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ISBN 978-92-4-011816-4 (electronic version)
ISBN 978-92-4-011817-1 (print version)

Suggested citation. WHO guidelines on the management of advanced HIV disease. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

Design and layout: blossom.it

Contents

Acknowledgements

WHO gratefully acknowledges the contributions of many individuals and organizations to update these guidelines. This update consolidates relevant WHO guidance published between 2021 and 2025. Those who contributed to the development of the guidelines published during this time frame are acknowledged in the respective source publications. Those acknowledged here contributed to developing the new recommendations on CD4 testing, support interventions for hospital discharge and Kaposi sarcoma treatment.

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Funding

WHO used funding provided by the Gates Foundation and Unitaid to develop these guidelines. Funders had no role in the Guideline Development Group's formulation of the recommendations or writing of the WHO publication.

Abbreviations

3HP or 1HP	three months or one month of rifapentine and isoniazid
6H or 9H	six months or nine months of isoniazid
ART	antiretroviral therapy
BCG	bacille Calmette-Guérin
CD4	cluster of differentiation subtype 4 (type of white blood cell)
CI	confidence interval
CSF	cerebrospinal fluid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRZE/2HR or 4HR	H – isoniazid R – rifampicin Z – pyrazinamide E – ethambutol 2HR/4HR – 2 or 4 months of isoniazid and rifampicin
LF-LAM	lateral flow assay – lipoarabinomannan
NAAT	nucleic acid amplification test
RR	relative risk
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS

Definitions of key terms

Advanced HIV disease	For adults, adolescents and children five years and older, advanced HIV disease is defined as a CD4 cell count ≤200 cells/mm^3.[a] At presentation, all children living with HIV younger than five years should be considered as having advanced HIV disease unless they have received ART for more than a year and are clinically stable.
Age groups	The following definitions for adults, adolescents, children and infants are used in these guidelines for the purpose of implementing recommendations for specific age groups. Countries may have other definitions under national laws: • An adult is a person older than 19 years of age. • An adolescent is a person 10–19 years of age inclusive. • A child is a person one year to younger than 10 years of age. • An infant is a child younger than one year of age.
Antiretroviral therapy	Antiretroviral therapy (ART) refers to using a combination of antiretroviral drugs for treating HIV infection
Antiretroviral	Antiretroviral drugs refer to the medicines used to treat HIV
People-centred care	People-centred care is focused and organized around the health needs and expectations of people and communities rather than diseases
Point-of-care testing	Point-of-care testing is conducted at the site at which clinical care is being provided, with the results being returned to the person being tested or caregiver on the same day as sample collection and test to enable clinical decisions to be made in a timely manner
Rapid ART initiation	Rapid ART initiation is initiation within seven days of HIV diagnosis, with a preference for starting on the same day as diagnosis
Task sharing	Task sharing is the rational redistribution of tasks between cadres of health-care workers with longer training and other cadres with shorter training, such as lay providers
Treatment failure	Lack of clinical or viral response among people who received suboptimal treatment or who received optimal treatment but failed to respond clinically. (refers to both viral and clinical failure)[b]
Viral suppression	Viral suppression is a viral load that is undetectable (less than 50 copies/mL)
Viral failure	Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/ml after at least six months of using ART.

a Where CD4 testing is unavailable, advanced HIV disease can be defined as a WHO clinical stage 3 or 4 event at presentation for care. AHD is often used interchangeably with the term “AIDS”.
b See Table 19 for the WHO definition of clinical, immune and viral failure.

Executive summary

Advanced HIV disease is the major cause of AIDS-related deaths among people living with HIV. In 2017, WHO recommended a package of care that should be provided to everyone with advanced HIV disease to help to reduce mortality and morbidity, along with rapid initiation of antiretroviral therapy (ART). Subsequently, WHO developed recommendations for the management of cryptococcal disease and histoplasmosis, both important fungal infections in advanced HIV disease, as well as key diagnostic approaches to identify tuberculosis (TB) in advanced HIV disease. These guidelines were integrated into a chapter in the 2021 WHO consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Encouraging HIV programmes to link these clinical recommendations with WHO recommendations for service delivery is critical, especially for ensuring sustained engagement as well as reengagement in services to both identify and prevent advanced HIV disease. These 2025 guidelines respond to the need for better approaches to identify advanced HIV disease, improve the poor outcomes of people living with HIV being discharged from hospital and provide updated guidance for treatment for Kaposi's sarcoma through evidence-informed recommendations.

The publication contains recommendations that are from previously published WHO guidelines documents and introduces new recommendations developed in 2025.

Summary of recommendations

Year of publication	Recommendations
Providing a package of care for advanced HIV disease	
2017	A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease. *(Strong recommendation, moderate-certainty evidence)*
CD4 testing for identifying advanced HIV disease	
New, 2025	CD4 testing is recommended as the preferred method to identify advanced HIV disease among people living with HIV. *(Strong recommendation, moderate-certainty evidence)* In settings in which CD4 testing is not yet available, WHO clinical staging can be used to identify advanced HIV disease. *(Conditional recommendation, very-low-certainty evidence)*

Year of publication	Recommendations
Interventions to provide at hospital discharge	
New, 2025	Hospitalized people with HIV may be provided interventions to support transitions to outpatient care and reduce avoidable readmissions. *(Conditional recommendation, low-certainty evidence)* Interventions may include: • pre-discharge goal setting • medication review • transitional care planning • telephone follow-up • home visits by health-care providers and/or peer supporters • individualized support.
Clinical management of cryptococcal meningitis	
Diagnosis of cryptococcal meningitis	
2018	For adults, adolescents and children living with HIV suspected of having a first episode of cryptococcal meningitis, prompt lumbar puncture with measurement of cerebrospinal fluid (CSF) opening pressure and rapid cryptococcal antigen assay is recommended as the preferred diagnostic approach. *(Strong recommendation, moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)* The following diagnostic approaches are recommended according to the context. **Settings with ready access to and no contraindication for lumbar puncture** 1. If both access to a cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) and rapid results (less than 24 hours) are available: lumbar puncture with rapid CSF cryptococcal antigen assay is the preferred diagnostic approach.[a] *(Strong recommendation, moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)* 2. If access to a cryptococcal antigen assay is not available and/or rapid results are not available, lumbar puncture with CSF India ink test examination is the preferred diagnostic approach. *(Strong recommendation, moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)* **Settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated**[b] 1. If both access to a cryptococcal antigen assay and rapid results (less than 24 hours) are available, rapid serum, plasma or whole blood cryptococcal antigen assays are the preferred diagnostic approaches. *(Strong recommendation: moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)* 2. If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured, prompt referral for further investigation and treatment is appropriate. *(Strong recommendation, moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)* *Note:* Other diseases that can present with symptoms and signs similar to cryptococcal meningitis (such as viral, bacterial or tuberculous meningitis) should also be considered.
Prevention and screening	
2018	**Overarching principle** Screening for plasma, serum or whole blood cryptococcal antigen is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying infection when managing people 10 years and older presenting with advanced HIV disease.

a For a first episode, CSF cryptococcal culture is also recommended in parallel with cryptococcal antigen testing if this is feasible.
b Contraindications include significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs (excluding cranial nerve VI palsy) or recurrent seizures and, where possible, confirmed by computed tomography. Raised intracranial pressure does not contraindicate lumbar puncture in (suspected) cryptococcal meningitis. Other contraindications include major spinal deformity and refusal by the patient after fully informed consent was sought.

Year of publication	Recommendations
Prevention and screening	
2018	Screening[c] for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating antiretroviral therapy (ART) for adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3. *(Strong recommendation, moderate-certainty evidence)* This may be considered at a higher CD4 cell count threshold of >200 cells/mm^3. *(Conditional recommendation, moderate-certainty evidence)* All people living with HIV with a positive cryptococcal antigen screening should be carefully evaluated for signs and symptoms of meningitis and undergo lumbar puncture, if feasible, with CSF examination and India ink or CSF cryptococcal antigen assay to exclude meningitis. India ink has low sensitivity and a negative result on India ink should be confirmed by CSF cryptococcal antigen testing or CSF culture. When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3. *(Strong recommendation, moderate-certainty evidence)* This may be considered at a higher CD4 cell count threshold of <200 cells/mm^3. *(Conditional recommendation, moderate-certainty evidence)*
Treatment	
Induction therapy	
2022	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) should be used as the preferred induction regimen for treating people with cryptococcal meningitis. *(Strong recommendation, moderate-certainty evidence for adults and low-certainty evidence for children)*
Alternative induction regimes	
2022	**If liposomal amphotericin is not available:** A seven-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by seven days of fluconazole (1200 mg daily for adults and 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). *(Strong recommendation, moderate-certainty evidence for adults and low-certainty evidence for children and adolescents)* **If no amphotericin formulation is available:** 14 days of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) and flucytosine (100 mg/kg per day, divided into four doses per day). *(Strong recommendation, moderate-certainty evidence)* *Note:* fluconazole and flucytosine is the only recommended oral combination regimen and has been associated with lower mortality compared with amphotericin B deoxycholate and fluconazole **If flucytosine is not available:** 14 days of liposomal amphotericin B (3–4 mg/kg per day) and fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). *(Strong recommendation, moderate-certainty evidence)* **If liposomal amphotericin B and flucytosine are not available:** 14 days of amphotericin B deoxycholate (1 mg/kg per day) and fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). *(Strong recommendation, moderate-certainty evidence)* *Note:* flucytosine-containing regimens are superior, and steps should be taken to ensure access to this drug.
Use of adjunctive systemic corticosteroids in treating people with cryptococcal meningitis	
2018	Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating adults, adolescents and children who have HIV-associated cryptococcal meningitis. *(Strong recommendation, high-certainty evidence for adults and adolescents and moderate-certainty evidence for children)*
Consolidation	
2018	Fluconazole (800 mg daily for adults or 6–12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) is recommended for the consolidation phase (for eight weeks following the induction phase). *(Strong recommendation, low-certainty evidence)*

c All people living with HIV with a positive cryptococcal antigen result on screening should be carefully evaluated for signs and symptoms of meningitis and undergo a lumbar puncture if feasible with CSF examination and cryptococcal antigen assay (or India ink if cryptococcal antigen assay is not available) to exclude meningitis.

Year of publication	Recommendations
Maintenance	
2018	Fluconazole (200 mg daily for adults or 6 mg/kg per day for adolescents and children) is recommended for the maintenance phase until immune reconstitution (CD4> 200 cells/mm^3) and suppression of viral loads on ART. *(Strong recommendation, high-certainty evidence)*
Timing of ART	
2018	Immediate ART initiation is not recommended among adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred 4–6 weeks from the initiation of antifungal treatment. *(Strong recommendation, low-certainty evidence for adults and very-low-certainty evidence for children and adolescents)*
Histoplasmosis	
Diagnosis of disseminated histoplasmosis among people living with HIV	
2021	Among people living with HIV, disseminated histoplasmosis should be diagnosed by detecting circulating *Histoplasma* antigens. *(Conditional recommendation, low-certainty evidence)*
Induction therapy	
2021	Treating people living with HIV for severe or moderately severe histoplasmosis: liposomal amphotericin B, 3.0 mg/kg, for two weeks is recommended. In settings in which liposomal amphotericin B is unavailable, deoxycholate amphotericin B, 0.7–1.0 mg/kg, is recommended for two weeks. *(Conditional recommendation, very-low-certainty evidence)*
2021	Treating people living with HIV for mild to moderate histoplasmosis: itraconazole 200 mg three times daily for three days and then 200 mg twice daily is recommended *(Conditional recommendation, very-low-certainty evidence)*
Maintenance therapy	
2021	Itraconazole 200 mg twice daily for 12 months is recommended. *(Conditional recommendation, very-low-certainty evidence)* Less than 12 months of therapy can be considered when the person is clinically stable, receiving ART, has suppressed viral load and the immune status has improved. *(Conditional recommendation, very-low-certainty evidence)*
Timing of ART	
2021	ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven. *(Conditional recommendation, very-low-certainty evidence)*
TB treatment for people with TB, HIV and histoplasmosis	
2021	People living with HIV who also have TB and histoplasmosis coinfection should receive TB therapy according to WHO treatment guidelines. *(Conditional recommendation, very-low-certainty evidence)*
Kaposi's Sarcoma	
Pharmacological treatment of Kaposi's sarcoma	
2025	WHO suggests paclitaxel or pegylated liposomal doxorubicin for pharmacological treatment for people living with HIV with Kaposi's sarcoma. *(Conditional recommendation, low-certainty evidence)*
Treatment of Mild to moderate Kaposi's sarcoma	
2014	In HIV-infected adults, adolescents and children diagnosed with mild or moderate Kaposi sarcoma, immediate ART initiation is recommended. *(Strong recommendation, low-certainty evidence)*
Treatment of severe or symptomatic Kaposi's sarcoma	
2014	Severe or symptomatic disease: in HIV-infected adults, adolescents and children diagnosed with severe symptomatic Kaposi sarcoma, immediate ART initiation in combination with systemic chemotherapy is recommended. *(Strong recommendation, low-certainty evidence)*

List of relevant HIV guidelines
1. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, 2017
2. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update
3. Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV, 2020
4. Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV, 2022
5. Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children, March 2018: supplement to the 2016 consolidated guidelines of the use of antiretroviral drugs for treating and preventing HIV infection, 2018
6. Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults, 2014
7. Clinical management and infection prevention and control for mpox: living guideline, 2025

These publications are available on the WHO website: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/guidelines.

Definition of advanced HIV disease

For adults, adolescents and children five years and older, advanced HIV disease is defined as a CD4 cell count ≤200 cells/mm^3.[a] At presentation, all children living with HIV younger than five years should be considered as having advanced HIV disease unless they have received ART for more than a year and are considered clinically stable.

A consensus process conducted in 2024 involved more than 900 participants, with 47% from the African Region. Nearly half represented civil society or frontline workers, and 44% identified as living with HIV. Consensus supported the clinical use of advanced HIV disease to differentiate levels of care and communicate disease status to individuals. The term advanced HIV disease can also help to inform the public, support health education and monitor programme outcomes. The older term of AIDS remains relevant for advocacy and education purposes.

a Where CD4 testing is unavailable, advanced HIV disease can be defined as a WHO clinical stage 3 or 4 event at presentation for care.

Objectives

These guidelines contribute to achieving the WHO Global Health Sector Strategy *(1)* for HIV 2022–2030 and the Triple Billion targets, which aim to: ensure universal health coverage for 1 billion more people, protect 1 billion more people from health emergencies and improve health and well-being for 1 billion more people.

These guidelines also align with the UNAIDS 95–95–95 targets, ensuring that 95% of people living with HIV know their HIV status, 95% of those diagnosed receive sustained antiretroviral therapy (ART) and 95% of those receiving ART achieve viral suppression *(2)*. Updated and integrated guidance on advanced HIV disease will help to support countries in remaining on track with the UNAIDS-recommended 2030 targets of reducing the number of people dying from AIDS-related causes by 90% from 2010 *(3)*.

Since people with advanced HIV disease are at high risk of severe illness and death, especially in resource-limited settings, these guidelines emphasize early detection, rapid ART initiation and optimized clinical management to reduce morbidity and mortality. By implementing these recommendations, countries can reduce progression to severe illness and mortality, improve treatment outcomes and advance global HIV elimination goals.

The objectives of these guidelines are:

- to provide evidence-informed clinical recommendations for screening, prophylaxis, treatment and management of opportunistic infections for individuals with advanced HIV disease;
- to guide the implementation of the WHO-recommended advanced HIV disease package of care, including rapid diagnostic tools, pre-emptive treatment and optimized ART regimens;
- to expand guidance to support strengthening health-care provision for both in- and outpatient services for advanced HIV disease;
- to strengthen service delivery approaches, ensuring timely identification, referral and management of advanced HIV disease in resource-limited settings; and
- to support national decision-makers and health programme planners in adapting and scaling up advanced HIV disease management strategies while integrating them into broader HIV and health system strengthening efforts.

Target audience

The guidelines are primarily intended for use by national HIV programme managers. They will also be of interest to the following audiences:

- national HIV treatment and prevention advisory boards;
- national TB programme managers;
- managers of maternal, newborn and child health and sexual and reproductive health and noncommunicable disease programmes (including mental health and substance use);
- clinicians and other health service providers;
- managers of national laboratory services;
- people living with HIV and community-based organizations;
- key population networks; and
- international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in resource-limited settings.

Guiding principles

The following principles have informed the development of the updated chapter on management of advanced HIV disease and should guide implementation.

- The guidelines are based on a public health approach to scaling up the use of antiretroviral drugs and related services along the continuum of HIV prevention, care and treatment.
- Efforts should be made to promote an enabling environment and protect the human rights of people who need HIV services, including ensuring informed consent, preventing stigma and discrimination in the provision of services, addressing laws and legislation that criminalize the behaviour of people and promoting gender equity.
- Rapid ART initiation, including same-day start, is a programmatic priority for all people living with HIV, regardless of CD4 cell count or immune status.
- Early diagnosis and prompt initiation of therapy for major opportunistic infections is essential to improving survival.
- People should be promptly referred for HIV testing and care following diagnosis of major opportunistic infections to facilitate prompt HIV diagnosis, linkage to care and uptake of ART.

Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost–effectiveness.

Burden of advanced HIV disease

Introduction

Advanced HIV disease is a serious public health issue, including in settings with good coverage of HIV testing and treatment and despite having achieved or made good progress towards the 95–95–95 targets.

A recent systematic review analysed evidence from 117 cohorts of people living with HIV in which CD4 cell counts were measured in health-care settings worldwide. The review found that in outpatient settings, a third of all CD4 counts measured (33.5%, 95% confidence interval (CI) 31.5–35.4%) were under 200 cells/mm^3. The rate of lower CD4 cell counts was similar among people starting ART (33.5%, 95% CI 32–36%) and people who were already taking ART (31%, 95% CI 24–37%), although it is likely that CD4 testing was offered routinely to people starting ART but only if clinically indicated to the people already taking ART *(4)*. Another study *(5)* of nationally representative household surveys from 13 countries in Africa found an estimated prevalence of CD4 cell count under 200 cells/mm^3 of 10% of adults (age 15 years and older). This corresponds to 1.9 million (95% CI 1.6 million–2.2 million) individuals with advanced HIV disease in sub-Saharan Africa.

