PROVIDING CARE TO PEOPLE WITH ADVANCED HIV DISEASE WHO ARE SERIOUSLY ILL

POLICY BRIEF

World Health Organization

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CONTENTS

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INTRODUCTION: WHY IS ADVANCED HIV DISEASE CARE IMPORTANT?

In 2021, 650 000 people died from AIDS-related causes, most of whom had advanced HIV. Reductions in these numbers have plateaued in recent years and are not on track to meet targets to end AIDS by 2030. Despite successes in expanding the availability of HIV testing and treatment worldwide, advanced HIV disease remains a persistent problem and drives AIDS-related deaths *(1–7)*. In many countries with a high burden of HIV, people living with HIV still comprise a large proportion of the people admitted to hospitals, and these people have a very high risk of death *(8–12)*.

To progress towards eliminating preventable AIDS-related deaths, HIV programmes should give priority to routinely identifying people who have developed advanced HIV disease and care for people who are seriously ill with complications of HIV. This involves diagnosing and treating the acute problem, linking these people to appropriate care, providing recommended prophylaxis and ensuring retention and adherence to antiretroviral therapy (ART) in the long term. These efforts should go alongside efforts to reduce late HIV diagnosis through an expanded diagnostic strategy linked to rapid ART initiation, efforts to retain people in care and optimise treatment to prevent progression to advanced HIV disease, and efforts to trace and re-engage those who have disengaged from care.

In 2017, WHO developed guidelines for advanced HIV disease (defined as people living with HIV with CD4 cell count <200 cells/mm^3 or a WHO stage 3 or 4 condition) *(13)*, and these recommendations were incorporated into the 2021 HIV guidelines *(14)*. New guidelines for diagnosis and management of histoplasmosis *(15)*, cryptococcal meningitis *(16)* and tuberculosis *(TB)* were published between 2020 and 2022 *(17,18)*. This policy brief is intended to support the uptake and implementation of the WHO-recommended advanced HIV disease package of care. It summarizes WHO guidance related to the care of people with advanced HIV disease who present at different levels of the health-care system and are seriously ill when they present.

Target audience and scope

This policy brief is primarily intended for use by country HIV programme officers and hospital management. It is also intended for use by clinicians and other health-care workers; international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in low- and middle-income countries; community-based organizations; and people living with HIV.

This policy brief summarizes WHO guidance and evidence relevant to advanced HIV disease care, with a focus on inpatient care and care for people who are seriously ill.

This policy brief summarizes various WHO guidelines relevant to the following groups of people:

- adults, adolescents and children living with HIV with a CD4 cell count <200 cells/mm^3;
- adults, adolescents and children living with HIV who are seriously ill, have WHO danger signs[1] or require admission to hospital; and
- adults, adolescents and children living with HIV with new WHO stage 3 or 4 disease.

People who are living with HIV, including those with advanced disease or who are seriously ill, may present to health care at a variety of different levels depending on local context. If a person presents to a primary care clinic, whether they could be safely managed at that clinic or need to be referred depends on several factors, including local organization of the health service network, how unwell the person is, what diagnostic and treatment resources are available and the cadre, number and skill set of staff at the primary care level. People may also come directly to a hospital emergency department without having a formal referral.

Community-based HIV services have a vital role to play in supporting HIV testing, raising awareness of advanced HIV disease and guiding unwell people to where they can receive care. Community-based services may be able to provide rehabilitation and support following recovery from illness but would not usually be expected to provide acute clinical care to people who are seriously ill.

[1] Danger signs for adults are: respiratory rate ≥30 breaths per minute; heart rate ≥120 beats per minute; or unable to walk unaided. Danger signs for children are any of the following: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; repeated vomiting; age defined tachycardia and/or tachypnoea.*(14)*

This policy brief focuses on hospital inpatient care. A person might require inpatient care for several reasons:

- for close clinical monitoring due to being seriously ill with deteriorating or fluctuating symptoms and clinical status as well as for higher levels of nursing care such as position change to prevent bedsores, assistance with mobility and pain management *(19)*;
- for advice and case management from professionals with knowledge and substantial clinical decision-making expertise, including making decisions in response to rapidly changing clinical conditions *(20)*;
- for treatments that are typically only delivered or available at a central location (such as supplemental oxygen or intravenous medicines); and
- for certain diagnostic or radiology services or procedures that are typically centralized or only provided at larger health-care facilities.

Clear referral criteria should be established so that people who initially present to primary health care but require inpatient care receive services in an expedited manner. Consideration should be given to removing barriers to accessing ambulance or other transport, so that people can be rapidly transferred to higher-level facilities when needed. There should be a mechanism for referral and communication back to a peripheral clinic following discharge from hospital to ensure appropriate follow-up.

INITIAL MANAGEMENT AND HIV TESTING

When unwell children, adolescents and adults first present to health care, immediately life-threatening conditions should be rapidly identified and treated. Guidance about emergency triage assessment and treatment for children *(21)* and guidance about emergency management of illness in adolescents and adults is available elsewhere *(22)*.

Many people who present to hospital with advanced HIV disease already know their HIV status, and HIV status should be confidentially asked about at admission to hospital. For people who do not know their HIV status, WHO recommends that, in settings with a high burden of HIV, HIV testing should be offered to all people presenting for care in all health-care settings (this is often referred to as provider-initiated testing and counselling). In settings with a low burden of HIV, people with conditions that could indicate HIV infection should be offered testing *(23)*.

Knowledge of HIV status is important for diagnostic decision-making when they are admitted as inpatients, especially if they are seriously ill. Consideration should therefore be given to making HIV testing services for inpatients available on evenings and weekends and available in all areas of hospitals. HIV testing algorithms and strategies are available to support high-quality testing *(23,24)*. Although HIV testing should be voluntary, if the person is unconscious, HIV testing should be considered where this is clinically judged to be in the person's best interests for optimal care and the reasoning explained to them when they regain mental capacity.

