noted that patients presenting with advanced disease have been on ART previously, it is important to take a careful ART history, going back many years, to establish the criteria noted in point 2 above.
4. The urgency with which the decision to switch needs to be taken is affected by the CD4.
 - a. CD4 is <100: the risk of developing a fatal OI in the next few months is high. Delaying for 3 months for adherence sessions and follow-up viral load may prove fatal. A rapid empirical switch may be indicated.
 - b. If CD4 <100 and there is a delay of >4 weeks in getting VL result (including not having VL at all), a fatal OI may develop while waiting. Therefore switch empirically.
 - c. CD4 >100: More time is available for a re-trial of first line medication to determine if there is resistance. If minimal change at follow-up VL at 3 months, switch to a new regimen. If significant change, defer switch for one month and repeat VL. (If the laboratory gives a log value, consider a log drop >2 to be significant.)
5. Sequential viral load results are important in the decision regarding a switch to a new regimen.
 - a. Viral load tests should therefore be prioritised and the results fast-tracked.
 - b. If the patient has currently interrupted treatment for >1 month the viral load will already be elevated, so it is not useful to do it.
6. A rapid switch outside standard guidelines may save lives:
 - a. In the hands of more experienced clinicians, this is merely a guide for management decisions in patients presenting with advanced disease so clinical judgment must be applied.
 - b. If there is insufficient experience or authority to make this decision, more experienced help must be sought the same day.
7. When to start ART or switch to 2nd line:
 - If TB and cryptococcal disease are excluded, offer same day initiation.
 - If serum CrAg positive + patient asymptomatic + LP not possible or LP has been done and CSF CrAg is negative, start ART the same day.
 - If non-CNS TB, once TB treatment has been initiated, start ART as soon as possible within 1–2 weeks.
 - If neurological TB or cryptococcal meningitis, delay ART till 4 weeks after OI treatment started.
8. PS (patient support) intervention recommended: both for suspected treatment failure and if starting a new regimen.

Figure 11.5 Care package for the unstable patient



TB is common major cause of death. Treat empirically if there is high suspicion.

TB LAM:

- TB LAM positive: Start TB treatment.
- TB LAM negative: **TB is not excluded!** Start empiric treatment if high suspicion of TB.

Xpert MTB/RIF:

Sputum or non-sputum samples: Pleural fluid, centrifuged CSF, centrifuged urine, pus. Bring patient back for result within 1 week:

- GeneXpert positive: start TB treatment.
- GeneXpert negative: **TB is not excluded!** Start empiric treatment if high suspicion of TB – do not wait for result if long turnaround time.

IPT: If no clinical evidence of TB, start isoniazid preventative therapy.

CrAg positive (finger-prick or serum):

- Symptoms of meningitis: Fluconazole 1 200 mg immediately and refer for lumbar puncture and ongoing treatment. If amphotericin B is available, start it while arranging transfer. See also Figure 11.6.
- Asymptomatic: Refer for lumbar puncture. If not possible, start fluconazole 800 mg daily for 2 weeks, 400 mg daily x 2 months, then 200 mg daily for at least one year or until CD4 >200.

Co-morbidities:

- Co-morbidities needing active follow-up mean the patient is categorised as 'unstable'.
- Common co-morbidities:
 - Diabetes, hypertension.
 - Cardiac failure, chronic kidney disease: Often caused by the above, look for other reversible causes.
 - Chronic liver disease: Check for hepatitis B and C, and alcohol excess.

Chronic diarrhoea:

This is often overlooked until patients need admission to hospital with severe dehydration, kidney failure and electrolyte wasting. Parasite opportunistic infections are a common cause, particularly *Isoospora belli*, and *cryptosporidium*. See **Chapter 15** for details.

CMV retinopathy:

In higher prevalence settings, ask about recent visual deterioration, and, if present, check visual acuity and refer for more comprehensive assessment.