Men and adults aged 30 years and older were more likely to have CD4 cell count under 200 cells/mm^3. About three quarters of adults living with HIV in Africa have viral load suppression, the study estimated that 43% of all low CD4 cell counts were among people with viral load suppression *(5)*.

This indicates that increasing testing and ART initiation are insufficient to tackle advanced HIV disease. Both reviews above used CD4 cell counts of less than 200 cells/mm^3 to define advanced HIV disease.

There are an estimated 1.4 million children (age 0–14 years) living with HIV worldwide *(6)*. Children living with HIV younger than five years are considered to have advanced HIV disease unless they have been receiving ART for a year or longer and are clinically stable. Among older children, 30.1% (95% CI 25.4–34.8%) had advanced HIV disease in outpatient settings *(4)*. There have been large declines in CD4 testing over time among children, which greatly limits the ability to better understand advanced HIV disease in this population *(7)*.

Causes of hospital admission and death among people living with HIV

Advanced HIV disease is a risk for becoming seriously unwell and requiring admission to hospital. Serious illness[1] is often defined by the presence of WHO danger signs, although hospital admission itself may serve as a proxy indicator in settings where formal clinical assessments are limited.

A systematic review *(9)* of studies reporting the cause of hospital admission of people living with HIV from 2014 to 2023 showed that the commonest causes of hospital admission worldwide were AIDS-defining clinical conditions (42% of all hospital admissions, 95% CI 35–49%), followed by severe bacterial infections (26% of hospital admissions, 95% CI 20–33%).

TB was the most common AIDS-defining clinical condition, causing 19% of hospital admissions worldwide among people living with HIV (95% CI 15–23%) *(9)*.

1 WHO danger signs for adults: 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; or tachypnoea *(8)*.

Among those who survive their hospital admission, the period following hospital discharge is also risky. In a systematic review of post-discharge outcomes, 19% of people living with HIV who were discharged from hospital alive were readmitted and 14% died shortly after hospital discharge (the duration of post-discharge follow-up varied by study from 30 days to 12 months) *(10)*.

The advanced HIV disease research landscape

At a WHO led expert consultation in September 2023, key topics were agreed for advanced HIV disease research. These were implementation research needs for CD4 testing and differentiated service delivery and clinical research needs for eight HIV-associated diseases: TB, cryptococcal meningitis, severe bacterial infections, *Pneumocystis* pneumonia, toxoplasmosis, cytomegalovirus, histoplasmosis and talaromycosis *(11)*.

Priority research gaps in advanced HIV disease were identified as part of the expert consultation and research roadmap. Research data and reliable monitoring and evaluation systems for advanced HIV disease are urgently needed. Other research gaps included: how best to operationalize point-of-care CD4 testing; the need for improved understanding of the burden of severe bacterial infection and antimicrobial resistance in the context of advanced HIV disease; improved TB diagnostics and TB screening algorithms; treatment guidelines based on modern evidence for *Pneumocystis* pneumonia, toxoplasmosis and talaromycosis; optimizing inpatient care bundles and inpatient and outpatient linkage to reduce mortality around the time of hospital admission; and qualitative research to determine why individuals are still presenting with advanced HIV disease despite widespread access to ART. Most evidence for the management of advanced HIV disease and related conditions arises from studies of adults, and research applicable to infants and children is needed.

Providing a package of care for advanced HIV disease

Recommendations

CD4 testing is recommended as the preferred method to identify advanced HIV disease in people living with HIV. (New, 2025)
Strong recommendation, moderate certainty evidence.

In settings where CD4 testing is not yet available, WHO clinical staging can be used to identify advanced HIV disease in people living with HIV. (New, 2025)
Conditional recommendation, very low certainty evidence.

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease. (2017)
Strong recommendation, moderate-certainty evidence

CD4 testing and WHO clinical staging

Background
WHO introduced HIV clinical staging in 2007 to facilitate rapid identification of the stage of HIV infection in settings in which HIV testing and CD4 testing were very limited or unavailable, primarily as a tool for surveillance *(12)*. This was considered feasible since it served as a guide for health-care workers to identify opportunistic infections and assign a degree of severity of illness. Clinical staging of HIV-related disease for adults and children was categorized into a four-stage system that included standardized descriptors.

A systematic review published in 2014 found that against a CD4 cell count threshold of <200 cells/mm^3, the sensitivity of correctly identifying a WHO stage 3 or 4 AIDS-defining illness was 60% and the specificity was 73% *(13)*. This has important implications for providing the WHO-recommended package of care for advanced HIV disease *(14)*, since it would result in being unable to provide disease prevention measures. Instead, treatment would more likely be required if a WHO stage 3 or 4 AIDS-defining illness was identified.

Through a consensus process in 2016 *(15)*, advanced HIV disease was defined as all adults, adolescents and children younger than five years living with HIV with a CD4 count of ≤200 cells/mm^3, considering the higher mortality below this threshold *(15, 16)*.

In 2015, WHO recommended ART initiation for all people living with HIV regardless of CD4 count and also recommended using viral load testing as the preferred approach for monitoring the response to ART *(17)*.

With the consequent scale-up of viral load testing to monitor treatment response, CD4 test use declined substantially in most settings with a high burden of HIV *(18)*. However, viral load testing does not provide information on immune status. WHO clinical staging is being used because of lack of availability of CD4 tests.

WHO currently does not provide recommendations on a preferred approach for identifying advanced HIV disease, and programmes primarily relied on the interpretation of the definition of advanced HIV disease. There has been a demand from HIV programmes worldwide and from representatives of civil society for WHO to provide clarity on identifying advanced HIV disease since it will highlight the importance of CD4 testing as well as advanced HIV disease, and drive demand for CD4 testing in countries. Thus, there was a need to systematically investigate the accuracy of WHO clinical staging compared with CD4 testing for identifying individuals with advanced HIV disease, to ensure that they urgently receive the WHO-recommended package of care for advanced HIV disease.

Rationale for the recommendations

Balance of benefits and harm

A systematic review[2] (Web Annex B) *(19)* was conducted on the diagnostic accuracy of clinical staging for detecting advanced HIV disease against CD4 cell count measurement (laboratory based), which served as the reference standard. Studies were included in which the WHO clinical staging classification was compared at CD4 cell count threshold of <200 or ≤200 cells/mm^3; 24 studies were included for review *(20–43)*, the majority (18 studies) conducted in the WHO African Region, with five conducted in the South-East Asia Region and one in the Eastern Mediterranean Region.

In relation to the conduct of testing, procedures for WHO clinical staging were largely poorly conducted. Fourteen of 24 studies did not specify who conducted clinical staging, with 10 specifying medically qualified clinicians of various cadres. The CD4 cell count in the included studies was largely measured using laboratory-based flow-cytometry measurement, with two studies reporting the use of a Coulter manual counting method.

Overall, pooled sensitivity was 61% (95% CI 48–73%) and pooled specificity was 72% (95% CI 60–81%). The positive likelihood ratio was 2.18 (95% CI 0.28–17.16) and negative likelihood ratio 0.54 (95% CI 0.11–2.56). Of a hypothetical population of 100 000 people living with HIV with a prevalence of advanced HIV disease of 25%, 15 250 (15%) would be correctly classified as having advanced HIV disease, 54 000 (54%) would correctly have advanced HIV disease ruled out, 21 000 (21%) would be falsely classified as having advanced HIV disease when they did not and 9750 (10%) would have advanced HIV disease but not be detected. If half of the people living with HIV being screened had advanced HIV disease, 30 500 (30%) would have advanced HIV disease correctly detected, 36 000 (36%) would have advanced HIV disease correctly excluded, 14 000 (14%) would be wrongly classified as having advanced HIV disease and 19 500 (20%) would have advanced HIV disease but not be detected. The results of the risk of bias assessment in the systematic review reported overall low certainty of evidence.

The Guideline Development Group agreed through consensus that the accuracy of clinical staging was low and judged the magnitude of undesirable effects (the magnitude to which the intended population is being misclassified or not) as being moderate to large. This was primarily because of the high rate of both false positives and false negatives. False-positive results could result in unnecessary additional testing with associated harm, such as increasing costs, burden on health-care workers and discomfort and delays for the individual being tested. For the increased false negatives, it would result in many cases of advanced HIV disease being missed (20%, as specified previously), resulting in substantially increased morbidity and mortality from missed cases of advanced HIV disease in HIV programmes.

The Guideline Development Group judged the overall certainty of evidence supporting clinical staging as being very low, owing to the additional uncertainty of the cadre conducting the clinical staging and heterogeneity in the included studies.

The Guideline Development Group judged that the balance of benefits and harm favoured CD4 testing owing to moderate to large potential harm identified with clinical staging. The Group also noted that, despite the very low certainty of evidence, there was no doubt that clinical staging is not an accurate method for identifying advanced HIV disease in regular clinical practice.

Preferences, acceptability and feasibility

The Guideline Development Group found that there was potentially important uncertainty or variability regarding the use of clinical staging to identify advanced HIV disease and that acceptability likely varies; some Guideline Development Group members also noted that it was probably not acceptable in certain contexts, owing to lack of trained workforce, to conduct a full clinical examination or also lack of supporting infrastructure to confirm diagnosis of specific opportunistic infections to stage the individual correctly. The Guideline Development Group also determined that feasibility of clinical staging might vary.

The rationale for the judgement on preferences was informed by evidence provided from the results of an online values and preferences survey (Web Annex C) conducted among people living with HIV and evidence compiled from published literature through a targeted literature search. The respondents expressed a strong desire to be informed about their immune status while receiving routine care and preferred a test that involves drawing a blood sample and provides good accuracy of testing. Half the respondents indicated a preference against undergoing an extended

2 Twabi HH, Ueno A, Ives J, Murtagh R, Mukoka M, Mortazavi SA, Lawrence DS, Choko AT, Semphere R, Balakasi K, Rangaraj A. Diagnostic accuracy of the WHO clinical staging system for detection of immunologically defined advanced HIV disease: A systematic review and meta-analysis. HIV medicine. 2025 Sep 18. DOI: https://doi.org/10.1111/hiv.70122

physical examination when comparing preferences of receiving a needle prick with a blood draw compared with a detailed physical examination to identify opportunistic infections or establish their risk status.

Evidence from an implementation study highlighted that most health-care workers agreed that undergoing training and performing the point-of-care CD4 count was straightforward and easy to perform and agreed that point-of-care CD4 was useful in their daily work and for informing patient management *(44)*. The Guideline Development Group also noted that clinical staging would likely be more acceptable to health-care workers if no CD4 testing was available; however, there was a lack of evidence around health-care worker preferences for clinical staging.

A study assessing the feasibility of implementing the WHO-recommended package of care using point-of-care CD4 testing concluded that delivering the package of care, including the point-of-care CD4 test, was considered feasible *(44)*.

Resources and cost–effectiveness

About 7.5 million CD4 tests were conducted in low- and middle-income countries in 2024, with conventional testing accounting for about 70% and point-of-care tests the remaining 30%. There is considerable unmet need for CD4 testing, with an estimated shortfall of 1.8 million–3.9 million tests *(45)*. The currently available cost per test is about US$ 3 for point-of-care CD4 tests and varies between US$ 2 and US$ 5 for conventional laboratory testing *(45)*. However, various initiatives are underway to help improve demand for CD4 testing. No evidence was available on the direct costs of conducting WHO clinical staging; however, the Guideline Development Group emphasized that the costs are likely to be moderate, owing to costs of missed diagnosis of opportunistic infections, additional testing needs to identify AIDS-defining conditions and personnel time to conduct an extensive physical examination. Relative to CD4 testing, the Guideline Development Group noted that costs were more difficult to judge given the varied levels of CD4 testing availability in settings.

Modelling work has demonstrated the incremental benefits of the advanced HIV disease package of care, with the full package demonstrating maximum cost–effectiveness *(46)*. The proper implementation of the package depends on the ability of CD4 testing to correctly identify someone with advanced HIV disease.

Equity

The Guideline Development Group determined that the equity would likely vary based on the setting. In settings where clinical staging is used, this may reduce equity compared with settings in which populations receive CD4 testing. However, in a setting with no CD4 testing, performing clinical staging would improve equity compared with no formal assessment for advanced HIV disease, even if the test performs poorly. The Guideline Development Group judged that clinical staging would probably reduce equity in most instances.

Rationale for recommendations

Based on the information presented, the Guideline Development Group chose to develop two separate recommendations, one on CD4 testing and the other on WHO clinical staging for identifying advanced HIV disease, given the public health importance of timely identification of advanced HIV disease in HIV programmes.

Recommendation on CD4 testing

The Guideline Development Group noted that since CD4 testing was the reference standard for the primary evidence review, the certainty of CD4 testing to correctly identify someone with advanced HIV disease was high, since the primary means by which CD4 counts are established is through this test. Owing to several sources of uncertainty identified by the Guideline Development Group relating to performance of point-of-care-CD4 testing, costs and access issues, the Guideline Development Group chose to downgrade the certainty of the evidence to moderate. Despite some reported concerns around the performance of point-of-care tests, the performance of these tests far surpassed the performance of clinical staging. CD4 testing has a long history of use within HIV programmes and can also be used as a prognostic test, adding further value to the test results. The Guideline Development Group thus agreed through consensus that CD4 testing should be strongly recommended as the preferred method to identify advanced HIV disease among people living with HIV.

Recommendation on WHO clinical staging

The Guideline Development Group noted that in settings where no CD4 testing was available, health-care workers may use clinical staging to identify advanced HIV disease. The Guideline Development Group thus chose to develop a conditional recommendation on the use of clinical staging, consistent with the public health approach, to account for settings with little or no resources available to conduct CD4 testing.

Implementation considerations

The Guideline Development Group identified several implementation considerations for both CD4 testing and clinical staging (Box 1).

Box 1. Who needs a CD4 test (adults, adolescents and children)? Indications for CD4 testing in HIV programmes

CD4 testing to identify advanced HIV disease among people living with HIV who are:

a. initiating or reinitiating ART
b. re-engaging in care following disengagement
c. have treatment failure or clinically identified treatment failure
d. hospitalized or seriously ill or are considered clinically unstable

CD4 testing to support the identification of treatment failure when viral load testing is unavailable

CD4 testing to assess eligibility to stop co-trimoxazole prophylaxis

CD4 testing to assess eligibility for fluconazole prophylaxis

Box 2. Key characteristics of CD4 tests

Point-of-care tests

- Lower sensitivity and specificity compared with conventional CD4 tests
- Test results are semiquantitative (CD4 <200 cells/mm^3 or >200 cells/mm^3)
- Device-free
- Challenging to implement in high-volume health-care facilities
- Suitable for task-sharing among cadres
- Training required for health-care workers before implementation
- Can support the rapid return of results in outreach settings
- Quality assurance systems required as well as job aids to improve the readability of results

Conventional CD4 tests

- Gold standard for measuring CD4 counts
- Provide quantitative results
- Require laboratory infrastructure and personnel
- Suitable for implementation in high-volume and high-demand health-care facilities, promoting efficiency in delivering results
- Requires laboratory personnel
- Less suitable for outreach settings unless accompanied by robust sample transport systems
- Quality assurance required, but no specific job aids required for health-care workers

Key considerations for point-of-care and lab-based tests

Programmes should give priority to developing job aids or tools to support the reading of point-of-care test results for health-care workers.

Current evidence on point-of-care testing

Point-of-care CD4 testing can provide more rapid test results, during a single health-care visit, to enable rapid clinical decision-making *(47)*. This is likely to be critical for people living with advanced HIV disease. Two assays remain on the market and are available for procurement *(48)*.

Training and task sharing

Health cadres (community health workers, nurses, and laboratory personnel) should undergo training on point-of-care CD4 tests and on conventional CD4 testing. Task-sharing approaches could help to lower implementation costs and improve CD4 coverage within HIV programmes *(49–52)*.

Monitoring and quality assurance

Implementation of robust monitoring and quality assurance systems to maintain testing standards for CD4 testing is an important component of implementing and scaling up CD4 testing.

Integration and referral pathways

The Guideline Development Group considered CD4 testing suitable for integrated care initiatives between HIV and other disease programmes or primary health care depending on the specific context. The Guideline Development Group noted the importance of having clear referral pathways for individuals who are identified to be seriously unwell with advanced HIV disease. Diagnostic networks

would need to be optimized in programmes in which more than one type of CD4 test (conventional and point-of-care tests) are being used and ensuring that the type of test is matched to the facility (conventional CD4 tests for higher-volume sites).

WHO clinical staging

The Guideline Development Group also developed specific implementation considerations for WHO clinical staging.

Training
Adequate training needs to be provided to health-care workers on conducting WHO clinical staging and giving priority to medical personnel for conducting clinical staging of clients.

Clinical protocols
Symptom-based diagnosis protocols should be developed along with support for additional diagnostics for opportunistic infections for completeness of clinical staging.

Referral pathways
Clear referral pathways need to be developed following clinical staging owing to limitations to correctly identify advanced HIV disease but also since sites offering clinical staging may not have access to other diagnostics necessary to complete clinical staging.

Monitoring, training and quality assurance
Programmes should adequately monitor the implementation of clinical staging and develop quality assurance systems, owing to the evidence around a lack of consistency and information on how clinical staging was conducted and who conducted it.

Resource priority-setting
Improving access to CD4 testing is critical rather than primarily investing resources in training health-care workers on clinical staging owing to the limited improvements in accuracy expected with its use and highly variable costs. Training health-care workers on performing a physical examination may contribute to improved clinical care overall but CD4 testing would have to be scaled up since many individuals with advanced HIV disease may not have any clinically identifiable signs or symptoms of disease but continue to have an elevated risk of developing opportunistic infections. Use of CD4 testing additionally would support the rapid roll-out of testing for advanced HIV disease and improve coverage of screening for advanced HIV disease compared with clinical staging.

Research gaps
There are research gaps, broadly classified under three main categories: comparative analysis of CD4 testing compared with clinical staging, CD4 testing and clinical staging (Table 1).