SCREENING AND DIAGNOSTIC TESTING

CD4 cell count and viral load test monitoring

When possible, people living with HIV admitted to hospital or presenting to care because of serious illness should have their CD4 cell count measured. CD4 cell counts are useful to determine the likelihood of various opportunistic infections and therefore help guide diagnosis and clinical management. CD4 cell counts can also help determine the likelihood that illness is due to immune reconstitution inflammatory syndrome. For people established on ART (i.e. taking ART for at least six months), a low CD4 cell count can indicate treatment failure (which should be confirmed by viral load monitoring) and is also useful to guide whether prophylaxis for opportunistic infections is needed. Point-of-care CD4 testing technologies based on flow cytometry can provide results within a few minutes. Several rapid tests, including tests based on lateral flow assay, to identify people with <200 cells/mm^3 are WHO prequalified *(25)*. Viral load testing, where available, is indicated for anyone taking ART for six months or longer to identify treatment failure *(14)* in the last three months.

Occasionally, people established on ART who started treatment with a very low CD4 cell count at baseline do not experience a rise in CD4 count despite a fully suppressed viral load; this is known as immune discordance *(26)*. People with low CD4 cell count but fully suppressed viral load should in general not switch ART regimens if the medication is well tolerated. If available, specialist advice could be sought in the situation of persistently low CD4 cell count and fully suppressed viral load.

Disease-specific tests for opportunistic infections

People living with HIV who are seriously ill need access to screening and diagnostic tests for certain opportunistic infections. Some tests are initial screening tests that should be offered to everyone with advanced HIV disease (criteria for screening are set out below), and some are diagnostic tests that should only be offered to people if there is clinical indication (signs and symptoms of the relevant disease), in a prespecified subgroup, or following a positive screening test. The screening tests mentioned below can be used both for screening and as a diagnostic test depending on the population investigated and clinical presentation.

Consideration should be given to making these tests available at all levels of the health system where people might benefit from them. It is important to make these tests available at places where seriously ill people might be evaluated or triaged (such as hospital emergency departments) that are not typically considered part of HIV services and ensuring availability on evenings and weekends.

Cryptococcal disease: cryptococcal antigen

Adults and adolescents with advanced HIV disease should receive serum cryptococcal antigen screening, followed by cryptococcal antigen testing in cerebrospinal fluid (CSF) if the serum cryptococcal antigen test is positive. The 2022 WHO guidelines on diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV outline screening and diagnostic algorithms depending on availability of diagnostic tests and lumbar puncture *(16)*.

Cryptococcal antigen screening among children younger than 10 years without symptoms of cryptococcal disease is not generally recommended, since children have a low prevalence of cryptococcal disease. However, if a child has signs and symptoms of cryptococcal meningitis, then diagnostic testing using serum cryptococcal antigen should be offered. If serum cryptococcal antigen is positive, then diagnostic testing using CSF cryptococcal antigen should be offered if lumbar puncture is available.

TB disease

WHO recommends that all people living with HIV be screened for TB and offers several methods. Screening can be conducted with the WHO-recommended four-symptom screen, which includes screening for any one of cough, fever, weight loss and night sweats. Screening can also be conducted with C-reactive protein assay, chest X-ray (with or without computer-aided detection) or sputum recommended molecular diagnostic test for TB. The choice of screening strategy depends on the characteristics of the population being screened and the resources available for screening and further diagnostic testing *(27)*.

Everyone with a positive screening test (i.e. everyone with presumptive TB) should have a recommended sputum TB molecular test and urine lateral flow lipoarabinomannan assay (LF-LAM). Adults and adolescents admitted to medical wards where the TB prevalence is estimated to be >10% should be tested with a recommended sputum TB molecular test, regardless of symptoms *(27)*.

Testing using urine LF-LAM should be used in all people living with HIV with signs and symptoms of TB (pulmonary and/or extrapulmonary). Testing using urine LF-LAM should also be performed irrespective of TB symptoms in adults, adolescents and children who are seriously ill, or have clinical Stage 3 or 4 disease or with CD4 count <200 cells/mm^3 among inpatients or with CD4 count < 100 cells/mm^3 among outpatients.(14) For programmatic reasons, some national guidelines include testing all people with AHD with urine LF-LAM, irrespective of setting *(28)*.

Extrapulmonary or disseminated TB with or without pulmonary TB occurs commonly among people with advanced HIV disease, and testing non-sputum samples with a recommended TB molecular test and testing using urine LF-LAM is important. Depending on the clinical scenario, other samples for molecular testing include: CSF (for TB meningitis), lymph node aspirates or biopsy (for TB lymphadenitis), urine (for genitourinary TB), blood (for disseminated TB) and lymph node, pleural, peritoneal, pericardial and synovial fluids for respective clinical indications.

For children with signs and symptoms of pulmonary or extrapulmonary TB, recommended TB molecular tests should be performed on sputum, nasopharyngeal aspirate, gastric aspirate, stool, blood or urine, together with urine LF-LAM *(18)*. The WHO operational handbook for TB in children and adolescents outlines integrated treatment decision algorithms for diagnosing pulmonary TB for children under 10 years old, including decision-making about diagnosing TB where specific tests are negative or not available. These algorithms are designed primarily for use in an outpatient settings, but may assist clinical decision making in inpatient settings *(29)*.

Other disease-specific tests

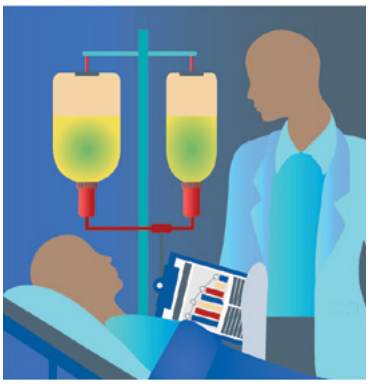
If histoplasmosis is clinically suspected, WHO recommends diagnostic testing using antigen detection assays *(14,15)*. Histoplasmosis is highly endemic in some regions of North America, Central America and South America and is also reported in certain countries of Asia and Africa *(15)*.