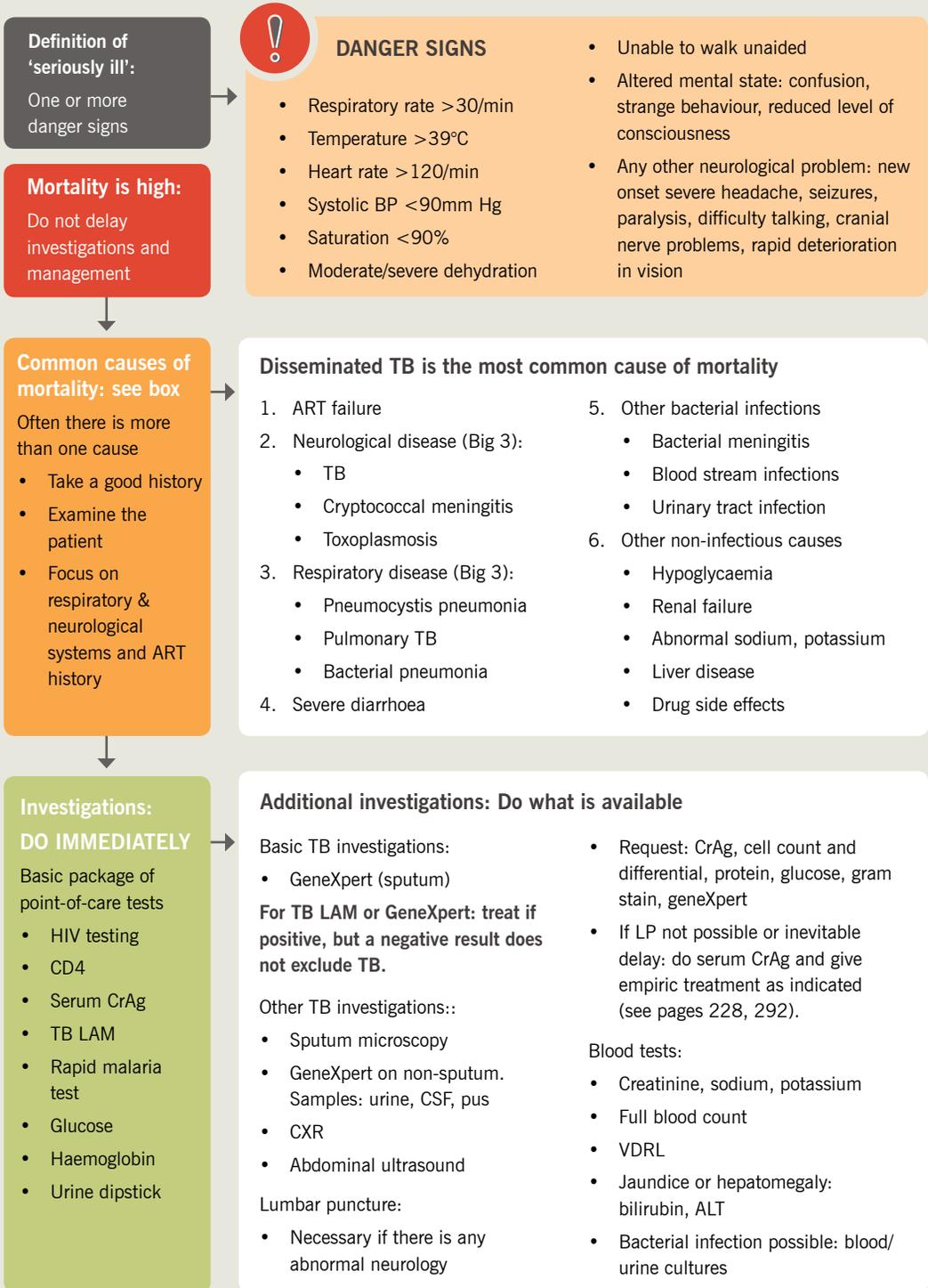
Follow-up:

- Arrange follow-up appointment to ensure continuity of care.
- Ensure ongoing care is done by clinician with appropriate level of experience.
- Educate patient regarding danger signs and other reasons to return sooner.

Avoid overuse of antibiotics – use only if bacterial infection is likely: (See **Chapter 23**)

- If antibiotics are used, document the reason.
- If a patient has had a course of antibiotics and has not improved, do not give another course without a clear reason. Look for other causes of symptoms, especially TB.

Figure 11.6 Management if transfer to hospital is delayed



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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.

Emergency management

Hypoglycaemia: 50 mls of 50% dextrose

Dehydration, renal impairment (see Chapter 17):

- IV fluids, electrolytes
- Chronic watery diarrhoea: empiric treatment for *Isospora belli* (cotrimoxazole)
- Beware nephrotoxic drugs

Liver failure: Beware hepatotoxic drugs (see Chapter 16)

Severe anaemia (Hb <5g/dL): Transfuse, oxygen (see Figure 18.1 in Chapter 18)

Bloodstream infection: If fever and other danger signs or other evidence suggesting bacterial infection, give empiric antibiotics

Neurological disease

Treat for cryptococcal meningitis if:

- CSF CrAg positive
- Abnormal neurology, serum CrAg positive and LP not possible (or CSF CrAg unavailable)

Give fluconazole prevention regimen if:

Serum CrAg positive and CSF CrAg negative

Treat for CNS TB if:

Neurology signs AND:

- Proven TB (LAM/GXP) or strongly suspected clinically
- CSF CrAg negative

Treat for toxoplasmosis if:

CD4 <200; new focal neurology; or other abnormal neurology and no other diagnosis

Respiratory disease

Respiratory danger signs: RR >30 or saturation <90%

- Give oxygen
- Empiric treatment for pneumocystis and bacterial pneumonia
- Empiric treatment for TB if indicated

No danger signs:

- CXR – treat accordingly
- CXR not available, consider empiric treatment: pneumocystis, bacterial pneumonia, TB

Clinical indications for immediate empiric TB treatment:

Do available investigations while starting treatment.

- CNS TB likely
- Miliary TB or other CXR evidence of TB
- Clinical presentation strongly suggests TB; investigations not available or unable to exclude TB
- Clinical condition life-threatening, patient deteriorating, or not improving after 3 days of hospitalisation