Table 1. Research needs for CD4 testing and WHO clinical staging

CD4 compared with clinical staging	CD4 testing	Clinical staging
Evidence around improved integrated and task-sharing approaches	Studies on CD4 testing among children and adolescents (both older and younger than five years)	Evaluating the apparent decline in sensitivity of clinical staging over time
Comparative analysis of cost–effectiveness of CD4 testing compared with clinical staging in resource-limited settings	Budget implication and impact analysis, cost analysis and cost-reduction analysis of CD4 testing in countries	Identifying approaches to improve the accuracy of clinical staging in settings where CD4 testing is unavailable
Research on the clinical utility of CD4 testing and clinical staging in a clinical situation of high viral load	Diagnostic performance and clinical utility of CD4 testing between individuals Identifying the optimal time period to perform a repeat CD4 test when a client re-engages in care following a period of disengagement from routine care services	Understanding the performance of clinical staging for people returning to care following disengagement
Mapping of existing CD4 resources in countries with a high burden of HIV	Pragmatic studies on CD4 testing in different categories of health facilities – hospitals, clinics and outreach settings	
Identifying barriers to accessing evaluation for advanced HIV disease	Clinical relevance of suboptimal immune recovery among individuals receiving ART Further research into the role of the CD4 nadir in predicting progression to advanced HIV disease	

Providing a package of care for advanced HIV disease (2017)

Recommendation

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease
Strong recommendation, moderate certainty evidence.

To address these leading causes of morbidity and mortality among people with advanced HIV disease, WHO recommends that a package of interventions, including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions, be offered to everyone (all populations and age groups) living with HIV presenting with advanced HIV disease *(53)*.

Rationale for the recommendation

The rationale for this recommendation is based on two randomized controlled trials: REMSTART *(54)* and REALITY *(55)*. REMSTART was conducted in the United Republic of Tanzania and Zambia and randomized 1999 ART-naive adults living with HIV with CD4 count <200 cells/mm^3 to either standard care or standard care plus enhanced clinic-based care with serum cryptococcal antigen screening and pre-emptive antifungal treatment for those who tested cryptococcal antigen positive and additional community support (comprising a weekly home or community visit by trained and paid lay workers who delivered ART, provided adherence support and monitored participants for signs and symptoms of drug toxicity or new symptoms). The intervention group had 28% fewer people dying: mortality was 13% in the intervention group versus 18% in the group receiving standard care.

REALITY enrolled 1805 mainly adults living with HIV (72 were 5–17 years old) with CD4 counts <100 cells/mm^3 in Kenya, Malawi, Uganda and Zimbabwe. All underwent screening for active TB at enrolment and were then randomized to the standard of care (co-trimoxazole) according to national guidelines or an enhanced prophylaxis package: 12 weeks of fluconazole (100 mg once daily), 12 weeks of a fixed-dose combination of co-trimoxazole (800 + 160 mg) + isoniazid (300 mg) + pyridoxine (25 mg) as a scored once-daily tablet, five days of 500 mg of azithromycin once daily and a single dose of 400 mg of albendazole. All drugs were started simultaneously, and ART was offered on the same day as the prophylaxis package *(55)*.

The enhanced prophylaxis package at the time of ART initiation reduced mortality by 27% (from 12.2% to 8.9%) over 24 weeks *(55)*. Mortality from *Cryptococcus* species declined considerably, from 1.5% to 0.4%, and mortality from unascertained causes (most people died at home) declined from 6.0% to 3.8%. TB incidence was reduced by 28%, cryptococcal disease by 62% and hospitalization by 17% in the enhanced prophylaxis group versus the standard-of-care group. Most of the deaths in this study occurred within the first three weeks, highlighting the value of early prophylaxis for people with advanced disease *(55)*.

Implementation considerations

Adults

Providing a package of essential interventions focuses attention on preventing, diagnosing and treating the most common causes of morbidity and mortality among people with advanced HIV disease. Identifying people with advanced HIV disease who are eligible for elements of a package of care requires CD4 testing. In addition, determining the immune status of people whose treatment is failing according to virological criteria can help in guiding clinical management decisions. Attention should also be paid to other important causes of severe illness not covered by the package, especially in regions in which specific comorbidities and coinfections are prevalent. Of note, increased pill burden and side-effects may affect treatment adherence, and intensified adherence support interventions are an important component of the advanced HIV disease package. To support treatment adherence, shorter regimens for TB preventive treatment are recommended *(56)*.

Identifying suitable screening tools for use is also an important research gap. Table 2 summarizes the specific components of the package of interventions that should be offered to people presenting with advanced HIV disease. Further information on current WHO recommendations is in the chapter on management of opportunistic infections. Additional detailed guidance on using systematic TB screening for people, including screening tools recommended for people living with HIV and diagnostic tools such as lateral flow urine lipoarabinomannan assay (LF-LAM), WHO-approved molecular rapid diagnostics and TB preventive treatment, are available in the consolidated guidelines and operational handbooks for TB modules 1, 2 and 3 *(56–58)*. Key considerations for managing TB disease are highlighted in the subsection on TB in this publication.

Children

All children younger than five years (who are not already receiving ART and clinically stable) are considered to have advanced HIV disease. Those who are established on ART and older than two years should not be considered to have advanced disease and should be eligible for multimonth dispensing *(8)*.

The main differences in the package of care for children compared with adolescents and adults is that routine cryptococcal antigen screening and pre-emptive therapy are not recommended for children younger than 10 years because of the low prevalence of cryptococcal meningitis in this age group. However, if a child younger than 10 years presents with signs and symptoms of meningitis, cryptococcal meningitis should still be considered and the appropriate investigations and treatment for this should be implemented (Tables 2, 3).

The burden of TB is high among children living with HIV. Table 3 highlights the main recommendations for TB screening. WHO now suggests using integrated treatment decision algorithms for children younger than 10 years and concurrent testing of (1) respiratory samples and (2) stool with molecular WHO-recommended rapid diagnostics along with (3) urine testing using point-of-care LF-LAM testing for children living with HIV *(59, 60)*. Concurrent use of the multiple sample types and tests should be given priority to maximize opportunities for confirming TB. Treatment for drug-sensitive TB among children comprises a four-drug regimen that includes rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) to be provided with available child-friendly, fixed-dose combinations in dispersible formulations to decrease the pill burden and facilitate administration for young children *(61).* Drug–drug interactions between rifampicin and lopinavir + ritonavir or dolutegravir need to be considered and ART dosing adjusted accordingly. Additional details are provided in the section on TB.

Although rapid ART initiation within seven days of diagnosis is a priority, especially for children older than five years, children with severe acute malnutrition, TB meningitis or other severe illnesses need urgent clinical stabilization. However, initiating ART is encouraged as part of the child's hospitalization, since referral after discharge may lead to loss to follow-up and failure to initiate ART. Among children with signs of or confirmed TB meningitis, ART initiation should be delayed in accordance with existing guidelines. Similarly, ensuring linkage to the facility in which the child will receive ongoing HIV care on discharge is critical.

Preventing opportunistic infections in advanced HIV disease among children comprises rapid ART initiation, preventing TB disease with bacille Calmette-Guérin (BCG) vaccination and TB preventive treatment, preventing *Pneumocystis jirovecii* pneumonia with co-trimoxazole prophylaxis and administering age-appropriate vaccinations and catch-up vaccine administration when indicated (Table 3).

Guidelines for managing HIV, TB, routine child health and development interventions (vitamin A, nutritional support, deworming and the Expanded Programme on Immunization) should align as much as possible to prevent multiple visits to health-care services.

At the facility level, centres introducing the advanced HIV disease package for children should provide a child-friendly environment and ensure access to child-specific resources such as drug formulations for children, a mid-upper arm circumference tape, stadiometer, appropriate scales and expertise in phlebotomy for children. Health-care providers should be sensitized on child-specific issues such as growth monitoring and other routine child health interventions. Efforts should additionally be put in place to support and equip parents and caregivers to recognize warning signs and be able to reliably administer the prescribed medications.

Clinical considerations

The role of presumptive treatment is important in settings in which access to diagnostic tests is limited, especially if the person presenting to care is seriously ill.[3] Other clinical conditions, such as elevated body temperature of ≥39°C, can also be considered based on local epidemiology and clinical judgement.

People with advanced HIV disease may start both ART and prophylaxis at the same time *(53)*. However, ART initiation should be deferred when clinical symptoms suggest TB meningitis or cryptococcal meningitis to avoid paradoxical worsening of the existing infection, which can be life-threatening *(62)*.

Research gaps

Adults

Research priorities related to diagnostics remain important. Further research is needed to develop simplified point-of-care diagnostics for TB, severe bacterial infections, *Pneumocystis jirovecii* pneumonia, toxoplasmosis, cytomegalovirus disease and other opportunistic infections specific to geographical regions, such as histoplasmosis and talaromycosis.

Other research priorities include defining the optimal package of prophylactic interventions for people who have not yet started ART, additional prophylaxis for severe bacterial infections, the benefit of primary fluconazole prophylaxis among those with advanced HIV disease for whom cryptococcal antigen screening is not feasible, the optimal pre-emptive treatment strategy for people identified as cryptococcal antigen–positive at screening and approaches to antibiotic therapy within a public health approach and, specifically, the independent effect of short-course azithromycin on mortality (trial underway) *(55, 63)*. Programmatic assessment of the intensity of follow-up required and adherence strategies for people with advanced HIV disease are important areas for future implementation research.

The optimal management approach for people presenting again for care with advanced HIV disease after treatment interruption may warrant further investigation. Several studies have reported outcomes of providing the advanced HIV disease package in routine care settings, and additional data would be of value *(44, 64, 65)*. In addition, since these trials have not investigated the benefit of an intervention package for infants and children younger than five years, specific components and optimal delivery warrant further research. Finally, region-specific packages of care should be defined and their effectiveness assessed.

Children

Multiple research gaps exist in addressing prevention and care for children living with advanced HIV disease. Better tools are needed to screen and diagnose TB among children living with HIV. Examples of critical knowledge gaps include better diagnostics, including the need to develop simplified point-of-care diagnostics for pneumonia (including *Pneumocystis jirovecii* pneumonia) and for cytomegalovirus disease, whether to empirically treat for TB and/or cytomegalovirus disease among children living with HIV who present with severe pneumonia and what the optimal package of prophylactic interventions for children living with HIV younger than five years should be.

3 A seriously ill adult is defined as having any of the following danger signs: respiratory rate ≥30 breaths per minute; heart rate ≥120 beats per minute; or unable to walk unaided.

Table 2. Components of the WHO-recommended advanced HIV disease package of care for adults, adolescents and children

Intervention	CD4 cell count	Adults	Adolescents	Children <10 years
Screening				
Systematic screening for TB disease	All people living with HIV	Yes	Yes	Yes
Cryptococcal antigen screening	Recommended for both <200 cells/mm^3 and <100 cells/mm^3	Yes	Yes	No
Diagnosis				
Diagnosis[a] of histoplasmosis with antigen testing	All people living with HIV	Yes	Yes	-
Concurrent testing with low-complexity automated nucleic acid amplification tests (NAATs) on respiratory samples and LF-LAM on urine should be used as the initial diagnostic strategy for diagnosing TB	All people living with HIV	Yes, and/or seriously ill or have advanced HIV disease	Yes, and/or seriously ill or have advanced HIV disease	Yes, and use of low-complexity NAATs on stool samples
Prophylaxis and presumptive treatment				
Co-trimoxazole prophylaxis	<350 cells/mm^3 or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections	Yes	Yes	Yes
TB preventive treatment	All people living with HIV	Yes (3HP preferred)	Yes (3HP preferred)	Yes
Fluconazole pre-emptive therapy for cryptococcal antigen–positive people without evidence of meningitis	Recommended for both <200 cells/mm^3 and <100 cells/mm^3	Yes	Yes	Not applicable (screening not advised)
ART				
Rapid ART initiation	Any	Yes	Yes	Yes
Defer if clinical symptoms suggestive of meningitis (TB or cryptococcal)	Any	Yes	Yes	Yes
Counselling				
Tailored adherence counselling, home visits if feasible	<200 cells/mm^3	Yes	Yes	Yes

Screen, Treat, Optimize and Prevent AIDS among children and adolescents living with HIV

Screen & diagnose

Tuberculosis

Children younger than 10 years should be systematically screened for TB disease using a symptom screen including any one of cough, fever, poor weight gain, or chest X-ray or both. Adolescents should be screened as per WHO guidelines for adults.

Concurrent testing with low-complexity automated NAATs (on respiratory and stool samples), along with LF-LAM testing (on urine samples) as the initial diagnostic strategy for diagnosis of TB in children who have signs or symptoms or screened positive for pulmonary TB. In children with presumptive pulmonary TB, integrated treatment decision algorithms may be used to diagnose pulmonary TB.

Cryptococcal infection among adolescents

Serum or plasma or blood cryptococcal antigen screening in individuals with CD4 <200 cells/mm^3, followed by CrAg antigen testing of CSF samples from a lumbar puncture if positive or symptomatic.
If asymptomatic, consider subclinical meningitis.

Managing nutritional needs

Conduct nutritional assessment at HIV diagnosis and at regular intervals, thereafter, using age-appropriate anthropometric measurements.

Examine for and address other underlying causes of undernutrition (e.g. helminth infections and diarrhoeal disease).

Provide nutritional counselling to family members or carers.

If undernutrition is present, refer for inpatient management where appropriate. Offer therapeutic or supplementary feeding as indicated to cover the nutrient needs for growth and development as per WHO guidelines.

Treat

Tuberculosis, severe pneumonia, severe bacterial infections, cryptococcal meningitis and manage nutritional needs according to WHO guidelines.

Optimize

Rapid initiation of antiretroviral therapy.

Appropriate caregiver counselling for antiretroviral therapy

Optimise nutritional needs and monitor nutritional recovery

Prevent

Co-trimoxazole prophylaxis as per WHO guidelines to prevent bacterial infections and Pneumocystis pneumonia

TB preventive treatment as part of a comprehensive package of HIV care to prevent TB

Food assistance to prevent TB among household contacts of people with TB in food insecure settings

Oral fluconazole prophylaxis to prevent cryptococcal disease in adolescents

Ensure up-to-date vaccinations as per WHO Essential Programme on immunisation recommendations

a WHO does not currently recommend routine screening for histoplasmosis.

Table 3. Screening, diagnosis and prevention components of the package of care for children and adolescents with advanced HIV disease

Intervention	Disease/ component	<5 years	5-9 years	10-19 years
Screening and diagnosis	*TB*	Yes	Yes	Yes
	Cryptococcal disease	No	No	Yes
	Nutritional assessment & counselling	Yes	Yes	Yes
Prevention, prophylaxis and pre-emptive treatment	*Up-to-date vaccinations as per WHO EPI recommendations*	Yes	Yes	Yes
	Fluconazole prophylaxis	Not applicable	Not applicable	Yes
	Co-trimoxazole	Yes	Yes	Yes
	TB preventive treatment	Yes	Yes	Yes

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(*) All information sources accessed September 18, 2025

Clinical management of advanced HIV disease

Background

People 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. The package of care for people with advanced HIV disease should be offered at both hospitals and decentralized primary care clinics according to the clinical status of the person living with HIV, the skills mix of health-care workers *(66)*, access to diagnostics and treatments and feasibility of transfer.

Management of advanced HIV disease in outpatient settings

Improving access at peripheral sites through mobile outreach or decentralization should be encouraged to increase access. This approach has been shown to be feasible and acceptable, supported by a range of tools *(67, 68)*.

Clear referral criteria should be established so that people who initially present to primary health care or outreach services but require inpatient care can access it in an expedited manner, so that people requiring further investigation or specialist management receive services in a timely manner. Whether a person could be safely managed at a primary care clinic 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 personnel at the primary care level. Consideration should be given to ensuring access to ambulances 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. Promotion of health literacy is also an important responsibility for programmes and helps to promote better understanding of HIV *(69)* and advanced HIV disease.

Management of advanced HIV disease in hospital settings

Hospitalization from complications relating to HIV infection, including coinfections associated with advanced HIV disease, remains substantial. People who are hospitalized with HIV-related illness have a high risk of death, and this risk persists after discharge from inpatient care *(10)*.

When unwell individuals first present to health care, immediately life-threatening conditions should be rapidly identified and treated. Guidance about emergency triage assessment and treatment for children *(70)* and guidance about emergency management of illness in adolescents and adults is available elsewhere *(71)*.

A person might require inpatient care for several reasons:

- for close clinical monitoring because of being seriously ill with deteriorating or fluctuating symptoms and clinical status or for higher levels of nursing care such as position change to prevent bedsores, assistance with mobility and pain management;
- 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;
- for treatments that are typically only delivered or available at a central location (such as supplemental oxygen or intravenous medicines); and
- for diagnostic or radiology services or procedures that are typically centralized or only provided at larger health-care facilities.

Initial management

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. For people who do not know their HIV status, WHO recommends that, in settings with a high burden of HIV, provider-initiated HIV testing and counselling be offered to all people presenting for care in all health-care settings. In settings with a low burden of HIV, people with conditions that could indicate HIV infection should be offered testing *(72)*. Consideration should be given to making HIV testing services for inpatients available on evenings and weekends in all areas of hospitals. HIV testing algorithms and strategies are available to support high-quality testing *(72)*. Although HIV testing should be voluntary and conducted with informed consent, if the person is unconscious, HIV testing may be considered when 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 *(73)*.

Managing ART among people who are seriously ill

A seriously ill adult is defined as having any of the following danger signs: respiratory rate ≥30 breaths per minute; heart rate ≥120 beats per minute; or unable to walk unaided. In general terms, in settings with a high burden of HIV, HIV testing should be given priority for individuals suspected to have HIV, and any individual living with HIV who is not receiving ART should start ART as soon as possible. Failure to identify HIV in a timely manner risks increased mortality from opportunistic infections.

People with central nervous system signs and symptoms should have investigations for meningitis before starting ART. 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 *(8, 74)*. WHO has no specific recommendation about timing of ART following bacterial meningitis *(75)* or other central nervous system opportunistic infections because data are lacking.

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 *(76, 77)*.

The 2025 WHO guidelines on the management of bacterial meningitis *(78)* state that the choice of antibiotic for bacterial meningitis is either ceftriaxone or cefotaxime as first-line agents for empirical treatment in suspected cases of acute bacterial infection. However, intravenous ceftriaxone is preferred over cefotaxime during meningococcal and pneumococcal disease epidemics. Further, ampicillin or amoxicillin should be added to the initial empirical regimen in the presence of advanced HIV disease if there is elevated risk of *Listeria monocytogenes* infection *(78)*. Antibiotics used for empirical therapy can be modified as needed based on CSF or blood culture and antibiotic sensitivity results.