In areas of geographical risk for malaria, early diagnosis is recommended, using microscopy or a rapid diagnostic test *(14)*.

Depending on clinical symptoms, local epidemiology and laboratory capacity, specific tests could be offered for other invasive fungal infections such as talaromycosis and other diseases such as visceral leishmaniasis.

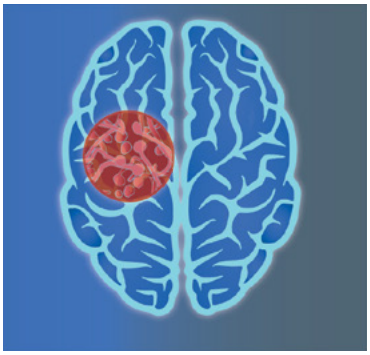
If a person is referred to hospital or a centre with diagnostic laboratory on site, or if additional rapid tests are available, it might be appropriate to take the opportunity to offer screening for chronic conditions or other relevant diseases – such as sexual health screening or screening for syphilis and chronic viral hepatitis B and C. This will depend on laboratory capacity, local epidemiology and the clinical scenario.

WHY DO PEOPLE HOSPITALISED WITH HIV HAVE POOR OUTCOMES?



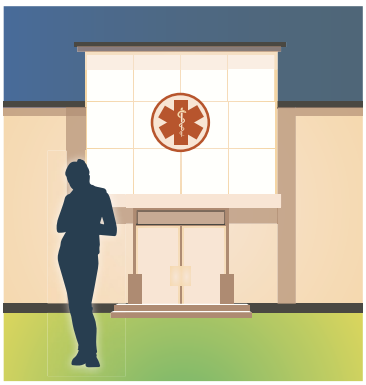
Seriously ill people living with HIV often suffer from a variety of life-threatening infections

20%
of people die in hospital



Tuberculosis, cryptococcal meningitis and severe bacterial infections are the most common causes

19%
of people successfully discharged from hospital are re-admitted within a year



Sometimes people are not linked to care following discharge from hospital

14%
die within a year of discharge

Patients often suffer with long-term disabilities following discharge and still need care

Table 1. Summary of recommended disease-specific tests for screening and diagnosis of opportunistic infections in advanced HIV disease

Offer as screening tests		
Test	**Use**	**Clinical considerations**
Serum cryptococcal antigen test	Adults and adolescents with CD4 count <100 cells/mm^3 and considered for those with CD4 count <200 cells/mm^3 [a] Adults, adolescents and children with signs and symptoms of cryptococcal meningitis	If serum cryptococcal antigen is positive, proceed to lumbar puncture and CSF cryptococcal antigen testing where available
TB screening procedures or tests	Adults, adolescents and children living with HIV should be screened for TB at every health-care visit. Screening can be performed using any of the following individually or in combination: • four symptom screen • chest X-ray with or without computer-aided detection • C-reactive protein • recommended sputum TB molecular tests [b]	All screened positive individuals should have a diagnostic test (see below). If an individual is screened positive with a TB molecular test, see the TB screening guidelines for further guidance *(27)*.

Offer as diagnostic tests to people with signs and symptoms or following a positive screening test or prespecified subpopulations		
Test	**Use**	**Clinical considerations**
Urine LF-LAM test for TB	Adults, adolescents and children with signs and symptoms of TB (pulmonary and/or extrapulmonary) Adults, adolescents and children who are seriously ill or who have clinical stage 3 or 4 disease. Asymptomatic adults, adolescents and children in inpatient settings with CD4 <200 cells/mm^3 and in outpatient settings of CD4 <100 cells/mm^3	A negative urine LAM test does not rule out TB If LAM is positive, TB treatment should be started. Further sputum or extrapulmonary TB tests should be requested in addition, since urine LAM cannot detect drug resistance
TB molecular test	**Screen-positive individuals: presumptive pulmonary TB** Adults and adolescents: sputum or other respiratory samples Children: sputum, nasopharyngeal aspirate, gastric aspirate or stool **Presumptive extrapulmonary TB:** All individuals: Blood, urine, CSF, lymph node aspirates, lymph node biopsy, pleural, peritoneal, pericardial, synovial fluids as indicted by symptoms and likely site of TB.	Non-sputum and child samples vary in mycobacterial load and may be negative in some people who truly have TB
CSF cryptococcal antigen test	Adults, adolescents and children with signs and symptoms of cryptococcal meningitis Adults and adolescents and children who have a positive serum cryptococcal antigen	If lumbar puncture is available and no contraindication to lumbar puncture For alternative diagnostic and treatment algorithms where lumbar puncture is not available, see the cryptococcal disease guidelines *(16)*
Histoplasma antigen test	Adults, adolescents and children with suspected histoplasmosis	Histoplasmosis is highly endemic in certain regions; see WHO guidelines *(15)*
Malaria rapid diagnostic test	All adults, adolescents and children with suspected malaria, including all people in malaria endemic area with fever *(30)*	For children younger than five years, practical algorithms from Integrated Management of Childhood illness should be used *(31)*
COVID-19 testing	Adults, adolescents and children for whom COVID-19 is clinically suspected	This is a rapidly changing area. See the WHO HIV and COVID webpage for up-to-date information *(32)* Information about the clinical features of people with HIV and COVID-19 from 2021 is available *(33)*

[a]WHO does not recommend systematic serum cryptococcal antigen screening for children due to low prevalence of cryptococcal disease. Serum cryptococcal antigen should be used only if cryptococcal disease is clinically suspected.
[b]Sputum TB molecular tests should be used for all people living with HIV admitted to hospital where TB prevalence >10% *(27)*.

Box 1. Considerations for diagnosing TB, including clinical diagnosis

TB is the most common cause of hospital admission and the most common cause of death among people living with HIV. Evidence from autopsy studies suggests that it is often missed as a diagnosis *(34–38)*.

Diagnosing TB among people with HIV can be complex. Everyone with TB symptoms should have a TB molecular test using sputum and other specimens if relevant. However, people are often unable to produce sputum, and for people who are seriously ill with advanced HIV (and therefore have a high pretest probability of TB), a negative sputum molecular test may not adequately rule out TB. Urine LF-LAM testing is useful and recommended but is not sensitive enough rule out TB. Radiological tests such as chest radiographs and ultrasound can be very helpful but only provide evidence to support a diagnosis rather than provide a definitive diagnosis.

Disseminated or extrapulmonary TB can present with non-specific symptoms, and diagnostics for disseminated TB can be challenging. The commonest forms of extrapulmonary TB include lymph node (especially in the neck or under the arms), pleural (usually one-sided pleural effusion), pericarditis, meningitis and disseminated TB (disease that is not limited to one site in the body). Molecular TB tests should be done on non-sputum samples where extrapulmonary or disseminated TB is clinically likely; however, the negative predictive values vary greatly depending on the subpopulation tested and the sample type. In particular, having a negative result for a molecular test on CSF is relatively common for people with TB meningitis. Diagnoses of TB meningitis are often made based on clinical signs and symptoms and CSF chemistry and cellular findings.

In countries and areas with a high TB burden and for people who are seriously ill with danger signs, careful consideration should be given to initiating TB treatment based on clinical or radiological diagnosis of TB without a positive TB test (sometimes called empiric treatment). Clinical judgement is required in this scenario. If empiric TB treatment is started based on clinical diagnosis, clinicians should remain alert to the possibility of an alternative diagnosis or co-infection (e.g. bacterial pneumonia or *Pneumocystis jirovecii* pneumonia). Co-infections should be managed appropriately. Investigations for TB, including drug susceptibility testing, should continue even if treatment has been started empirically, to guide future management, in case of non-responsiveness to treatment.

Other laboratory diagnostic tests (not specific to one disease)

Several other diagnostic tests may be useful where available and depending on clinical scenarios. The following tests are in the WHO Model List of Essential In Vitro Diagnostics for healthcare facilities with clinical laboratories *(39)* and may be particularly useful for making a diagnosis, adjusting drug doses, or monitoring in inpatients with HIV.

Clinical chemistry and immunoassays

Blood urea nitrogen, creatinine, electrolytes: to estimate glomerular filtration rate, monitor organ damage, identify renal failure, as a key clinical marker for management of severe infections and antimicrobial regimen dose adjustment.

C-reactive protein: to detect inflammation as an indicator of various conditions.

Alanine amino-transferase, aspartate amino-transferase, bilirubin: to assess liver function.

Haematology and blood transfusion

Haemoglobin, platelet count or complete blood count with automated differential: diagnosis and monitoring of anaemia, diagnosis of thrombocytopaenia. Leukocytosis may suggest infection.

Microbiology, mycology and parasitology

Urine dipstick: detection of urinary tract infection and investigation of cause of renal failure.

CSF microscopy: useful to detect meningitis and can give an indication of type of pathogen causing meningitis.

Stool microscopy: may help diagnose the cause of diarrhoea.

Bacterial blood and CSF culture and antimicrobial susceptibility testing: tests for presence of bacterial infection, type of bacteria causing infection and identification of antimicrobial resistance.

Histopathological testing is not included in the WHO Model List of Essential In Vitro Diagnostics, but where available, pathology services can be helpful for diagnosing malignancy (particularly Kaposi's sarcoma and lymphoma) and differential diagnosis of severe anaemia (bone marrow biopsy). Mycobacteriology, mycology and parasitology tests not included in the Essential Diagnostic List may be offered depending on clinical presentation, local epidemiology and laboratory capacity.

It is important to use all available diagnostic tools to support clinical decision-making, but individual input from experienced clinicians is sometimes needed. For many HIV-associated diseases, no good specific diagnostic test is widely available (for example, toxoplasmic encephalitis or *Pneumocystis jirovecii* pneumonia). For some conditions where tests are available, turnaround time can be long (for example, blood cultures) (40), and urgent treatment based on presumptive diagnosis is needed before the diagnosis can be confirmed. For most diseases, a combination of suggestive non-specific tests, radiological investigations, consideration of individual symptoms and risk stratification (for example, based on CD4 cell count) is used to make a diagnosis.

Radiology and imaging

Where available, radiological examinations can provide supportive evidence for a diagnosis.

Chest X-ray can provide supporting evidence of TB, bacterial pneumonia and *Pneumocystis jirovecii* pneumonia (41). WHO recommends that computer-aided detection software can be used to read digital chest radiographs and detect abnormalities that could be compatible with TB, including people with HIV aged over 14 years.

Ultrasonography: can support a wide variety of diagnoses *(42)*.

Computed tomography: can be particularly useful for identifying intracranial space occupying lesions in central nervous system opportunistic infections and malignancies. Magnetic resonance imaging can also be used where available, particularly for intracranial imaging.

MANAGEMENT OF MAJOR INFECTIOUS AND NON-INFECTIOUS HIV-ASSOCIATED CONDITIONS

A systematic review published in 2015 identified the most common causes of hospitalization for adults living with HIV as TB, cryptococcal disease and severe bacterial infections *(8)*.