The use of intravenous corticosteroids administered as adjunctive treatment for suspected acute bacterial meningitis among children and adults with advanced HIV disease has not proven to be beneficial in reducing mortality and morbidity *(78)*.

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 (delay ART by 4–6 weeks) or multidrug-resistant TB (initiate ART as soon as possible but within eight weeks). In cases of suspected or confirmed TB meningitis, ART should be delayed for at least four weeks and started within eight weeks *(8)*. 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 *(79)*; more research is needed to inform guidance. Countries may consider initiating ART among people living with HIV who present with signs and symptoms suggesting TB, except for those with symptoms suggesting meningitis, while rapidly investigating for TB, with close follow-up within seven days to initiate TB treatment if TB is confirmed.

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 the cause of illness is unclear; two small studies found no statistically significant difference between early and delayed ART among unwell adults *(80, 81)*. 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 *(14)*.

People who have previously been taking ART but who have interrupted treatment should be offered ART reinitiation; if their initial ART regimen was based on non-nucleoside reverse-transcriptase inhibitors, they should restart a dolutegravir-based regimen. It is advised to discuss the reasons for having interrupted care and provide counselling support that might help prevent 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. 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 *(8)*. Programmes could consider reducing the time for repeat viral load to one month for people with advanced HIV disease to reduce the amount of time with treatment failure.

Timing of ART

Rapid ART initiation is a critical programmatic action to reduce the risk of progression among individuals with advanced HIV disease and should be provided alongside the WHO-recommended advanced HIV disease package of care *(14)*.

Table 4. Summary of timing of ART for individuals with opportunistic infections and comorbid conditions *(8, 58, 82, 83)*

Clinical status of people living with HIV	Timing of ART initiation
No signs and symptoms of TB	Rapid ART initiation, including starting ART on the same day that a diagnosis is confirmed should be offered to all people living with HIV following clinical assessment.
Suspected TB	Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment and to people living with HIV with signs and symptoms suggesting TB. Except for central nervous system disease (meningitis), initiate ART while rapidly investigating for TB, with close follow-up within seven days to initiate TB treatment if TB is confirmed.
TB disease	ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV (except for tuberculous meningitis and multidrug-resistant TB)
Diagnosed with TB meningitis	ART should be delayed at least four weeks (and initiated within eight weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered adjuvant treatment for TB meningitis, but cryptococcal meningitis should be ruled out since steroid use can lead to more adverse events.
Cryptococcal meningitis	ART initiation should be deferred by 4–6 weeks from the initiation of antifungal treatment.
Histoplasmosis	ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven.
Kaposi's sarcoma	ART should be rapidly initiated alongside management of Kaposi's sarcoma.

Managing side-effects of treatment

Immune reconstitution inflammatory syndrome and adverse antiretroviral 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 (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 exist for TB immune reconstitution inflammatory syndrome and for other opportunistic infections *(14, 84, 85)*.

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 *(85)*. For individuals with more severe immune reconstitution inflammatory syndrome, especially caused by TB, steroids may be used *(85, 86)*, although a clinical trial conducted in 2023 suggests that benefits may be small to none *(87)*. 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 *(88)*, but some expert guidelines suggest steroids in severe immune reconstitution inflammatory syndrome due to cryptococcal meningitis *(77)*. This is of particular importance when considering a differential diagnosis of TB meningitis – since steroids may be considered for use – thus, ruling out cryptococcal meningitis is critical in this context since steroid use is strictly contraindicated. In general, ART should not be interrupted during 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, ART should be discontinued until symptoms have resolve, and a substitution regimen can be safely initiated. If possible, people who have symptoms of ART toxicity should have laboratory testing as indicated (for example, renal function, liver function or haemoglobin measurement) *(8)*. Specialist advice should be sought if available. 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.

Planning for discharge and follow-up care (new, 2025)

Recommendation for improving re-engagement and reducing readmissions

Hospitalized people with HIV may be provided interventions to support transitions to outpatient care and reduce avoidable readmissions.
Conditional recommendation, low-certainty evidence

Interventions may include:
- pre-discharge goal setting
- medication review
- transitional care planning
- telephone follow-up
- home visits by health-care providers and/or peer supporters
- individualized support.

The outcomes of people following discharge from hospital are poor. A systematic review up to 2022 found that 19% of people living with HIV were subsequently readmitted to hospital after discharge and 14% had died *(10)*. More recent studies have confirmed that post-discharge outcomes are poor for both adults and children *(89–91)*.

Rationale and supporting evidence
Linkage to care can be considered a core health-care principle in most settings. However, assessing the effectiveness of programmatic activities (such as transitional care planning, discharge protocols and health-care worker visits) to hospitalized people with HIV provides important information on the activities to which programmes should give priority in the context of limited resources while working across different divisions of a national health programme structure.

Recent studies suggest that providing support following hospital discharge can improve outcomes. A systematic review of hospitalized patients with HIV identified 10 studies assessing interventions to improve outcomes following hospital discharge *(92)*. Four studies were randomized trials conducted in Spain *(93)*, South Africa *(94)*, the United Republic of Tanzania *(95)* and the United States of America *(96)*. Six studies were observational designs from Canada *(97)*, the United States of America *(98–100)*, Zambia *(101)* and Thailand *(102)*.

Across the randomized trials, there was no clear evidence of a difference in mortality between those who did and did not receive an intervention (relative risk (RR) 0.98, 95% CI 0.59–1.63); this estimate is imprecise, and there were few deaths with pooled risk differences across the trials, ranging from seven fewer to six more per 100 patients. The interventions might be associated with reduced likelihood of readmissions (RR 0.82, 95% CI 0.52–1.30) and might be associated with a slight increase in the likelihood of linkage or retention (RR 1.10, 95% CI 0.95–1.27) although the confidence interval is wide, including no effect. Outcomes were similar across the observational studies, which reported no difference in mortality (RR 1.0, 95% CI 0.63–1.59),

possibly decreased likelihood of readmissions (RR 0.77, 95% CI 0.48–1.25) and increased likelihood of linkage or retention in care (RR 1.42, 95% CI 1.11–1.81). Pooling all data across study designs gave similar results: no difference in mortality (RR 1.02, 95% CI 0.79–1.32) and a possible reduction in readmissions (RR 0.87, 95% CI 0.69–1.09). Linkage or retention in care increased (RR 1.24, 95% CI 1.07–1.44), which translated into 18 more patients of every hundred (6–30 patients) being linked or retained. The certainty of the evidence was rated as low because of concerns about the risk of bias across the studies and uncertainty around the reported benefits, thus likely small.

The systematic review was complemented by an umbrella review that assessed post-discharge interventions among people without HIV hospitalized for comparable chronic conditions. The reviews reported on pre- and post-discharge interventions, including communication interventions *(103)*, transitional care interventions *(104–109)* and tele-transitions interventions *(110)*. Individual intervention components included education interventions *(103–109)*, discharge planning needs assessment *(109)*, medication reconciliation *(103, 105, 108, 109)*, linking with community or social care contact *(109)*, case management and health assessment *(105, 107, 109)*, telephone follow-up *(104–107, 109, 110)*, home visits *(104–109)*, peer support *(109)*, needs assessment *(108, 109)* and telemonitoring *(104, 105, 107, 109, 110)*.

A systematic review focusing on medical inpatients – those with cardiac and respiratory diseases – reported a significant reduction in hospital readmission associated with education and medical reconciliation interventions for patients with respiratory diseases (RR 0.32; 95% CI 0.18–0.57) and other chronic conditions (RR 0.78; 95% CI 0.64–0.96) *(103)*. A systematic review focusing on multiple chronic conditions reported significant reduction in hospital readmission associated with education, telephone follow-up and home visits interventions (RR 0.84; 95% CI 0.71–0.99) *(106)*. Two systematic reviews focusing on chronic conditions reported significant reduction in readmission associated with multiple pre- and post-discharge interventions *(104, 105)*. One of the reviews showed a significant reduction in readmission associated with education, medical reconciliation, case management, telephone follow-up, home visits and telemonitoring (RR 0.63; 95% CI 0.44–0.91) *(105)*. Another review showed significant reduction in readmission associated with education, telephone follow-up, home visits and telemonitoring interventions but only for patients with heart failure (RR 0.90; 95% CI 0.81–0.99) and patients with chronic obstructive pulmonary disease (RR 0.52, 95% CI 0.32–0.83) *(104)*. A systematic review focusing on older adults with high risk of readmission showed significant reduction in readmission associated with telephone follow-up and telemonitoring (RR 0.59, 95% CI 0.45–0.77) *(110)*.

Taking the HIV-specific evidence and the evidence for non-HIV chronic conditions together, the Guideline Development Group considered that the following interventions can be considered to improve linkage to post-hospital care and reduce the occurrence of avoidable readmissions: pre-discharge goal setting and counselling *(93, 95–97)*, medical review *(98, 100, 101)*, transitional care planning *(98, 99)*, telephone follow-up *(93–99, 102)* and home visits by a nurse and/or peer supporter *(94, 95, 100, 101)*.

Preferences, acceptability and feasibility

Two studies that assessed post-discharge follow-up of people with HIV by telephone or home visit reported that the interventions were acceptable *(93, 101)*.

From the umbrella review, two systematic reviews reported on acceptability and satisfaction with interventions of patients and/or their caregivers *(103, 109)*. A systematic review focusing on medical inpatients, cardiology and respiratory diseases patients reported a significant association between communication interventions and patient satisfaction *(103)*. A systematic review that included patients with any health conditions reported increased patient satisfaction associated with high complexity interventions *(109)*.

It is important to respect privacy and confidentiality: consent should be sought before post-discharge follow-up at home, and if a person would prefer not to have home visits and or telephone calls from the clinic, this should be recorded.

Few studies included in the review reported on cost, and when this information was available, it was limited to crude data with no economic analysis. The costs likely vary depending on the type or complexity of the intervention, setting etc.

Three studies that assessed post-discharge follow-up by telephone or home visit reported that the interventions were feasible *(94, 97, 101)*.

Resource use and equity

One study that assessed social worker hospital and home care in the United Republic of Tanzania reported the cost of delivering the intervention to be US$ 22 per person *(95)*. A study from Thailand reported that the intervention (enhanced inpatient rounds and telephone follow-up) was cost neutral *(102)*; a study from the United States of America reported that the intervention (telephone follow-up) saved costs through reduced readmissions *(98)*.

All studies relied on existing cadres of non-specialist health personnel and community or peer workers. This supports the feasibility of delivering these interventions. Nevertheless, attention is needed to ensure that resources are not diverted away from the provision of other essential health-care services.

In terms of equity, the Guideline Development Group noted that hospitalized patients are a vulnerable group with high mortality. Higher rates of readmission lead to additional costs to the health system and individual that could be directed to serve other health needs, thus highlighting the need to reduce readmissions.

Implementation considerations
Certain activities, such as medical review and transitional care planning, should be considered as standard of care for all patients before hospital discharge. This includes ensuring that all patients are receiving ART and prophylaxis and have clear information about where to receive follow-up care. Differentiated approaches to support provision should be considered according to the presence of coinfections and comorbidities, including referral to mental health services as appropriate. Indirect support, such as nutritional assistance, can be considered as a way to strengthen care engagement *(94)*.

It is important to consider which cadres will provide post-discharge support and follow-up. Whenever possible, the existing health workforce could deliver the post-discharge interventions but with consideration of workforce capacity and sustainability. Peer counsellors, volunteers and support groups could also be engaged to provide support. Careful consideration should be given to the resources required for the support activity. This will vary according to context and should not divert resources away from other priority support needs.

Referral mechanisms and optimal communication following discharge back to the peripheral clinic should be reinforced to ensure appropriate follow-up (such as continuation of fluconazole, TB treatment or switching ART regimen when indicated). Referral back to the hospital should be assured for the individuals whose condition deteriorates after discharge. Referral and assessment should not result in unwarranted delays in starting ART and prophylaxis.

Research needs
Adequately powered randomized controlled trials of interventions are needed to identify effective ways to reduce mortality both during hospitalization and following discharge. These could include biomedical interventions (such as better diagnostics or treatments), process interventions (such as linkage to primary care services) or social interventions (such as ART adherence support). A priority area for research is identifying interventions to prevent TB mortality; other common comorbidities can be considered according to local prevalence and endemicity. Research studies should consider the often-substantial post-hospital discharge mortality for people living with HIV.

More research is needed to identify which interventions are most effective both before and after discharge to reduce avoidable readmissions and improve linkage to primary care in the community. Such research should include assessment of the acceptability and cost–effectiveness of providing support.

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

An important starting-point for research is to better characterize what is currently implemented as standard of care in hospital and following discharge, since this can identify areas that should be strengthened. Such research can include clearly characterizing the health status of people living with HIV at admission and discharge, research and clinical criteria for discharge and risk factors for poor post-discharge outcomes to identify patients who need more intensive follow-up.

Managing opportunistic infections

Background

Fungal priority pathogens for people living with HIV

WHO has identified 19 fungal pathogens that are categorized into three priority groups in terms of their impact on public health, antimicrobial resistance, knowledge gaps and epidemiology (Table 5) *(111)*. Several of these pathogens (*Cryptococcus* spp., *Histoplasma* spp., *Pneumocystis* spp., *Paracoccidiodes* spp. and invasive *Talaromyces marneffei* often affect people living with HIV. Although treatment guidelines are available for several of the high-burden infections, access to high-quality treatment is lacking in most settings. Importantly, people living with HIV remain susceptible to other pathogens specified in the priority pathogen list.

Table 5. WHO list of fungal priority pathogens

Critical group	High group	Medium group
Cryptococcus neoformans	*Nakaseomyces glabrata (Candida glabrata)*	*Scedosporium* spp.
Candida auris	*Histoplasma* spp.	*Lamentospora prolificans*
Aspergillus fumigatus	Eumycetoma causative agents	*Coccidiodes* spp.
Candida albicans	Mucorales	*Pichia kudriavzeveii (Candida krusei)*
	Fusarium spp.	*Cryptococcus gattii*
	Candida tropicalis	*Talaromyces marneffei*
	Candida parapsilosis	*Pneumocystis jirovecii* *Paracoccidiodes* spp.

Another WHO report *(112)* has found that the clinical pipeline of therapeutics for fungal infections approved in the past decade is insufficient considering the key targets and innovation needs. Drug–drug interactions are a major issue with currently available antifungal agents, and child-friendly formulations are lacking. The report also identifies at-risk categories of individuals, which includes people living with HIV or advanced HIV disease *(112)*.

Cryptococcal disease (2022)

Cryptococcal disease is an important opportunistic infection for people living with advanced HIV. After TB, cryptococcal disease is one of the most common opportunistic infections in advanced HIV disease, accounting for about 152 000 [133 000–219 000] cases in 2020, which resulted in 112 000 related deaths. Globally, this accounts for about 19% of AIDS-related deaths *(113)*.

Clinically significant or invasive disease is primarily caused by reactivation of latent infection among immunocompromised individuals, such as people living with HIV, months to years after initial exposure.

By far the most common presentation, representing up to 90% of HIV-related cryptococcal disease, is central nervous system involvement. Less frequent disease presentations include pulmonary disease, skin, lymph node and bone involvement *(114)*. Cryptococcal disease is uncommon among children with HIV *(115, 116)*, even in areas with a high disease burden among adults *(117)*.

Mortality from cryptococcal meningitis remains highest in low-income countries *(113)*. The reasons for this high mortality include limited access to lumbar puncture and rapid diagnostic assays, which result in delays in diagnosing cryptococcal disease. Currently available antifungal drugs are costly and unavailable in many settings globally *(118)* as is intensive care, which is often required.

In addition, there is limited ability to monitor and manage treatment-limiting toxicity and the frequent complications of raised intracranial pressure as well as immune reconstitution inflammatory syndrome associated with cryptococcal meningitis and ART *(119–122)*.

A public health approach leading to prevention, earlier diagnosis and improved treatment of cryptococcal disease and its complications is critical to reduce the incidence and associated high mortality of cryptococcal meningitis in low- and middle-income countries.

Prevention and screening for cryptococcal disease

The 2018 WHO recommendations for diagnosing cryptococcal disease remain unchanged *(123)*.

Background
Early HIV diagnosis and initiation of ART remains the most important preventive strategy to reduce the incidence of cryptococcal disease and the associated high mortality among people living with HIV *(123)*.

Screening for cryptococcal antigenaemia is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying infection when managing people aged 10 years or older presenting with advanced HIV disease *(54, 123)*. There remains a role for fluconazole primary prophylaxis in settings in which cryptococcal antigen screening is not available.

Since 2018, WHO guidelines have recommended that all adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3 be screened for cryptococcal antigen before ART initiation or reinitiation; cryptococcal antigen screening may also be considered for adults and adolescents living with HIV who have a CD4 cell count <200 cells/mm^3.

These recommendations were supported by evidence favouring the clinical benefit and cost–effectiveness of cryptococcal antigen screening. All individuals screening positive for cryptococcal antigen should be given pre-emptive antifungal therapy (fluconazole 800–1200 mg/day for adults and 12 mg/kg per day for adolescents for two weeks) followed by consolidation and maintenance fluconazole therapy *(124)*.

Another example for dosing pre-emptive antifungal therapy is the Southern African HIV Clinicians Society guidelines from 2019, recommending 1200 mg for the first two weeks given safety and concerns over breakthrough infection *(77)*.

Summary of recommendations for individuals with a CD4 count <100 cells/mm^3

Screening[a] for cryptococcal antigen followed by pre-emptive antifungal therapy (3 among cryptococcal antigen– positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3.
(Strong recommendation; moderate-certainty evidence)

When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3.
(Strong recommendation; moderate-certainty evidence)

Summary of recommendations for individuals with a CD4 count <200 cells/mm^3

Screening may be considered at a higher CD4 cell count threshold of <200 cells/mm^3.
(Conditional recommendation; moderate-certainty evidence)

fluconazole primary prophylaxis may be considered at a higher CD4 cell count threshold of <200 cells/mm^3. *(Conditional recommendation; moderate-certainty evidence)*

All people living with HIV testing positive for serum, plasma or whole blood cryptococcal antigen during screening should be carefully evaluated for signs and symptoms of meningitis and undergo lumbar puncture, if feasible, with CSF examination with CSF cryptococcal antigen assay or India Ink preparation to exclude meningitis.