TB (pulmonary, extrapulmonary or disseminated)

The WHO-recommended treatment for drug-sensitive pulmonary TB for adults is two months of rifampicin, isoniazid, ethambutol and pyrazinamide followed by four months of rifampicin and isoniazid (2RHZE/4RH) *(17)*. Where possible, these should be given in fixed dose combinations. In 2021, WHO conditionally recommended a four-month regimen (isoniazid, rifapentine, moxifloxacin and pyrazinamide for two months, and isoniazid, rifapentine and moxifloxacin for two months) for treatment of drug-sensitive pulmonary TB in adults and adolescents age 12 years and older. Only 8% of participants in the trial that informed this recommendation were living with HIV, and all the people living with HIV in the trial had CD4 count >100 cells/mm^3 *(43)*. This four-month regimen is not recommended for people living with HIV with a CD4 cell count <100/mm^3, people weighing less than 40 kg and pregnant and breastfeeding women.

WHO recommends that people with extrapulmonary TB also receive six months' treatment (2HRZE/4RH) *(17)*, except for TB meningitis or osteoarticular TB. There is no formal WHO recommendation about duration of treatment for TB meningitis for adults, and several expert groups recommend treatment durations of longer than six months *(44)*. Many national guidelines recommend 2RHZE followed by 7–10 months of RH for treatment of TB meningitis in adults *(45)*. People with TB meningitis should receive adjuvant corticosteroid therapy with dexamethasone or prednisolone, with dose tapered over 6–8 weeks *(17)*.

Most children living with HIV should also receive six months of TB treatment. For children aged three months to 16 years with pulmonary TB, WHO recommends a four-month regimen for non-severe TB (2HRZ(E)/2RH). However, most children with HIV who are seriously ill will not meet the criteria for non-severe disease and should receive six months of treatment. For children and adolescents with HIV-associated TB meningitis, WHO recommends 12 months of treatment 2HRZE/10RH *(18)*.

Cryptococcal disease

The WHO-recommended treatment of cryptococcal meningitis is detailed in 2022 guidelines *(16)*. The preferred induction regimen for adults, adolescents and children is a single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). The guideline contains alternative induction regimens if these medicines are not available *(16)*.

People with cryptococcal meningitis should receive fluconazole consolidation and maintenance treatment after induction treatment; the recommended doses and durations are outlined in the guideline (16). The guidelines also include recommendations for treatment of non-meningeal cryptococcosis *(16)*.

Severe bacterial infections

Severe bacterial infections are estimated to cause more than one third of hospital admissions among adults and children living with HIV *(8)*. Severe bacterial infections can lead to sepsis and septic shock, especially if not treated early. Urgent antibiotic treatment is needed for severe bacterial infections. The choice of antibiotic should be guided by suspected source of infection and national or local antimicrobial guidelines. National groups, and where possible local hospital committees, should develop antimicrobial guidance to use antibiotics appropriately to reduce the risk of drug resistance. The policy should also provide advice on which antibiotics to use when drug-resistant bacterial infection is proven or suspected, especially for hospital-acquired infections *(40,46)*.

Other opportunistic infections

- **Respiratory infections**
  As well as bacterial community-acquired pneumonia, people living with HIV are at risk of developing *P. jirovecii* pneumonia and other fungal respiratory infections, such as cryptococcal pulmonary disease. Symptoms of *P. jirovecii* pneumonia classically include dry cough, hypoxia (low oxygen saturation), often out of keeping with symptoms, and worsening hypoxia on walking. On chest X-ray, *P. jirovecii* pneumonia infections typically cause diffuse bilateral changes in both lungs. Treatment for *P. jirovecii* pneumonia is usually with high dose co-trimoxazole and steroids if severe disease. Several expert groups have guidelines for treating adults with community-acquired pneumonia, including *P. jirovecii* pneumonia, which include details on doses and duration *(47-49)*.

- **Diarrhoea**
  A wide variety of opportunistic infections can cause acute or chronic diarrhoea. These include protozoa parasites (such as cystoisospora and cryptosporidium), helminths (ascaris, strongyloides), bacteria (shigella and salmonella) and viral infections. Stool microscopy can be useful to diagnose protozoan infections. Guidance on diagnosis and treatment (including drugs and doses) is available from the Southern African HIV Clinicians Society *(50)* and other expert groups *(48,49)*.

- **Other intracranial infections**
  Meningitis (infection of the fluid and membranes surrounding the brain) is the most common type of intracranial infection in advanced HIV; this includes TB meningitis and cryptococcal meningitis. Meningitis can also be caused by bacteria (acute bacterial meningitis) or viruses (viral meningitis). Acute bacterial meningitis is an emergency that requires prompt treatment with appropriate antibiotics.

  Some types of intracranial infection cause space-occupying lesions, with one or more areas of the brain affected. Space-occupying lesions can cause focal nervous system symptoms, seizures or symptoms related to increased pressure in the brain. They can be seen on computed tomography or magnetic resonance imaging scan of the brain if this is available. The most common cause of space occupying lesions are toxoplasmic encephalitis, TB, cryptococcosis, but there are and many other parasitic, bacterial or fungal pathogens (51); they can also be caused by non-infectious diseases (such as lymphoma).

  There are many other types of intracranial infections. One of the most clinically relevant other types of infections is HIV-associated progressive multifocal leukoencephalopathy, which is a condition caused by JC virus that causes central nervous system impairment.

  An approach to diagnosis and treatment of meningitis and space-occupying lesions for people with advanced HIV disease in hospital is available from the Southern Africa HIV Clinicians Society *(50)*.

- **Other disseminated infections**
  Sometimes opportunistic infections can spread to multiple organ systems; their diagnosis can be challenging, and symptoms can be non-specific (such as fever, weight loss and lethargy). Disseminated infections include fungal infections such as histoplasmosis and talaromycosis, parasitic diseases such as visceral leishmaniasis and disseminated non-tuberculous mycobacteria. These are often geographically restricted. WHO guidelines exist for managing visceral leishmaniasis *(52)* and histoplasmosis *(15)*.

Several guidelines and documents from national expert committees are available about managing HIV-associated opportunistic infections *(48-50)*.

Kaposi's sarcoma

Kaposi's sarcoma is a WHO AIDS-defining illness associated with herpesvirus type 8. It commonly causes skin or mucous membrane lesions among adults and adolescents but can also sometimes cause lymphadenopathy, lymphoedema and pulmonary infiltration and occasionally can become widely disseminated throughout the body. Skin lesions are often absent among children. The prevalence of Kaposi's sarcoma among adults and children with advanced HIV who are severely ill is unknown *(55)*. Limited Kaposi's sarcoma will usually respond to ART initiation without any other specific treatment. More severe forms should be treated with systemic chemotherapy, where therapeutic drugs, skilled staff and the monitoring needed are available *(56)*. There is ongoing research about the optimal chemotherapy regimens for Kaposi's sarcoma, with a recent randomized trial showing increased progression-free survival for paclitaxel compared to an alternative regimen *(57)*. WHO guidelines on the treatment of skin and oral HIV-associated conditions include recommendations for managing Kaposi's sarcoma *(56)*.

HIV and COVID-19

WHO has developed an online HIV and COVID-19 hub that contains up-to-date information about managing testing, treatment and infection prevention and control for people with HIV and confirmed or possible COVID-19 *(32)*. The differential diagnosis between COVID-19 and *P. jirovecii* pneumonia can be challenging, and both can coexist. After recovery from acute illness, people living with HIV should be encouraged to have vaccination for COVID-19 in line with national vaccination policies.

HIV and mpox

Mpox (previously called monkeypox) is a viral illness that is usually self-limiting with symptoms lasting two to four weeks. Severe disease with protracted clinical courses tend to occur among immunosuppressed individuals, including those with advanced HIV disease, and may make an individual seriously ill *(53)*. Of the people hospitalized with mpox during the 2022 outbreak, many were living with HIV and had advanced HIV disease *(53)*. Up-to-date information about mpox, including diagnosis, treatment and epidemiology, is available at the WHO website *(54)*.

Other HIV-associated malignancies

Malignancies represented 3% of all admissions to hospital for adults living with HIV and 1% of children living with HIV *(8)*. Lymphoma, cervical and anogenital cancer are more common among adults living with HIV. Treatment and diagnosis of advanced cancer remains a specialist area and likely accessed by referral to a specialist centre.

Non-infectious HIV-related conditions

Non-infectious HIV-related conditions can be important for people with advanced HIV disease who are seriously ill.

- **HIV-associated central nervous system conditions**
  HIV can be associated with infectious and non-infectious chronic central nervous system conditions, some of which might make an individual seriously unwell. Among suppressed individuals, HIV-associated neurocognitive disorder is thought to be caused by chronic inflammation and potentially ongoing HIV replication in the brain. There is no specific treatment for HIV-associated neurocognitive disorder, but effective ART and viral suppression might help.

  People living with HIV are at higher risk of cerebrovascular disease, including strokes, than HIV-negative people. Acute hospital management of stroke is the same for people living with HIV as for HIV-negative people.

- **Anaemia**
  There are many causes of anaemia in the setting of HIV disease *(58)*. Blood transfusions may be needed in certain situations to manage the consequences of anaemia. Treatment depends on the underlying cause.

- **Renal impairment**
  Renal failure can be acute or chronic. There are many causes of renal failure, including HIV itself (HIV-associated nephropathy), opportunistic infections and critical illness. Some medicines used in treating HIV or opportunistic diseases can cause renal impairment, and some require dose adjustments if renal impairment is present *(59)*. WHO has guidelines for monitoring renal function during cryptococcal meningitis induction treatment. For other conditions, specialist input may be helpful, if available.

- **Liver impairment**
  Liver impairment can be acute or chronic. Alcohol use and viral hepatitis B and C are common causes of chronic liver disease and may present with "decompensated" liver failure (sudden worsening of liver impairment on a background of chronic liver impairment). Some medicines, especially TB medicines, efavirenz and protease inhibitors, can also cause or worsen liver impairment.

- **Wasting syndrome and malnutrition**
  Malnutrition and wasting are important causes of hospitalization, representing 3% of all adult hospital admissions and 17% of children's hospital admissions *(8)*, and are often associated with chronic diarrhoea for multiple pathogens, usually parasites. Nutritional assessment for people living with HIV in hospital should be an integral component of HIV care. WHO has guidelines on managing severe acute malnutrition among children, including considerations for children living with HIV *(17,60)*.

MANAGING ART AMONG PEOPLE WHO ARE SERIOUSLY ILL

Individuals not receiving ART (ART naive or interrupted treatment)

In general terms, any HIV-positive individual who is not receiving ART should start it as soon as possible. WHO does not currently have differentiated guidance for starting ART for people who are seriously ill or admitted to hospital compared with people attending primary care clinics.

People with central nervous system signs and symptoms should have investigations for meningitis before starting ART; if TB meningitis or cryptococcal meningitis is diagnosed, ART initiation should be delayed until after four weeks of TB treatment (TB meningitis) or until four to six weeks from the start of cryptococcal meningitis treatment *(14,61)*. There is no specific WHO recommendation about timing of ART following bacterial meningitis *(62)* or other central nervous system opportunistic infections, given lack of data. Expert opinion about managing ART among adults with cryptococcal meningitis, including certain situations in which stopping ART among people with cryptococcal meningitis (and restarting once recovered) is suggested, has been summarized *(63, 64)*.

WHO recommends that people with TB start ART as soon as possible and within two weeks of having started TB treatment (unless they have TB meningitis). One trial showed that giving prednisone concurrent with starting ART to people already receiving treatment for TB reduced the incidence of paradoxical TB-immune reconstitution inflammatory syndrome *(65)*; more research is needed to inform guidance. WHO also recommends that people with TB symptoms but awaiting TB diagnostic test results should start ART as soon as possible, with close timely follow up to receive and act on TB test results.