India ink has low sensitivity, and a negative result on India ink should be confirmed by CSF cryptococcal antigen testing or CSF culture.

These recommendations would apply equally to people who present to care again after a period of disengagement from care with advanced HIV disease. Cryptococcal antigen screening followed by pre-emptive therapy would be preferrable over providing fluconazole primary prophylaxis when considering cost, the potential for developing antifungal resistance and concerns about fetal safety among women of childbearing age without access to adequate contraception.

Fluconazole primary prophylaxis should be made available in settings in which cryptococcal antigen screening is not available or there may be prolonged delays in receiving the result since cryptococcal disease and mortality peak in the first four weeks among people presenting with a CD4 cell count <100 cells/mm^3 *(55)*.

This recommendation is based on a systematic review that found a 70% reduction in mortality from cryptococcal disease among people living with HIV with low CD4 cell counts (95% CI 12–89%); the review also found a 71% reduction in cryptococcal disease incidence; the incidence of serious adverse events did not differ, but some evidence indicated an increased risk of fluconazole-resistant *Candida* infection *(125)*.

National guidelines should determine the optimal duration of prophylaxis based on available resources. The duration of fluconazole primary prophylaxis differed in the randomized trials that support the clinical benefit of this intervention. In the REALITY trial conducted in Kenya, Malawi, Uganda and Zimbabwe, fluconazole (100 mg once daily) was discontinued after 12 weeks *(55)*. In another trial conducted in Uganda in the era of ART, fluconazole (200 mg three times per week) was discontinued when participants' CD4 cell counts reached 200 cells/mm^3 *(126)*.

a All people living with HIV with a positive cryptococcal antigen result on screening should be carefully evaluated for signs and symptoms of meningitis and undergo a lumbar puncture if feasible with CSF examination and cryptococcal antigen assay (or India ink if cryptococcal antigen assay is not available) to exclude meningitis.

Recommendations for children

These recommendations apply to adults and adolescents with advanced HIV disease. The decision to not extend these recommendations to children was based on the recognition that cryptococcal disease in this age group is rare, even in countries with high incidence *(117, 127)*.

Diagnosing cryptococcal disease

The 2018 WHO recommendations remain unchanged for diagnosing cryptococcal disease *(123)*.

Background

Early diagnosis and treatment of cryptococcal disease is key to reducing mortality from cryptococcal disease. Health-care professionals should have a low threshold for suspecting cryptococcal meningitis among with people with advanced HIV disease.

National programmes require appropriate priority-setting is required by to ensure reliable access to rapid diagnostic cryptococcal antigen assays, preferably lateral flow assays, for use in CSF, serum, plasma or whole blood. In addition, health-care professionals need to have a low threshold for suspecting cryptococcal meningitis.

Lumbar puncture in people suspected with cryptococcal meningitis

For adults, adolescents and children living with HIV suspected of having a first episode of cryptococcal meningitis, prompt lumbar puncture with measurement of CSF opening pressure and rapid cryptococcal antigen assay is recommended as the preferred diagnostic approach. *(Strong recommendation; moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)*

The following diagnostic approaches are recommended, according to the context.

Settings with ready access to and no contraindication for lumbar puncture

1. If both access to a cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) and rapid results (less than 24 hours) are available, lumbar puncture with rapid CSF cryptococcal antigen assay is the preferred diagnostic approach.[a] *(Strong recommendation; moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)*
2. If access to a cryptococcal antigen assay is not available and/or rapid results are not available, lumbar puncture with CSF India ink test examination is the preferred diagnostic approach. *(Strong recommendation; moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)*

Settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated such as significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs or recurrent seizures[b]

1. If both access to a cryptococcal antigen assay and rapid results (less than 24 hours) are available, rapid serum, plasma or whole blood cryptococcal antigen assays are the preferred diagnostic approaches. *(Strong recommendation; moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)*
2. If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured, prompt referral for further investigation and treatment is appropriate. *(Strong recommendation; moderate-certainty evidence for adults and adolescents and low-certainty evidence for children)*

Note: Other diseases that can present with symptoms and signs similar to cryptococcal meningitis (such as viral, bacterial or tuberculous meningitis) should also be considered.

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a For a first episode, CSF cryptococcal culture is also recommended in parallel with cryptococcal antigen testing if this is feasible

b Contraindications include significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs (excluding cranial nerve VI palsy) or recurrent seizures and, where possible, confirmed by computed tomography. Raised intracranial pressure does not contraindicate lumbar puncture in (suspected) cryptococcal meningitis. Other contraindications include major spinal deformity and refusal by the patient after fully informed consent was sought.

Rapid cryptococcal antigen assays in CSF, serum, plasma or whole blood (depending on access to lumbar puncture) are preferred based on the much higher diagnostic accuracy of these rapid cryptococcal antigen assays versus the India ink test and the fact that these rapid assays depend less on the health-care provider's skills.

Advantages of the lateral-flow assay over the latex agglutination assay include its rapid (<10 minutes) turnaround time, cost–effectiveness, minimal training requirements and laboratory infrastructure, no need for refrigerated storage and higher clinical and analytical sensitivity.

A serum, plasma or whole-blood cryptococcal antigen test is recommended as an initial diagnostic option in settings in which access to lumbar puncture is limited or contraindicated. The use of serum, plasma or whole blood cryptococcal antigen diagnosis does not replace the need for lumbar puncture with CSF examination when this is feasible, considering also the important survival benefit of facilitating control of intracranial pressure *(128)*.

In low- and middle-income countries, the use of rapid low-cost assays that rely on limited technical skills and laboratory infrastructure facilitates prompt diagnosis and the initiation of antifungal therapy. A low index of suspicion is needed for cryptococcal meningitis in regions with moderate to high HIV prevalence.

Limited data from retrospective cohorts suggest that diagnostic performance among children is similar to that of adults *(129, 130)*. The recommendations for adults have therefore been extended to children (Table 6).

Table 6. Indications for cryptococcal antigen testing

	Lumbar puncture available	Lumbar puncture contraindicated or unavailable
Rapid cryptococcal antigen test available	CSF cryptococcal antigen (preferably lateral flow assay)	Serum, plasma or whole-blood antigen cryptococcal antigen (preferably lateral flow assay), treat immediately and refer for further investigation
No rapid cryptococcal antigen test available	CSF India ink preparation	Prompt referral for further investigation

Recommendations on induction, consolidation and maintenance antifungal treatment regimens

Background

Amphotericin B deoxycholate has been known to be associated with several side-effects such as anaemia, nausea, vomiting, rigors, fever, hypertension or hypotension, hypoxia and metabolic derangements such as hypokalaemia, hypomagnesaemia and nephrotoxicity *(131–133)*. The 2018 WHO guidelines noted that liposomal amphotericin B was preferred as a formulation over amphotericin B deoxycholate, considering equivalent efficacy and better safety *(123)*.

However, access to liposomal amphotericin B remains limited in low- and middle-income countries, mainly because of its high price, lack of registration of the product locally and limited. number of quality-assured manufacturers and the need for close monitoring for seven to 14 doses through intravenous infusion, similar to amphotericin B deoxycholate. A single high-dose liposomal amphotericin B–based regimen is the preferred option to treat individuals, with fewer side-effects and adverse events. Flucytosine accessibility, affordability and registration are also limited in low-and middle- income countries. Despite these access challenges, the use of high-dose fluconazole monotherapy is not recommended, considering the limited evidence of improved patient survival with this option *(33, 34)*.

WHO continues to recommend the alternative regimens in settings in which single high-dose liposomal amphotericin is unavailable. However, the 2022 WHO Guideline Development Group noted that fluconazole + flucytosine is associated with lower mortality than amphotericin B deoxycholate + fluconazole *(134)*, and efforts should be made to ensure access to a flucytosine-containing regimen.

Recommendations for induction therapy for cryptococcal meningitis

Induction therapy *(123)* (2022 recommendations)
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) should be used as the preferred induction regimen for treating people with cryptococcal meningitis. *(Strong recommendation, moderate-certainty evidence for adults and low-certainty evidence for children)*

Alternative induction regimens
If liposomal amphotericin B is not available: A seven-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by seven days of fluconazole (1200 mg daily for adults and 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). *(Strong recommendation, moderate-certainty evidence for adults and low-certainty evidence for children and adolescents)*

If no amphotericin B formulations are available: 14 days of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) + flucytosine (100 mg/kg per day, divided into four doses per day). *(Strong recommendation, moderate-certainty evidence)*

Note: fluconazole + flucytosine is the only recommended oral combination regimen and has been associated with lower mortality compared with amphotericin B deoxycholate + fluconazole.

If flucytosine is not available: 14 days of liposomal amphotericin (3–4 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). *(Strong recommendation, moderate-certainty evidence for adults)*

If liposomal amphotericin B and flucytosine are not available: 14 days of amphotericin B deoxycholate (1 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). *(Strong recommendation, moderate-certainty evidence)*

Note: flucytosine-containing regimens are superior, and steps should be taken to ensure access to this drug.

Preventing, monitoring and managing amphotericin B deoxycholate toxicity
Infusion-related toxicity and side-effects from amphotericin B therapy are barriers to optimal induction treatment, especially in low- and middle-income countries. Safe administration of amphotericin B should be given priority and may require referral to a centre with access to the recommended package of preventing, monitoring and managing toxicity.

Liposomal amphotericin B has fewer risks of drug toxicity than amphotericin B deoxycholate and requires a less intensive package for preventing, monitoring and managing toxicity.

The recommended package of preventing, monitoring and managing toxicity should be provided to minimize the serious types of amphotericin B–related toxicity when using amphotericin B deoxycholate–based regimens, especially hypokalaemia, nephrotoxicity and anaemia. A single 10 mg/kg dose of liposomal amphotericin B and the seven-day amphotericin B deoxycholate regimen are better tolerated than a 14-day amphotericin deoxycholate regimen, but these regimens still require careful monitoring.

Adverse events associated with amphotericin B deoxycholate include hypokalaemia, nephrotoxicity and anaemia (136–138). A protocol for monitoring potassium, magnesium (if available) and creatinine and weekly haemoglobin monitoring is advised, together with a simplified protocol for pre-hydration and electrolyte replacement before each amphotericin B infusion. If clients are also receiving a dolutegravir-based regimen, time-separated supplementation of magnesium is necessary to avoid affecting the absorption of dolutegravir *(62)*.

Dose adjustment is needed for people with significant renal impairment.

Liposomal, deoxycholate and lipid complex amphotericin B formulations are not interchangeable. Various formulations of amphotericin B are available commercially, including liposomal, deoxycholate and lipid complex formulations. These formulations are not interchangeable. For the indication of cryptococcal meningitis, only amphotericin B deoxycholate and liposomal amphotericin B have been recommended. In health-care settings in which both amphotericin B deoxycholate and liposomal amphotericin B are available, health-care providers must be cautious to avoid mixing up these products since the doses are different and significant adverse events have been reported when the deoxycholate formulation was given at a higher dose than recommended.

Table 7. Monitoring single high-dose amphotericin B administration

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Single high-dose liposomal amphotericin B														
Pre-emptive hydration and electrolyte supplementation (adults and adolescents)														
1 litre of normal saline solution with 20 mEq KCl over two hours before infusion	X													
8-mEq KCl tablets orally (twice daily)	X	X	X											
Magnesium supplementation if available[a]	X	X	X											
Monitoring (adults, adolescents and children)														
Serum potassium	X		X											
Serum creatinine	X		X											
Haemoglobin	X						X[b]							

a 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily or magnesium chloride 4 mEq twice daily.
b If still in hospital.

Table 8. Monitoring of amphotericin B deoxycholate (seven- and 14-day treatment regimens)

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Amphotericin B deoxycholate: seven days														
Pre-emptive hydration and electrolyte supplementation (adults and adolescents)														
1 litre of normal saline solution with 20 mEq KCl over two hours before each controlled infusion	X	X	X	X	X	X	X							
2 times 8-mEq KCl tablet (twice daily)	X	X	X	X	X	X	X							
Magnesium supplementation if available[a]	X	X	X	X	X	X	X							
Monitoring (adults, adolescents and children)														
Serum potassium	X		X		X		X		X[b]					
Serum creatinine	X		X		X		X							
Haemoglobin	X						X							
Amphotericin B deoxycholate: 14 days														
Pre-emptive hydration and electrolyte supplementation (adults and adolescents)														
1 litre of normal saline solution with 20 mEq KCl over two hours before each controlled infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2 times 8-mEq KCl tablet (twice daily)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
1 time 8-mEq KCl tablet (twice daily)								X	X	X	X	X	X	X
Magnesium supplementation if available[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitoring (adults, adolescents and children)														
Serum potassium	X		X		X		X		X		X		X	
Serum creatinine	X		X		X		X		X		X		X	
Haemoglobin	X						X							X

Additional notes:

- Amphotericin B is incompatible with normal saline.
- Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia.
- Careful attention should be given to monitoring the intake and output of fluid and daily weight, especially among children.
- Flucytosine: because of concerns about bone marrow suppression, regular monitoring of full blood counts should be considered; guidelines from the Southern African HIV Clinicians Society recommend monitoring full blood counts at baseline and at least weekly for as long as the person is taking flucytosine *(21)*.

If standard dose liposomal amphotericin B is being given for 14 days with fluconazole, the incidence of renal dysfunction and electrolyte disturbance is lower than with amphotericin B deoxycholate, but renal function and electrolytes still need to be monitored. In such cases, follow the standard recommendations for amphotericin B deoxycholate.

a 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily or magnesium chloride 4 mEq twice daily.
b If still in hospital.

Drug–drug interactions
Drug–drug interactions in the context of concurrent use of amphotericin, flucytosine and fluconazole alongside ART regimens have not been well documented *(135)*. However, individuals receiving tenofovir disoproxil fumarate (TDF)–based regimens who are receiving amphotericin or recently received amphotericin B preparations should be closely monitored for nephrotoxicity. Liposomal preparations of amphotericin B are considered to be safer *(133)* than deoxycholate but would still require close follow-up.

The dose of tenofovir disoproxil fumarate should be adjusted for renal function. Flucytosine may slightly alter levels of TDF in the blood through reduced renal clearance, but this remains a theoretical risk. Haematological parameters should be monitored, and the dose of tenofovir disoproxil fumarate should be adjusted in individuals with reduced renal function who are also receiving amphotericin *(136)*. Fluconazole induces cytochrome (CYP)3A4 and P-glycoprotein *(137)*. No dose adjustment of ART is required.

Consolidation and maintenance treatment
WHO recommends fluconazole at 800 mg/day for eight weeks following an amphotericin B deoxycholate–based induction regimen; these recommendations were based primarily on expert opinion, considering the limited evidence from two trials that compared itraconazole versus fluconazole at lower doses *(137, 138)*.

Guidelines from the European AIDS Clinical Society recommend 400 mg for eight weeks after a single loading dose of 800 mg on the first day of therapy *(123)*. Maintenance or secondary prophylaxis until there is evidence of sustained ART-related immune reconstitution is an integral part of managing cryptococcal meningitis. Among ART-naive people, fluconazole was effective at preventing relapse in one randomized controlled trial *(139)* and was superior to weekly amphotericin B or itraconazole *(139, 140)*.

Consolidation
Fluconazole (800 mg daily for adults, 6–12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) is recommended for the consolidation phase (for eight weeks following the induction phase). *(Strong recommendation, low-certainty evidence)*

Maintenance
Fluconazole (200 mg daily for adults, 6 mg/kg per day for adolescents and children) is recommended for the maintenance phase until immune reconstitution (CD4 >200 cells/mm3) and suppression of viral loads on ART. *(Strong recommendation, high-certainty evidence)*

Clinical considerations for managing cryptococcal disease

Preventing, monitoring and managing amphotericin B toxicity
For people living with HIV receiving amphotericin B–containing regimens for treating cryptococcal disease, a minimum package for preventing, monitoring and managing toxicity is recommended to minimize the serious types of amphotericin B–related toxicity, especially hypokalaemia, nephrotoxicity and anaemia *(139–142)*.

Monitoring for and managing raised intracranial pressure
Adults, adolescents and children living with HIV with suspected cryptococcal meningitis should have an initial lumbar puncture and an early repeat lumbar puncture (within 3–5 days) with measurement of CSF opening pressure to assess for raised intracranial pressure regardless of the presence of symptoms or signs of raised intracranial pressure *(122, 128)*.

Managing raised intracranial pressure
Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient *(88, 143)* to reduce the CSF pressure to <20 cm or halving the baseline pressure if extremely high; the persistence or recurrence of symptoms or signs of raised intracranial pressure should determine the frequency of repeat therapeutic lumbar puncture *(144)*. For people with persistent symptoms of intracranial pressure, repeat daily therapeutic lumbar puncture (with measurement of CSF opening pressure when available) and CSF drainage, if required, are recommended until the symptoms resolve or the opening pressure is normal for at least two days *(123)*.

Monitoring treatment response

Clinical response (including resolution or recurrence of fever, headache and symptoms or signs of raised intracranial pressure) should be assessed daily during the initial two weeks of induction therapy. Among people for whom evidence indicates a sustained clinical response, routine follow-up lumbar puncture after completing induction treatment to assess antifungal treatment response (CSF fungal culture and CSF cryptococcal antigen) or serum or plasma cryptococcal antigen is not recommended in low- and middle-income countries *(123)*.

Managing treatment failure

For people who present with cryptococcal meningitis relapse, the following steps are recommended: start or restart induction treatment according to the recommendations for induction treatment; manage raised intracranial pressure with therapeutic lumbar puncture; and provide adapted adherence support. If ART has not already started, initiating ART after 4–6 weeks of optimal antifungal therapy is recommended *(123)*.

Paradoxical cryptococcal immune reconstitution inflammatory syndrome occurs among 10–50% of people with cryptococcal disease initiating ART *(145)* and is associated with high mortality *(120)*. The median time to onset in reported cohort studies is 1–10 months but typically is 3–12 weeks after initiating ART *(145)*.

Raised intracranial pressure is a common feature of cryptococcal immune reconstitution inflammatory syndrome and an important contributor to high mortality *(146)*. Multiple repeat lumbar puncture may be necessary. Optimizing antifungal therapy and reinduction with an amphotericin-based regimen are important if suboptimal antifungal treatment is considered to contribute to developing immune reconstitution inflammatory syndrome *(123)*.

Research needs

Further research is needed to assess the value of cryptococcal antigen screening at CD4 cell count thresholds between 100 and 200 cells/mm^3, which has been suggested to save costs if carried out in inpatient settings.

High cryptococcal antigen titres (>1:160) in blood have been found to predict subclinical meningitis. It has been suggested that blood titres could be used to predict meningitis in settings in which lumbar puncture cannot be performed or in which providing lumbar puncture for everyone screening cryptococcal antigen–positive is operationally challenging; the feasibility of this approach should be further investigated in a diversity of settings.

Second-generation cryptococcal antigen lateral-flow assays that can give a high or low cryptococcal antigen result need to be evaluated as part of this approach.

Research could help to improve the understanding of how to manage relapse or treatment non-response in public health settings, since the current course of action would be referral to a tertiary care centre. In tertiary care settings, intrathecal and intraventricular administration of amphotericin B have been attempted successfully, but further research is needed to establish safety and tolerability.

Managing space-occupying lesions among people with a positive serum cryptococcal antigen test, the concurrent treatment of HIV-associated TB and cryptococcal meningitis and the best approach for treating immune reconstitution inflammatory syndrome are other research needs.

WHO has issued a prequalification expression of interest for sustained-release flucytosine to simplify inpatient and outpatient treatment of cryptococcal infections.

The role of azoles other than fluconazole, notably voriconazole and isavuconazole, as well as novel oral antifungal agents (such as oral encochleated amphotericin B) for treatment and prophylaxis for cryptococcosis could benefit from further study.

There remains a need to better understand the prevalence of cryptococcal disease among children and the best diagnostic approach to enable the timely identification of disease.

Implementation science research is encouraged on the feasibility and impact of cryptococcal antigen screening delivered together with other components of an advanced ART package (such as TB lipoarabinomannan assay and TB prophylaxis).

Histoplasmosis (2021)

Background

Histoplasmosis is a disease caused by the fungus *Histoplasma capsulatum*; the most frequent clinical presentation among people living with HIV is disseminated histoplasmosis. Symptoms of disseminated histoplasmosis are nonspecific and may be indistinguishable from those of other infectious diseases, especially TB, thus complicating diagnosis and treatment *(147)*. 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. Histoplasma antigen can be detected in urine, which enables an approach of rapid detection and linkage to treatment and is recommended by WHO as a preferred approach. WHO does not currently recommend routine screening for histoplasmosis, pending further investigation *(147)*.

The lack of access to appropriate antifungal therapies and in vitro diagnostics for rapid detection of histoplasmosis and the co-occurrence of other infectious diseases, especially TB, may affect clinical outcomes and underlie the high mortality of disseminated histoplasmosis among people living with HIV *(148, 149)*. Note that TB and histoplasmosis, in addition to being often misclassified, frequently recur together in endemic settings *(148, 150)*.

Access to liposomal amphotericin is a significant challenge in many settings worldwide, especially in low- and middle-income settings. Licensing is a key barrier for access to this formulation in addition to highly variable costs *(151)*. An analysis of data from 55 countries showed that 72% of liposomal amphotericin is sold in high-income settings and 28% in low-income settings, where the need is the greatest. Additionally, low-income settings continue to purchase conventional amphotericin B deoxycholate or lipid complex formulations in greater quantities than in high-income settings *(118)*.

Severe or moderately severe histoplasmosis is defined as the presence of at least one sign or symptom involving vital organs: respiratory or circulatory failure, nervous system signs, renal failure, coagulation anomalies and a general alteration of the WHO performance status greater than 2, in which the person is confined to a bed or chair more than half of the waking hours and only capable of limited self-care *(147)*.

In 2020, WHO published *Guidelines on diagnosing and managing disseminated histoplasmosis among people living with HIV (147)*. Below are the recommendations, which are all based on evidence reviewed by the Guideline Review Committee *(147)*.

Monitoring toxicity of amphotericin B therapy and drug–drug interactions associated with itraconazole use are important for the successful treatment of individuals with histoplasmosis. Renal function monitoring is important to identify, prevent and manage toxicity (such as nephrotoxicity, hypokalaemia, infusion-related reactions and anaemia). Appropriate fluid hydration is necessary to prevent kidney damage through fluid and electrolyte reposition over 4–6 hours.

Diagnosis of disseminated histoplasmosis among people living with HIV

Among people living with HIV, disseminated histoplasmosis should be diagnosed by detecting circulating *Histoplasma* antigens *(152). (Conditional recommendation, low-certainty evidence)*

Management of disseminated histoplasmosis

Induction therapy
Treating people living with HIV for severe or moderately severe histoplasmosis: liposomal amphotericin B, 3.0 mg/kg, for two weeks is recommended. In settings in which liposomal amphotericin B is unavailable, deoxycholate amphotericin B, 0.7–1.0 mg/kg, is recommended for two weeks *(153–155). (Conditional recommendation, very-low-certainty evidence)*

As a good clinical practice for people with renal failure, or at risk of renal injury, measures to prevent or treat toxicity are recommended. Induction therapy should be given for two weeks. Since deoxycholate amphotericin B may be associated with renal toxicity, therapy may need to be shorter than two weeks based on the clinical assessment of how the person responds to treatment. Involvement of the central nervous system may require extending induction therapy or increasing dosage.

Treating people living with HIV for mild to moderate histoplasmosis: itraconazole 200 mg three times daily for three days and then 200 mg twice daily is recommended (156, 157). *(Conditional recommendation, very-low-certainty evidence)*

Maintenance therapy
Itraconazole 200 mg twice daily for 12 months is recommended (158–160). *(Conditional recommendation, very-low-certainty evidence)*

Less than 12 months of therapy can be considered when the person is clinically stable, receiving ART, has suppressed viral load and the immune status has improved (161). *(Conditional recommendation, very-low-certainty evidence)*

Timing of ART initiation
ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven *(81). (Conditional recommendation, very-low-certainty evidence)*

TB therapy for people with TB, HIV and histoplasmosis
People living with HIV who also have TB and histoplasmosis coinfection should receive TB therapy according to WHO treatment guidelines *(147). (Conditional recommendation, very-low-certainty evidence)*

Implementation considerations

1. Access to optimal antifungal medicines
The WHO Model List of Essential Medicines includes optimal antifungal medicines for treating people with histoplasmosis (conventional amphotericin B and itraconazole). Increased advocacy for drug price reduction is needed, expanding coverage of the global access price of liposomal amphotericin B for leishmaniasis and cryptococcal meningitis, promoting local manufacturing of generic formulations. Additionally, it is important to ensure quality assurance of available generic formulations, ensuring national registration of all antifungal drugs on the WHO Model List of Essential Medicines.

Medicines can be procured through joint regional procurement mechanisms such as the PAHO Strategic Fund, ensuring adequate supply chains at the national level and developing proper drug forecasting and monitoring systems.

2. Educating and training health-care providers
Health-care providers should be trained to have a low threshold for suspecting histoplasmosis among people living with HIV, especially in advanced HIV disease, with the differential diagnosis of TB and other systemic fungal infections. Greater efforts need to be made to educate health-care providers and to provide policy guidance at the national level on managing histoplasmosis among people living with HIV. Effectively implementing guidelines also requires supportive supervision systems and prescribing decision-making aids.

Research needs

- What is the antigen detection performance outside the context of advanced HIV disease?
- Among people with advanced HIV disease, can *Histoplasma* antigen detection be used as a screening approach for histoplasmosis?
- Can antigen detection performance be increased by designing new antibodies through significant support in developing basic science on *Histoplasma capsulatum*?
- Will a *Histoplasma* interferon-gamma release assay be useful to screen for latent histoplasmosis in advanced HIV disease, prevent histoplasmosis-associated immune reconstitution inflammatory syndrome and help to reduce the time to ART initiation among people recently diagnosed with HIV?
- Can antigen detection screening studies inform about the true burden of histoplasmosis from a global perspective?
- Will *Histoplasma* antigen detection by lateral flow become the standard diagnostic method for disseminated histoplasmosis among hospitalized people with histoplasmosis, as an outpatient screening tool or both?
- How can the specific impact of antigen detection on the incidence and mortality trends of HIV-associated histoplasmosis be evaluated compared with conventional practices for diagnosing histoplasmosis and the future development of more molecular biology assays?
- What are the best definitions for severity of disease among people with histoplasmosis?
- Among people with a clinical and immune response to therapy, can maintenance antifungal therapy be safely discontinued earlier than 12 months?
- Do people with central nervous system involvement have a higher incidence of *Histoplasma*-related immune reconstitution inflammatory syndrome and associated mortality? In relation to this, what is the optimal time to start ART?
- When will *Histoplasma* antigen detection and liposomal amphotericin B be affordable to people with histoplasmosis in low- and middle-income countries?
- What are the outcomes of treating TB and histoplasmosis coinfection?
- What is the impact of genetic varieties of *Histoplasma* on the epidemiology and treatment response to histoplasmosis?
- What are the alternative antifungal drugs or alternative treatment stewardship in the pipeline that might help to increase the efficacy and decrease the secondary effects and toxicity of the recommended therapy?
- What is the optimal dosing for liposomal amphotericin B among people living with HIV with disseminated histoplasmosis?

TB in advanced HIV disease (2025)

People living with HIV are about 13 times more likely to develop TB disease, have poorer TB treatment outcomes and higher mortality during TB treatment than people without HIV *(162)*. The presence of advanced HIV disease (CD4 <200 cells/mm^3) among people with disseminated TB is an independent predictor of mortality, in addition to being considered either a WHO clinical stage 3 or 4 AIDS-defining illness. Despite advances in the screening, diagnosis, treatment and prevention of TB disease, TB remains the leading cause of death among people with HIV worldwide and is second to only AIDS-related illnesses for hospitalizations among people living with HIV *(8)*.

WHO provides recommendations and practical guidance for people living with HIV of all ages, including advanced HIV disease, for prevention, screening, diagnosis and treatment for TB, including models of care within the guidelines and related operational handbooks contained within the WHO TB Knowledge Sharing Platform *(163, 164)*.

This section summarizes key recommendations and considerations for advanced HIV disease.

Screening

Screening for TB is a critical component of the advanced HIV disease package of care and is part of the algorithm for managing advanced HIV disease. Screening for TB is considered standard care for all people living with HIV *(58)*.

Age-appropriate screening should be performed at every health-care visit with a WHO-approved TB symptom screening algorithm along with a combination of screening tools as appropriate, to minimize the risk of missed cases of TB. Screening tools include C-reactive protein, chest X-ray and molecular WHO-recommended rapid diagnostic tests. Interferon-gamma release assays are not considered useful tests for TB screening *(58)*.

For children living with HIV, screening opportunities also include visits for vaccination days, during nutritional screening, at maternal health appointments and at food programme visits *(60)*. Screening children for TB can be challenging since they may present with atypical symptoms, thus requiring a strong clinical suspicion of TB for anyone living with HIV in settings with a high TB burden. The risk of over-investigation is outweighed by the benefits of TB treatment *(60)*. TB preventive treatment should be initiated for those screening negative for TB *(56)*.

Recommendations for TB screening for people living with HIV *(58)*

People living with HIV should be systematically screened for TB disease at each visit to a health facility. *(Strong recommendation, very-low-certainty evidence)*

Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four-symptom screen, and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases. *(Strong recommendation, moderate-certainty evidence)*

Among adults and adolescents living with HIV, C-reactive protein with a cut-off of >5 mg/L may be used to screen for TB disease. *(Conditional recommendation, low-certainty evidence for test accuracy)*

Recommendations for TB screening for people living with HIV *(58)*

Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease. *(Conditional recommendation, moderate-certainty evidence for test accuracy)*

Adult and adolescent inpatients with HIV in medical wards where the TB prevalence is >10% should be tested systematically for TB disease with a molecular WHO-recommended rapid diagnostic test. *(Strong recommendation, moderate-certainty evidence for test accuracy)*

Among individuals younger than 15 years who are close contacts of someone with TB, systematic screening for TB disease should be conducted using a symptom screen including any one of cough, fever or poor weight gain, or chest X-ray; or both. *(Strong recommendation, moderate- to low-certainty evidence for test accuracy)*

Among children younger than 10 years living with HIV, systematic screening for TB disease should be conducted using a symptom screen including any one of current cough, fever, poor weight gain or close contact with a TB patient. *(Strong recommendation, low-certainty evidence for test accuracy)*

Diagnosis

TB is frequent among individuals with advanced HIV disease and is a common cause of hospital admission for these individuals. Postmortem studies report a high proportion of undiagnosed TB among people who have died from HIV *(165, 166)*. Establishing a diagnosis of TB is critical for ensuring early initiation of TB treatment and for reducing mortality.

However, identifying TB among individuals with low CD4 counts is a challenge, and using a combination of diagnostic tests for individuals with advanced HIV disease is therefore recommended. The recommendations are described in full in the *WHO consolidated guidelines on tuberculosis: module 3: diagnosis (59)*. Clinical diagnosis plays an important role for people with advanced HIV disease since bacteriological confirmation is not always possible. For children, integrated treatment decision algorithms can help guide decisions about starting TB treatment *(60)*.

Further investigation is warranted for diagnosing drug-resistant TB. The *WHO consolidated guidelines on tuberculosis: module 3: diagnosis* provide details on diagnosing and detecting drug-resistant TB *(59)*.

Monitoring and evaluation considerations

- Monitor simultaneous specimen collection and turnaround time for the test results in a concurrent testing approach.
- Monitor patient access to and loss to follow-up from a second test in a concurrent testing approach.
- Monitor patient access to and loss to follow-up from follow-on drug-susceptibility testing among those with a positive LF-LAM result but a negative low-complexity automated NAAT result.
- Monitor trends in the discordance rate between the LF-LAM and low-complexity automated NAAT results. If these differences vary from other local or regional patterns, or if the trends change, further investigation is required, and outcomes should be tracked for recurrence over time.

Recommendations for diagnosing TB disease

Adults and adolescents

For adults and adolescents with HIV who have signs or symptoms, screen positive for TB, are seriously ill or have advanced HIV disease, concurrent testing using low-complexity automated NAATs on respiratory samples and LF-LAM on urine should be used as the initial diagnostic strategy for diagnosing TB rather than low-complexity automated NAATs on respiratory samples alone.
(Strong recommendation, low-certainty evidence)

Remarks

- Serious illness for people living with HIV is defined based on any of the following symptoms: respiratory rate ≥30 breaths per minute, temperature ≥39°C, heart rate ≥120 beats per minute or unable to walk unaided.
- Advanced HIV disease is defined for people living with HIV as having a CD4 cell count of <200 cells/mm^3 or presenting with a WHO stage 3 or 4 AIDS-defining illness.
- This concurrent testing recommendation supersedes previous guidance on using LF-LAM for people living with HIV and using a single molecular test for diagnosing TB in this group.
- This recommendation is strong despite the low-certainty evidence because the findings indicate large desirable effects (rapid and accurate diagnosis of TB for a highly vulnerable population – people living with HIV – for whom diagnosing TB is often challenging) and small undesirable effects (negative consequences of this testing strategy).
- The low-complexity automated NAAT products for which eligible data met the class-based performance criteria for this recommendation were Xpert® MTB/RIF Ultra and Truenat MTB Plus. Data for the performance of Truenat MTB Plus and MTB-RIF Dx were only available for testing among people living with HIV without concurrent LF-LAM testing.

Children with HIV

For children with HIV who have signs or symptoms or screen positive for pulmonary TB, concurrent testing using low-complexity automated NAATs on respiratory and stool samples and LF-LAM on urine may be used as the initial diagnostic strategy for diagnosing TB rather than low-complexity automated NAATs on respiratory or stool samples alone. *(Conditional recommendation, low-certainty evidence for test accuracy)*

Remarks

- This recommendation gives priority to concurrent testing over molecular testing and LF-LAM in isolation for diagnosing TB among children living with HIV.
- Using low-complexity automated NAATs on isolated specimens was also evaluated. The findings supported the use of low-complexity automated NAATs for initial diagnostic testing for TB among children living with HIV with signs or symptoms or who screen positive for pulmonary TB, using sputum, gastric aspirate, stool or nasopharyngeal aspirate rather than smear or culture.
- This recommendation is conditional because the findings indicate moderate undesirable effects (reduced specificity, resulting in more false-positive test results) compared with a single test strategy.
- The product for which eligible data met the low-complexity automated NAAT class-based performance criteria for this recommendation was Xpert® MTB/RIF Ultra. The performance of Truenat MTB Plus and MTB-RIF Dx for this recommendation could not be assessed, since data were unavailable.

Implementation considerations for diagnosing TB

Adults and adolescents living with HIV and children living with HIV

- Global and national HIV and TB programmes need to communicate regularly and clearly, indicating responsibilities for concurrent testing for people living with HIV.
- Concurrent testing maximizes the diagnostic access and accuracy, is a more efficient way to address the needs of people living with HIV and is preferred even if the testing workload may increase.
- A positive result on either test is sufficient to confirm a TB diagnosis.
- Loss to follow-up for the second test result should be monitored and prevented. Patients should be given information to understand the concurrent testing approach and the need for follow-up.
- The LF-LAM performed in point-of-care settings may be the first positive result and is sufficient to make the initial diagnosis. A respiratory sample is still required for detecting rifampicin resistance. It is also required when the LF-LAM is negative.
- Efforts are needed to improve access to LF-LAM.
- LF-LAM does not differentiate *Mycobacterium tuberculosis* from other mycobacterial species. However, the LAM antigen detected in a clinical sample in TB endemic areas is most likely attributable to *Mycobacterium tuberculosis*. When LF-LAM is commonly positive without positive low-complexity automated NAATs, further investigation of the quality of testing and local epidemiology of non-TB mycobacteria and extrapulmonary TB in the tested population is warranted to understand the difference.
- Bands on the LF-LAM test strip should be interpreted using the manufacturer's reading card to minimize incorrect results.
- LF-LAM test strips must be stored according to the manufacturer's instructions (such as between 2°C and 30°C) in sealed bags and not used after expiration.
- Infrastructure to collect a urine sample privately should be available. Patients should be instructed how to properly and sanitarily collect urine to minimize environmental contamination and prevent false-positive results.
- Trained personnel are required to perform the LF-LAM test at the point of care.
- Similar to all WHO-recommended TB diagnostics, quality assurance programmes for both tests are required.
- LF-LAM is designed to detect mycobacterial LAM antigen in human urine. Other samples (such as sputum, serum, plasma, CSF and other body fluids) or pooled urine specimens should not be used.