There is no specific recommendation about when to start ART for people in hospital who are seriously ill, who have opportunistic infections other than TB or cryptococcal meningitis or while diagnostic tests are pending and cause for illness is unclear; three small trials in adults *(66–68)* and two in children generally showed no statistically significant difference between early and delayed ART. A WHO expert advisory group for children concluded that appropriate care for clinical conditions requiring acute management is the first priority, and ART initiation should follow *(13)*.

People who have previously been taking ART but who have interrupted treatment should be offered ART reinitiation on the same time scales as people who are ART naive. If their initial ART regimen was based on non-nucleoside reverse-transcriptase inhibitors, individuals should restart a dolutegravir-based regimen *(13)*. It is advised to discuss reasons for having interrupted care and provide counselling strategies that might help prevent a further interruption.

People starting ART in hospital should have the same counselling, information and opportunity to ask questions as people starting ART in primary care settings.

Individuals currently taking ART

A detailed history about ART intake should be taken *(14)*. An individual who is unwell and has been taking ART for more than six months should have their adherence evaluated and an HIV viral load test, if available. People who are taking a regimen based on non-nucleoside reverse-transcriptase inhibitors and have a viral load greater than 1000 copies/mL should switch immediately after a single elevated viral load to a dolutegravir-containing ART regimen. People with an elevated viral load who are taking a regimen containing dolutegravir or a protease inhibitor should have enhanced adherence counselling for at least one month, and a repeat viral load test done at three months or earlier according to local standards *(14)*. The WHO guidelines for managing advanced HIV disease suggest that programmes could consider reducing the time for repeat viral load to one month (rather than three months) for people with advanced HIV disease *(13)* to reduce the amount of time with treatment failure.

More evidence about timing of an ART switch, appropriate second-line regimens and actions to be taken on identifying failure to suppress viral loads among people who are seriously ill is a priority.

Managing immune reconstitution inflammatory syndrome and suspected ART drug reactions

Immune reconstitution inflammatory syndrome and ART drug reactions are both more common in the first few months after starting or changing ART, although drug reactions can occur at any time.

After starting ART, immune reconstitution inflammatory syndrome may manifest as a worsening of a previously diagnosed disease (termed paradoxical immune reconstitution inflammatory syndrome) or present as the unmasking of a previously undiagnosed disease with an unusually heightened inflammation (unmasking immune reconstitution inflammatory syndrome). Consensus definitions for research purposes exists for TB immune reconstitution inflammatory syndrome *(69)* and for other opportunistic infections *(70,71)*.

WHO does not have a specific recommendation for managing ART when immune reconstitution inflammatory syndrome is suspected. Most expert guidelines recommend symptomatic treatment (such as analgesia) and reassurance for mild immune reconstitution inflammatory syndrome *(70)*. For individuals with more severe immune

reconstitution inflammatory syndrome, especially immune reconstitution inflammatory syndrome caused by TB, steroids may be used *(70,72)*. Steroids should not routinely be used for people with cryptococcal meningitis due to an increase in adverse events and delayed clearance of fungus from CSF *(73)*, but some expert guidelines suggest steroids in severe immune reconstitution inflammatory syndrome due to cryptococcal meningitis *(64)*. In general, ART should not be interrupted in immune reconstitution inflammatory syndrome, but advice should be sought from an experienced HIV clinician if possible.

ART side-effects associated with currently available drug regimens are usually mild and unlikely to require hospitalization. In the event of severe and life-threatening toxicity or hypersensitivity (such as severe hepatitis or Stevens-Johnson syndrome), ART should be discontinued until symptoms have resolved and a substitution regimen can be safely initiated *(14)*. If possible, people who have symptoms of ART toxicity should have laboratory testing as indicated (for example, renal function, liver function or haemoglobin; see the toxicity section of 2021 consolidated HIV guidelines *(14)*). Specialist advice may be required.

WHO recommends monitoring antiretroviral drug toxicity at the national level, so if someone who is seriously ill is identified as having antiretroviral drug toxicity, this should be reported as part of routine pharmacovigilance.

PROPHYLAXIS AND PRE-EMPTIVE TREATMENT

The package of care for people with advanced HIV disease includes prophylaxis and pre-emptive treatment. Prophylaxis and pre-emptive treatment should be started as soon as possible and before hospital discharge (for inpatients), if possible. Further details about when to start and stop are in the 2021 consolidated HIV guidelines *(14)* or the consolidated guidelines on TB preventive treatment *(14,74)*.

Table 2. Prophylaxis and pre-emptive treatment

	Population	Drug regimen	Clinical considerations
TB preventive therapy	Adults, adolescents and children who are unlikely to have active TB disease	A variety of different TB preventive therapy regimens are recommended; see the TB prevention guidelines *(74)*	Consider giving pyridoxine alongside TB preventive therapy to reduce the risk of peripheral neuropathy
Cryptococcosis pre-emptive treatment	Adults and adolescents with serum cryptococcal antigen test positive but CSF cryptococcal antigen negative	Fluconazole 800 mg/day for two weeks, then 400 mg/day for eight weeks and continued maintenance with fluconazole 200 mg/day *(16)*	Maintenance treatment should continue until person is stable on ART with CD4 cell count >200 cells/mm^3
Co-trimoxazole prophylaxis	Adults and adolescents with CD4 cell count <350 cells/mm^3, consider for all in areas where malaria and/or severe bacterial infections are highly prevalent All children.	Adult dose is 960 mg of co-trimoxazole once per day; the 2021 consolidated guidelines contain doses for children and adolescents *(14)*	Prophylaxis against bacterial infections, malaria and P. *jirovecii* pneumonia

SYMPTOM MANAGEMENT AND PALLIATIVE CARE

People living with HIV admitted to hospital have a very high risk of death in hospital and in the 12 months following hospital discharge *(8,9)*. Whilst many people will recover fully, health-care providers are likely to encounter people with life-limiting illnesses. Regardless of whether an illness is likely to fully resolve or is life-limiting, people may have distressing symptoms and functional impairment or disability.

People should receive adequate analgesia for pain and a holistic approach to care, including alleviating suffering, managing disability and focusing on what is most important to individuals and their families. Consideration should be given to incorporating palliative care into inpatient hospital care and outpatient care for seriously ill people. WHO has guidelines for palliative care services and integrating palliative care into primary health care and paediatric health care *(75)*.

MANAGEMENT OF HOSPITALISED INDIVIDUALS WITH ADVANCED HIV DISEASE

ASSESSMENT

- Conduct emergency triage (including in children) and treat immediately life-threatening conditions

REFER

- Rapidly refer to higher level facility if needed
- Do not delay treatment

DIAGNOSE

- In people who are seriously ill, test for HIV, ask about ART use
- Test CD4 cell count to identify advanced HIV disease
- If no CD4 testing available use WHO staging for HIV

IDENTIFY

- Offer a molecular diagnostic test for TB, urine LF-LAM and cryptococcal antigen testing
- Offer other lab and radiological investigations as available
- Establish a diagnosis, consider empirical treatment for TB

TREAT

- Start appropriate treatment, monitor closely
- Provide high quality nursing care, physical assistance, nutrition, and regular clinical review

ART

- Start/change ART as indicated
- If not already on ART offer rapid initiation of ART
- Do not start ART if a working diagnosis of meningeal disease has been established
- Treat TB meningitis or cryptococcal meningitis first, consider ART start in 4-8 weeks

PLAN/LINK

- Develop a discharge plan through joint decision making with the patient and their family.
- Ensure good communication with the HIV clinic to link to care following discharge

IMPLEMENTATION, QUALITY OF CARE AND LINKAGE BETWEEN HEALTH SYSTEM LEVELS

HIV programmes should ensure high-quality care for people living with HIV across all tiers of the health-care system. Particular attention should be given to the needs to people living with HIV who are seriously ill, such as those requiring inpatient care.

The human resources needed to provide care to people who are seriously ill, especially those in hospital, will vary depending on contextual factors and resources available. It is likely that staff members with expertise and experience in clinical decision making will be required *(20)*, and consideration should be given to how care (including diagnostics and access to medicines) is provided outside normal working hours.

When care is provided through referral between clinics or from a clinic to a centralized hospital, appropriate communication and linkage are critical to ensure smooth transition of individuals. This is especially important for continuing ART started in hospital, for communicating decisions around ART start (including whether to defer) or communicating the need for a repeat viral load test. WHO's advanced HIV guidelines note that health-care workers from decentralized clinics should seek advice from an experienced clinician when referral is not feasible or not indicated. To implement this, programmes should consider mechanisms for health-care staff to seek expert advice without referring the client, including through using telemedicine. Community groups have an important role to play in prompting people who are unwell to seek health care, in supporting people who are recovering following acute illness and to support ongoing adherence and retention in care.

Box 2. Examples of providing advanced HIV care to people who are seriously unwell

In Malawi, advanced HIV care to inpatients has been provided through an "in reach" system supporting the medical and nursing staff on medical wards in a joint programme between the Ministry of Health and Lighthouse, a nongovernmental organization *(76)*. An advanced HIV disease room was set up beside the hospital wards and staffed by a counsellor, a nurse and a clinical officer. The team offered provider-initiated testing and counselling to all inpatients, and those who were HIV-positive were offered CD4 cell count, LF-LAM and serum cryptococcal antigen screening tests. The team also started ART among people not already taking ART, made ART and co-trimoxazole preventive therapy available on wards for rapid initiation and supported Kaposi's sarcoma diagnosis and treatment *(76)*.

Nine countries in Africa have adopted a hub-and-spoke model to provide decentralized advanced HIV care, supported by the Elizabeth Glaser Pediatric AIDS Foundation. This model includes referral and transport for patients from primary health clinics to hospitals, transport of samples to more centralized laboratories and bidirectional advice, support, mentoring and quality improvement of hospital and peripheral clinics. A toolkit of resources, including those to support a hub-and-spoke model is available *(77)*.

AFTER HOSPITAL DISCHARGE

People living with HIV and advanced disease admitted to hospital often have poor outcomes after hospital discharge, notably death or readmission (9). Providing support for these people to link to a primary care clinic for treatment after discharge and interventions such as patient-centred discharge instructions and telephone follow-up calls may be helpful to improve outcomes after discharge from hospital *(9,78)*. Where possible, enough medicines (including ART) should be provided at hospital discharge to avoid gaps in medicine provision to people moving back into primary care services. Clear communication with primary health care is important to ensure seamless linkage into care after hospital discharge

CONCLUSIONS

People living with HIV who have advanced disease, are seriously ill or need admission to hospital have a very high risk of death.

Health-care systems should ensure mechanisms for providing care to seriously ill people at all health system levels, including by referral or ability to seek advice and guidance from expert clinicians when needed.

ART should be rapidly initiated where clinically appropriate, and treatment failure should be addressed according to WHO or local guidelines (depending on the initial ART regimen used). Access to HIV testing, CD4 testing and HIV viral load monitoring is important to identify people with advanced HIV disease and to identify people with HIV treatment failure and intervene. Screening and diagnostic testing for major opportunistic infections should be made available to people who will benefit from access to these tests; the WHO Essential Diagnostic List is an important guide to what should be made available. Where possible, access to radiology and laboratory services should be provided to assist with diagnosis and monitoring.

Person-centred care, including good communication, adherence support, provision of symptom relief and rehabilitation, are important and should be given priority.

Community groups have an important role to play in prompting people who are unwell to seek health care, in supporting people who are recovering following acute illness and to support ongoing adherence and retention in care.

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