Prevention

TB preventive treatment

TB preventive treatment is a critical component of prophylaxis in the WHO-recommended package of care for advanced HIV disease, along with co-trimoxazole and fluconazole. TB preventive treatment should be rapidly initiated among people with advanced HIV disease, after TB has been ruled out through systematic TB screening with a WHO-recommended approach *(56, 58, 164)*. The short-course TB preventive treatment regimen – three months of weekly isoniazid and rifapentine – is the preferred option for adolescents and adults living with HIV. However, the ART regimen should be considered, and evidence on coadministration of rifapentine and preferred ART regimens is still being generated for children, infants and pregnant women living with HIV.

Recommendations on eligibility for TB preventive treatment

Adults and adolescents living with HIV who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those receiving ART, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if testing for TB infection is unavailable. *(Strong recommendation, high-certainty estimates of effect)*

Infants aged <12 months living with HIV who are in contact with a person with TB and who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment. *(Strong recommendation, moderate-certainty estimates of effect)*

Children aged ≥12 months living with HIV who are considered unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB. *(Strong recommendation, low-certainty estimates of effect)*

All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment. *(Conditional recommendation, low-certainty evidence)*

Recommendations on the choice of TB preventive treatment regimen for people living with HIV

Preferred TB preventive treatment regimen among people living with HIV
For adults and adolescents living with HIV eligible for TB preventive treatment, three months of rifapentine and isoniazid (3HP) is the suggested preferred regimen; six or nine months of isoniazid (6H or 9H) are alternative regimens. *(Conditional recommendation, low-certainty evidence)*

Recommendation on available TB preventive treatment regimensregardless of HIV status
The following TB preventive treatment options are recommended regardless of HIV status: six or nine months of daily isoniazid or a three-month regimen of weekly rifapentine plus isoniazid or a three-month regimen of daily isoniazid plus rifampicin. *(Strong recommendation, moderate- to high-certainty estimates of effect)*
The following alternative TB preventive treatment options may be used regardless of HIV status: a one-month regimen of daily rifapentine plus isoniazid or four months of daily rifampicin. *(Conditional recommendation, low- to moderate-certainty estimates of effect)*

BCG
Neonates diagnosed with HIV infection, as confirmed by early virological testing, should not receive BCG vaccination at birth. Vaccination should be delayed until ART has been started and the infant is confirmed to be immunologically stable (CD4% exceeding 25% for children younger than five years; CD4 count of 200/mm^3 or higher for children older than five years).

The current WHO position paper on BCG vaccination *(167)* states that children known to be living with HIV should not receive BCG vaccination because they are at increased risk of developing disseminated BCG disease. However, if they are receiving ART, are clinically well and immunologically stable they should be vaccinated. Immunologically stable children have a CD4% exceeding 25% (children younger than five years) or a CD4 count of 200/mm^3 or higher (children older than five years). In settings without access to CD4 testing, immunological stability may be assessed clinically based on the absence of new opportunistic infections and any other symptoms *(167)*.

The *WHO operational handbook on tuberculosis: module 5: management of tuberculosis in children and adolescents* details the administration of BCG, important adverse events and other aspects of the full cascade of care for children and adolescents with or at risk of TB *(60)*.

Treatment

Linkage to treatment following diagnosis of TB disease is important, and co-management of TB and HIV requires close attention. Treatment regimens for drug-susceptible TB range from four to six months, which are also applicable to people with advanced HIV disease. There are, however, important considerations such as severity or type of TB disease, level of immunosuppression and body weight. More details on the treatment of drug-susceptible and drug-resistant TB are available in the respective treatment guidelines within the WHO TB Knowledge Sharing Platform.

Timing of ART initiation is a critical consideration when managing TB disease among people living with HIV while also ruling out signs and symptoms of meningitis. Clinically distinguishing between TB meningitis and cryptococcal meningitis is challenging and is critical if using steroids is being considered, since steroids are recommended for TB meningitis but not for cryptococcal meningitis. Using steroids may also be considered for tuberculous pericarditis as part of initial adjuvant therapy, although the interaction of steroids and HIV infection is complex and not fully understood. Table 6 provides information on the appropriate timing of ART in the context of TB disease and cryptococcal meningitis. Comprehensive guidance is available from the *WHO consolidated guidelines on tuberculosis: module 4: treatment and care (61)*.

Treatment

It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients. *(Strong recommendation, high-certainty evidence)*

ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.[a]

Adults and adolescents *(Strong recommendation, low- to moderate-certainty evidence)*

Children and infants *(Strong recommendation, very-low-certainty evidence)*

ART is recommended for all patients with HIV and drug-resistant TB requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very-low-certainty evidence)*

In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used. *(Strong recommendation, moderate-certainty evidence)*

In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used. *(Conditional recommendation, very-low-certainty evidence)*

a Except when signs and symptoms of meningitis are present.

Severe bacterial infections

Severe bacterial infections are an important cause of mortality for people living with HIV and are a common cause of hospital admission, about 26% (95% CI 20–33%) *(8)*. Severe bacterial infections present a wide range of disease manifestations and causative organisms. This includes pneumonia, bacterial meningitis, bloodstream infections and organ-specific infections.

There is generally very limited access in low- and middle-income countries to reliable microbiology diagnostic tools, including blood cultures, and relatively poor assessment of the prevalence of drug-resistant organisms. Consequently, clinical diagnosis is the key tool for screening for severe illness. Common bacterial pathogens include *Streptococcus* spp., invasive non-typhoidal *Salmonella*, *Escherichia coli* and *Staphylococcus aureus*. The WHO AWaRe antibiotic book provides considerations for rationale use of antibiotics for all populations *(168)*.

Oral co-trimoxazole remains a critical WHO recommendation *(8)* for use in prophylaxis and is part of the WHO-recommended package of care for advanced HIV disease, although its primary use is in preventing pneumonia caused by *Pneumocystis jirovecii (111)*, but it may provide additional coverage for several bacterial infections.

WHO provides several key considerations and knowledge gaps in managing severe bacterial infections *(11)*.

- Severe bacterial infections are a priority issue for individuals with advanced HIV disease.
- Severe bacterial infections affect both inpatient and outpatient settings, and tiered guidance is essential.
- Implementation research can help to address gaps in understanding the profile of severe bacterial infections.
- Studies are needed to document the causes of premature death among people living with HIV.
- Specific guidance on managing severe bacterial infections is needed in inpatient settings.
- Antimicrobial resistance implications must be weighed carefully when considering using antimicrobial agents for prophylaxis.
- Cost and cost–effectiveness studies and modelling of emergent drug resistance comprise important accompanying evidence for understanding severe bacterial infections.

WHO will continue to monitor available evidence for developing further guidance on this topic.

Kaposi’s sarcoma (new, 2025)

Recommendation for treatment of Kaposi’s sarcoma (new, 2025)

WHO suggests paclitaxel or pegylated liposomal doxorubicin for pharmacological treatment for people living with HIV with Kaposi’s sarcoma. *(Conditional recommendation, low-certainty evidence)*

Recommendation for treatment of mild or moderate Kaposi’s sarcoma *(83)* (2014)

In HIV-infected adults, adolescents and children diagnosed with mild or moderate Kaposi sarcoma, immediate ART initiation is recommended. *(Strong recommendation, low-certainty evidence)*

Recommendation for treatment of severe or symptomatic Kaposi’s sarcoma *(83)* (2014)

Severe or symptomatic disease: in HIV-infected adults, adolescents and children diagnosed with severe symptomatic Kaposi sarcoma, immediate ART initiation in combination with systemic chemotherapy is recommended. *(Strong recommendation, low-certainty evidence)*

Background

Despite significantly improved availability of ART, HIV-associated Kaposi’s sarcoma remains among the most common type of cancer among people living with HIV. The African continent alone accounts for more than 70% of the burden of disease. HIV-associated Kaposi’s sarcoma among people living with HIV receiving ART has an estimated incidence of 289 per 100 000 person years *(169)*. Survival following diagnosis is poor, with some estimates being 39–44% dying from Kaposi’s sarcoma–related causes, and the rest from other causes (Box 3) *(170, 171).*

ART remains the first-line treatment for everyone with Kaposi’s sarcoma and can help to treat early-stage Kaposi’s sarcoma to achieve regression of lesions and reduce Kaposi’s sarcoma-related deaths *(83)*; this is also supported by evidence in published literature *(173)*. However, moderate to severe Kaposi’s sarcoma requires additional treatment – ranging from chemotherapy to radiotherapy. The goal is to ensure long-term control of symptoms (Table 9, Box 4).

Box 3. Case definition of Kaposi's sarcoma *(83)* (2014)

Mild or moderate Kaposi's sarcoma may include the following:

- confined to skin and/or lymph nodes;
- no symptomatic visceral disease;
- no significant oral disease (does not interfere with chewing or swallowing);
- no significant oedema affecting function; and
- not functionally disabling or immediately life-threatening.

Severe Kaposi's sarcoma may include the following:

- symptomatic visceral disease (pulmonary[a] or gastrointestinal[b]);
- extensive oral Kaposi's sarcoma lesions that interfere with chewing or swallowing;
- painful or disabling tumour-associated facial, genital or peripheral oedema or ulcerated tumours;
- life-threatening or functionally disabling disease; and
- progressive[c] or persistent Kaposi's sarcoma despite ART.

Note: these case definitions are modified from the original ACTG (172) T0 and T1 definitions and are intended as a general guide for treatment decision-making *(83)*.

Table 9. Tumour–immune system–systemic illness staging system for HIV-related Kaposi's sarcoma and prognosis in adults (2014) *(83)*

	Good prognosis (all the following)	Poor prognosis (any of the following)
Tumour (T)	(T0) Tumour confined to skin and/or lymph nodes and/or minimal oral disease[d]	(T1) Tumour-associated oedema or ulceration; extensive oral Kaposi's sarcoma; gastrointestinal Kaposi's sarcoma; Kaposi's sarcoma in other non-nodal viscera
Immune system (I)	(I0) CD4 cells ≥150 cells/mm^3	(I1) CD4 cell count <150 cells/mm^3
Systemic illness (S)	(S0) No history of opportunistic infections and/or thrush Absence of B symptoms[e] Performance status: Karnofsky score ≥70	(S1) History of opportunistic infections and/or thrush Presence of B symptoms[e] Performance status: Karnofsky score >70 Other HIV-related illness (such as nervous system disease or lymphoma)

a Symptomatic pulmonary Kaposi's sarcoma, suggested by shortness of breath, haemoptysis or moderate or severe cough, that cannot be attributed to other pulmonary conditions.
b Symptomatic gastrointestinal Kaposi's sarcoma, suggested by bleeding from mouth or rectum, which cannot be attributed to other gastrointestinal conditions.
c Progressive disease is defined as: an increase of 25% or more in the size of previously existing lesions and/or the appearance of new lesions or new sites of disease and/or a change in the character of 25% of more of the skin or oral lesions from macular to plaque-like or nodular. The development of new or increasing symptomatic tumour-associated oedema or effusion is also considered to represent disease progression.
d Minimal oral disease defined as non-nodular Kaposi's sarcoma confined to the palate.
e B symptoms: unexplained fever, drenching night sweats, >10% involuntary weight loss or diarrhoea persisting more than two weeks.

Box 4. Staging of Kaposi's sarcoma for children

Children with HIV have a different clinical presentation of disease, thus requiring an alternative approach to staging. Children have been documented to more frequently have lymph node involvement, lymphadenopathies or cytopathies *(174)*. It has been previously documented that the ACTG and modified ACTG staging approach do not correlate well with treatment outcomes *(172, 175, 176)*. Several approaches have been proposed but are similar to the staging included in the 2014 WHO guidelines on treatment of skin and oral HIV-associated conditions in adults and children *(83)*.

- Stage I: <10 Kaposi's sarcoma lesions isolated to the skin without significant associated oedema.
- Stage II: ≥10 Kaposi's sarcoma lesions isolated to the skin, or lesions involving the palate or oral mucosa, subcutaneous nodules, lymph nodes and/or bone marrow (two cytopaenia not otherwise explained).
- Stage III: disseminated Kaposi's sarcoma involving the lymphatics resulting in lymphoedema ("woody" oedema) in the extremities and/or groin.
- Stage IV: systemic Kaposi's sarcoma, defined as pulmonary Kaposi's sarcoma with noted infiltrates or effusions on chest radiography, abdominal involvement with intra-abdominal nodes, hepatomegaly and/or ascites and/or cardiac involvement with cardiomegaly and associated pericardial effusion.

More recent classifications include the Lilongwe paediatric Kaposi's sarcoma staging system *(174, 175, 177)*, where stage 1 = mild or moderate Kaposi's sarcoma limited to cutaneous or oral involvement, stage 2 = primarily lymphadenopathic disease, stage 3 = woody oedema Kaposi's sarcoma and stage 4 = visceral and/or severe or disseminated mucocutaneus disease.

Further validation studies of the various staging systems are required to help to improve prognostication for children with Kaposi's sarcoma.

In 2014, WHO provided recommendations on treatment for advanced Kaposi's sarcoma, noting greatly restricted access to chemotherapeutic agents and concerns relating to ensuring safety, toxicity monitoring and available infrastructure *(83)*. Since 2014, additional evidence is available that supports advances in managing HIV-associated Kaposi's sarcoma.

A systematic review (Web Annex B) summarized the currently available evidence around preferred treatment regimens for Kaposi's sarcoma *(11)*. The review identified five randomized trials; no meta-analysis was possible because of wide variation in reporting in the included studies *(178–181)*.

Since no meta-analysis was possible, for evaluating the evidence comparisons were split and discussed by the Guideline Development Group as paclitaxel and non-paclitaxel-based treatment comparisons. All arms were conducted with individuals receiving ART concurrently.

Rationale for the recommendations

Paclitaxel-based treatment comparisons
Three interventions were evaluated against paclitaxel. These included:

- paclitaxel versus liposomal pegylated doxorubicin;
- paclitaxel versus etoposide; and
- paclitaxel versus the combination of bleomycin and vincristine.

Non-paclitaxel-based treatment comparisons
Two studies or arms had non-paclitaxel evaluations:

- gemcitabine versus the combination of bleomycin and vincristine; and
- pegylated liposomal doxorubicin versus liposomal daunorubicin.

Balance of benefits and harm

When paclitaxel was compared with liposomal pegylated doxorubicin, paclitaxel showed slightly better or similar tumour response, progression-free survival (17.5% versus 12.2%) and two-year survival (56% versus 46%). These overall benefits were considered to be small. Paclitaxel was associated with moderate increase in harm related to the incidence of toxicity *(178, 179)*. The Guideline Development Group concluded that the balance of benefits and harm was likely similar for both treatments.

When paclitaxel was compared with etoposide, paclitaxel was associated with improved progression-free survival (50% versus 20%), mortality (11% versus 26%), and tumour response (34% versus 18%) and fewer adverse events (46% versus 58% of any grade 3 or 4 adverse event). When paclitaxel was compared with bleomycin + vincristine, paclitaxel was associated with improved progression-free survival (64% versus 44%), mortality (10% versus 19%) and tumour response (91% versus 80%) and similar or decreased adverse events (46% versus 48% of any grade 3 or 4 adverse event). For these two comparisons, the Guideline Development Group concluded that the balance of benefits and harm probably favoured paclitaxel. The overall certainty of evidence was low.

Among the non-paclitaxel treatment comparisons, two studies informed the systematic review *(180–182)*. Gemcitabine compared with combination bleomycin + vincristine showed better complete and partial tumour response (86%) compared with those on bleomycin + vincristine (76%) and improved three-year survival, although this was not statistically significant. Bleomycin + vincristine was associated with more events related to peripheral neuropathy (grade 3 or 4); 26% with bleomycin + vincristine versus 14% with gemcitabine. There were similar rates of neutropaenia (grade 3 or 4) and anaemia (grade 1 or 2). The overall certainty of evidence in the GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment was very low. The Guideline Development Group concluded that the balance of benefits and harm would probably favour gemcitabine.

One study compared pegylated liposomal doxorubicin with pegylated liposomal daunorubicin. More people on pegylated liposomal doxorubicin experienced clinical benefit (both by protocol[4] definition (45%) and conservative definition (37%)) versus liposomal daunorubicin. The median time to response was similar for pegylated liposomal doxorubicin and pegylated liposomal daunorubicin (30 days versus 27 days). Liposomal doxorubicin had higher rates of grade 3 or 4 neutropaenia (30%) than liposomal daunorubicin (16%) but reported similar rates of nausea (any grade). The overall certainty of evidence was very low. The Guideline Development Group concluded that the balance of effects does not favour either the intervention or the comparison.

Preferences, acceptability and feasibility

A survey was conducted among people living with HIV (Web Annex C). The respondents rated survival and quality of life as the most important outcomes, followed by rapid response to treatment. Avoiding serious adverse events was also a relatively high priority. Treatment-related toxicity and recurrence were rated as less important. The analysis of the open-ended questions reiterated that financial worries were a major theme, with respondents concerned about the ability to pay hospital bills and afford necessary medications after discharge; how their health conditions financially affected their lifestyle and family was also a recurrent theme.

For the comparison of paclitaxel to liposomal doxorubicin, paclitaxel was associated with modest benefits, but there were concerns around increased adverse events; thus, client preferences may vary when deciding to use paclitaxel as a treatment option. However, paclitaxel would be preferred because of the associated benefits along with similar or decreased adverse events versus either etoposide or bleomycin + vincristine.

Members of the Guideline Development Group noted that because gemcitabine was associated with some potential benefits and not associated with increased harm, decisions to use gemcitabine may not be sensitive to preferences or values regarding potential benefits versus harm. In the comparison involving pegylated liposomal doxorubicin versus pegylated liposomal daunorubicin, pegylated liposomal doxorubicin is associated with potential clinical benefit but also potential harm (increased neutropaenia); therefore, decisions to use pegylated doxorubicin may be sensitive to preference and values regarding potential benefits versus harm.

4 The clinical trial that provides evidence on this comparison used two definitions for treatment response: clinical benefit, which was defined as an improvement from baseline in at least one of five AIDS-related Kaposi's sarcoma symptom categories that lasted for 28 days in the absence of disease progression or severe disease; and defined as an improvement from baseline in at least one AIDS-related Kaposi's sarcoma symptom category that lasted for 28 days with no worsening of other symptom categories and no increase in medical interventions either before or during that period.

The Guideline Development Group concluded that there was probably no important uncertainty or variability when comparing gemcitabine versus bleomycin + vincristine and possibility important uncertainty or variability when comparing pegylated liposomal doxorubicin versus liposomal daunorubicin.

The results from the values and preferences survey highlighted the importance of survival, quality of life and rapid treatment response in managing HIV-associated Kaposi's sarcoma. These priorities suggest a preference for newer, more effective therapies.

The Guideline Development Group also concluded that the non-paclitaxel combination was probably feasible to implement in settings that administer chemotherapy.

Resources and cost–effectiveness

A report *(183)* on the cost of currently available formulations indicates that using pegylated doxorubicin and gemcitabine is associated with large costs. Using paclitaxel or bleomycin + vincristine is associated with moderate costs. The price of daunorubin was found to vary depending on the setting and context. The overall certainty of costs was judged to be moderate *(183)*.

A cost–effectiveness analysis of four chemotherapeutic regimens in Kenya found that paclitaxel offers survival benefit and is highly cost-effective compared with bleomycin vincristine in this setting. Pegylated liposomal doxorubicin provides additional life expectancy benefits but only becomes cost-effective if its cost is significantly reduced *(184)*.

The systematic review did not identify any cost–effectiveness analysis of gemcitabine versus bleomycin + vincristine. One study was identified that compared liposomal doxorubicin versus liposomal daunorubicin and reported that pegylated liposomal doxorubicin cost less (US$ 11 976 per respondent) than liposomal daunorubicin (US$ 26 483 per respondent) (Web Annex C).

Equity

Having additional effective and well-tolerated options for treatment for Kaposi's sarcoma could improve equity if it increases access to treatment. However, if paclitaxel is widely available and implemented, the impact of additional chemotherapeutic options for Kaposi's sarcoma is unclear.

Treatment of Kaposi's sarcoma for children and during pregnancy

Paclitaxel has shown efficacy in HIV-associated Kaposi sarcoma among children and adolescents in a retrospective cohort of 17 people (5–21 years old) in the United Republic of Tanzania with an 82% overall survival rate and 71% complete remission with manageable toxicity *(185)*. There is very limited evidence in published literature on Kaposi's sarcoma among children; a review conducted in 2016 estimated that the incidence is about 67 per 100 000 children living with HIV, about 30 times more frequent than among children generally *(186)*. In Mozambique, a study of 28 children on monthly paclitaxel plus ART achieved long-term remission in 19 cases (68%) *(187)*.

Although pegylated liposomal doxorubicin lacks child-specific clinical trial data, its documented efficacy and tolerability for adults with Kaposi's sarcoma have led to off-label use for children, especially in severe cases.

The WHO Essential Medicines List for Children *(188)* acknowledges pegylated liposomal doxorubicin as "not approved for use in children" and advises caution because of the absence of formal safety and efficacy data on children.

In the context of pregnancy, data are extremely limited, with only limited case reports detailing case management *(189–194)*. The safety of using chemotherapeutics agents in the context of pregnancy would be similar to using these agents for other types of cancer and would have to be considered on a case-by-case basis. Initiation of ART is a priority in this population, along with appropriate monitoring for development of Kaposi's sarcoma immune reconstitution inflammatory syndrome *(83)*. WHO explicitly states that pegylated liposomal doxorubicin is contraindicated, citing potential teratogenicity, and strongly supports pregnancy testing before initiating chemotherapeutic agents, with additional consideration for initiating treatment in the first trimester, which may result in serious fetal adverse effects.

The guidance *(188)* notes: "Avoid use in pregnancy and in women and girls of childbearing potential, unless alternative treatments are ineffective or not tolerated."

Implementation considerations

Chemotherapeutic treatment for HIV-associated Kaposi's sarcoma is only for those with Kaposi's sarcoma diagnosis confirmed by histopathology. Clinical diagnosis of Kaposi's sarcoma, which is based on the macroscopic appearance of the Kaposi's sarcoma lesions, has suboptimal positive predictive value – about 23–42% of diagnoses based on clinical suspicion alone are not Kaposi's sarcoma *(195–197)*.

The Guideline Development Group noted that in special situations in which access to the preferred treatment options is lacking, other available treatments can be considered, noting their limitations and side-effects, such as the combination of bleomycin + vincristine, gemcitabine or etoposide. No specific recommendation was made for these treatment options.

- Importance of diagnosis and screening for Kaposi's sarcoma: correctly identifying Kaposi's sarcoma is a challenge in many low- and middle-income settings and is often misdiagnosed as other diseases. Training health-care workers is critical for ensuring accurate clinical diagnosis. Linking to histopathological infrastructure is also important.

- Timely ART initiation: ART remains central to the treatment approach for Kaposi's sarcoma.

- Importance of access to cancer treatment: countries should take steps to promote and provide access to cancer treatment (Table 10).

- Integrated care models may be considered to distribute limited resources in the most effective manner.

- Capacity building and training: important to support and train health-care workers for identifying and managing Kaposi's sarcoma, identifying and managing toxicity from treatment and approaches to counselling individuals with Kaposi's sarcoma.

- Monitoring and follow-up: since Kaposi's sarcoma is known to recur among people previously treated for Kaposi's sarcoma, regular follow-up and identifying potential adherence challenges in individuals who present to care with Kaposi's sarcoma recurrence and retreatment are important.

- Stigma and psychosocial support: HIV programmes must take steps to support individuals with Kaposi's sarcoma who report stigmatization through counselling and psychosocial support to ensure that these individuals access and complete treatment for Kaposi's sarcoma.

Research gaps

- Effectiveness of targeted therapies: need for clinical trials evaluating targeted therapies and how they affect Kaposi's sarcoma progression and survival rates, also specifically a trial comparing gemcitabine versus paclitaxel and comparative trials on novel immunotherapy treatment approaches.

- Limited data on ART-integrated Kaposi's sarcoma management: insufficient research on the long-term outcomes of combining ART with chemotherapy or immunotherapy.

- Treating children with Kaposi's sarcoma: lack of specific treatment guidelines and clinical data on the safety and efficacy of Kaposi's sarcoma therapies for children.

- Feasibility studies and cost–effectiveness analysis to support country adoption of treatment strategies.

- Understanding the epidemiology, identification and management of Kaposi's sarcoma inflammatory cytokine syndrome.

- Need for understanding patient-level outcomes and quality-of-life measures in the research on treatment for managing Kaposi's sarcoma.

Table 10. Commonly used chemotherapy regimens for HIV-associated Kaposi's sarcoma in adults *(83)*

Regimen	Dose per cycle	Route	Frequency of cycles
Paclitaxel	100 mg/m^2	Intravenous	Every 3–4 weeks
Pegylated liposomal doxorubicin	20 mg/m^2	Intravenous	Every 3 weeks
Etoposide	100–200 mg daily for seven days	Oral	Every 2–3 weeks
Bleomycin (B) + vincristine (V)	B: 15 U/m^2 V: 1.4 mg/m^2 (maximum 2 mg)	Intravenous	Every 3 weeks
Gemcitabine *(181)*	1000 mg/m^2	Intravenous	Every 2 weeks
Liposomal daunorubicin	40 mg/m^2	Intravenous	Every 2 weeks
Doxorubicin (A) + bleomycin (B) + vincristine (V)	A: 15–20 mg/m^2 B: 10–15 mg/m^2 V: 1–1.4mg/m^2; maximum 2 mg)	Intravenous	Every 3–4 weeks

Note: This list is not intended to be comprehensive; alternative drug doses and schedules have been used. Drug doses and schedules may need to be modified for pre-existing organ dysfunction and/or treatment-associated adverse events. The maximum cumulative dose of doxorubicin is 450 mg/m^2 and maximum cumulative dose of bleomycin is 400 U/m^2 of body surface area. The maximum cumulative dose of pegylated liposomal doxorubicin is unknown; cardiac toxicity has been documented at doses above 550 mg/m^2. The known maximum cumulative dose for liposomal daunorubicin is 550 mg/m^2.

Table 11. Major toxicities of chemotherapy drugs used in Kaposi's sarcoma *(83)*

Drug	Common toxicities	Less common but serious
Etoposide	Neutropaenia, thrombocytopaenia, anaemia, alopecia, nausea and vomiting	Leukaemia and myelodysplastic syndromes
Liposomal anthracyclines (doxorubicin, daunorubicin)	Neutropaenia, thrombocytopaenia, anaemia, myelosuppression and drug may turn urine red	Hand-foot syndrome, acute infusion reactions and cardiac toxicity
Paclitaxel	Neutropaenia, thrombocytopaenia, anaemia, peripheral neuropathy, tiredness and alopecia	Serious allergic reactions (anaphylaxis)
Vincristine	Peripheral neuropathy, constipation and ileus	Vesicant skin ulcers if extravasated
Bleomycin	Pulmonary fibrosis (late), fever, chills and myalgias (infusion reactions)	Skin changes, including distal digital necrosis
Gemcitabine	Leukopaenia, thrombocytopaenia, anaemia, grade 3 or 4 neutropaenia, febrile neutropaenia, somnolence, dyspnoea, liver enzyme elevation, flu-like symptoms, nausea and vomiting	Thrombocytosis, thrombotic microangiopathy, anaphylactoid reaction, posterior reversible encephalopathy, myocardial infarction, heart failure, arrythmia and hypotension

Other coinfections and comorbidities

Individuals with advanced HIV disease have an elevated risk of developing numerous opportunistic infections, and timely identification is critical. WHO recently launched the fungal priority pathogens list, which also includes fungal species that primarily affect people living with HIV *(111)*. Of the 19 fungal pathogens within the WHO fungal priority pathogens list, four opportunistic pathogens in particular cause invasive diseases among people living with HIV: *Cryptococcus neoformans*, *Histoplasma* spp., *Pneumocystis jirovecii* and *Talaromyces marneffei*.

Cryptococcosis and histoplasmosis have been discussed previously in this publication *(111)*.

Pneumocystis jirovecii

Pneumocystis pneumonia is a leading cause of mortality among hospitalized adults and children living with HIV. *Pneumocystis jirovecii* is transmitted from person to person through the air. The main ways to prevent and treat this infection are co-trimoxazole and rapid early initiation of ART.

Diagnosis has traditionally relied upon clinical symptoms, radiographic findings and microscopy because *Pneumocystis jirovecii* cannot be cultured. Non-culture-based diagnostics on sputum or bronchoalveolar lavage, such as polymerase chain reaction, have entered clinical use, but resource-limited settings often have inadequate infrastructure for these assays. A disease prevalence of 19% has been reported among symptomatic adults living with HIV in Africa *(198)*. It is also important to consider *Pneumocystis* as part of a differential diagnosis while evaluating other respiratory conditions such as TB and bacterial pneumonia.

The use of co-trimoxazole for the prevention and treatment of *Pneumocystis* infections as well as a range of bacterial infections is an important part of the standard package of care for people living with HIV *(8)*. WHO developed recommendations for using co-trimoxazole as prophylaxis, based on moderate-certainty evidence that its use reduces the mortality of people living with HIV, with a CD4 count <350 cells/mm^3 or with a stage 3 or 4 AIDS-defining illness *(8)*.

Box 5 summarizes the current guidance for using co-trimoxazole for people living with HIV and those who are severely immunocompromised *(199)*.

Box 5. WHO recommendations for co-trimoxazole prophylaxis (2014)

Co-trimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with CD4 cell count ≤350 cells/mm^3. *(Strong recommendation, moderate-certainty evidence)*

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage. *(Conditional recommendation, moderate-certainty evidence)*

Co-trimoxazole prophylaxis may be discontinued for adults (including pregnant women) with HIV who are clinically stable on ART, with evidence of immune recovery and viral suppression. *(Conditional recommendation, low-certainty evidence)*

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage. *(Conditional recommendation, moderate-certainty evidence)*

Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, regardless of clinical and immune conditions. Priority should be given to all children younger than five years old regardless of CD4 cell count or clinical stage and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 cell count ≤350 cells/mm^3. *(Strong recommendation, high-certainty evidence)*

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood whether or not ART is being taken. *(Conditional recommendation, moderate-certainty evidence)*

In settings of low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children five years of age and older who are clinically stable and/or virally suppressed on ART for at least six months and CD4 cell count >350 cells/mm^3. *(Strong recommendation, very-low-certainty evidence)*

Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from four to six weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding. *(Strong recommendation, very-low-certainty evidence)*

Routine co-trimoxazole prophylaxis should be given to all people living with HIV with TB disease regardless of CD4 cell count. *(Strong recommendation, high-certainty evidence)*

Talaromycosis

Talaromycosis is an invasive fungal infection that has been increasingly reported in South-East Asia among individuals with advanced HIV disease. Talaromycosis is understood to be transmitted by inhaling the causative organism, *Talaromycosis marneffei (200)*. The disease is associated with a high mortality rate, with up to one third of individuals diagnosed with talaromycosis dying *(201–203)*. Despite the association with higher mortality, relatively little is known about its prevalence in the general population. Countries such as China, Thailand and Viet Nam report talaromycosis as a leading cause of HIV-related deaths. It also disproportionately affects poorer or rural areas of affected countries. It is often difficult to identify, regularly mimicking other infections *(202, 203)*.

Diagnosis is usually established with fungal culture, but this approach is often subject to delays and consequently late initiation of appropriate treatment. Polymerase chain reaction–based assays have high reported specificity but are not well suited for screening approaches because of lower sensitivity (204). Several promising antigen-based tests are undergoing clinical validation, which can in the future enable point-of-care screening for early disease and support early treatment to prevent fulminant disease (205–207).

People with advanced HIV disease are at risk of illness and death from a wide range of infectious diseases. *Candida* spp., *Paracoccidioides* spp., *Coccidioides* spp. and *Aspergillus fumigatus* most commonly cause severe disease for other populations, but they are also important opportunistic pathogens for people living with HIV *(111)*. Severe disease is common among people living with HIV, caused by most of the pathogens on the fungal priority pathogens list.

Each country should further assess any additional coinfections that are endemic and adapt the package of care to ensure that critical diagnostics, treatment and prevention tools are made available for the diseases afflicting people with advanced HIV disease. WHO will continue to monitor emerging therapeutics and diagnostics to support the response to managing opportunistic infections.

Mpox

In 2025, WHO published updated recommendations (208) for the management of mpox, including people living with HIV. Studies conducted among people living with HIV and/or advanced HIV disease have found significantly more severe disease compared with the general population at lower CD4 counts *(209)*. Mortality is higher among individuals with advanced HIV disease (CD4 count <200 cells/mm^3) *(209)*. The risk of hospitalization from mpox is 1.79 (95% CI 1.07–3.00) times higher among people living with HIV and 2.45 (95% CI 1.19–5.02) times higher among those with a CD4 cell count <350 cells/mm^3 *(208)*. The risk of all-cause mortality is 10-fold for people living with HIV who had mpox *(208)*.

Rapid initiation of ART *(8)* remains an important programmatic component in the management of mpox. An expert consensus meeting hosted by WHO concluded that the general mortality reduction benefits of rapid ART initiation extend to patients with mpox, accepting the risk of paradoxical immune reconstitution inflammatory syndrome, and reiterating that delaying ART initiation may possibly be harmful *(208)*.

Owing to the nature of disease outbreaks, WHO provides living recommendations that may be updated as new evidence is available for this topic.

WHO recommendations for managing mpox (May 2025) *(208)*

WHO recommends rapid initiation of ART in people with mpox and HIV who are ART naive or have had a prolonged interruption of ART *(Strong recommendation, moderate-certainty evidence)*

- Early HIV testing should be conducted when patients present with suspected or confirmed mpox infection.
- The patient should be referred to appropriate services for ART initiation as soon as possible, aiming to provide therapy within seven days of HIV diagnosis, including the offer of same-day start.
- In people who are already on ART and with undetectable viral load, ART regimen should be continued without interruption or change. The viral load test result should be less than one year old; if not, a new viral load test should be conducted.

Nontuberculous mycobacterial infections

Nontuberculous mycobacterial infections, most commonly disseminated mycobacterium avium complex infections, present a significant challenge for people living with HIV who have profound immunosuppression (CD4 cell count <50 cells/mm^3) *(210).*

With the increased availability of highly effective ART, the incidence of mycobacterium avium complex infections has declined over time but is frequently reported in autopsy studies of individuals with HIV who were hospitalized with severe illness *(210)*.

The main challenge countries face is timely identification of mycobacterium avium complex infections. TB and mycobacterium avium complex infections may often have similar presentations and result in false-positive acid-fast sputum tests. which may result in an incorrect diagnosis of TB.

Microbiological culture remains the preferred method (210) to identify mycobacterium avium complex infections but is challenging to implement in most resource-limited settings. Other approaches include radiological imaging. A combination of these approaches helps to establish the severity of disease *(211–213)*.

Treatment of mycobacterium avium complex infections includes antibiotics such as azithromycin, ethambutol, rifabutin and rifampicin. The Southern African HIV Clinicians Society provides detailed guidance on managing people living with HIV who have nontuberculous mycobacterial infections *(211)*.

WHO will continue to monitor available evidence on nontuberculous mycobacterial infections and provide updates when possible.

Palliative care

Individuals with advanced HIV disease present a range of symptoms from opportunistic infections or comorbidities or may have no symptoms at all. Implementing a comprehensive palliative care framework *(214)* will help to reduce health-related suffering and support individuals' return to health and restoration of immune status. Health conditions such as TB *(215)* and cryptococcal meningitis and cervical cancer *(216, 217)* among women living with HIV contribute significant morbidity during illness and during the recovery phase, but little attention is paid to this public health issue *(218)*. Sensitizing health-care workers through validated courses on palliative care helps to support early identification of needs and thus contributes to improving the quality of care *(219)*.

Monitoring advanced HIV disease

Importance of monitoring advanced HIV disease in programmes

Monitoring advanced HIV disease is essential for reducing mortality among people living with HIV. Effective monitoring ensures that people with advanced HIV disease are rapidly identified and linked to appropriate services, which is important for improving health outcomes and reducing the risk of life-threatening complications. Obtaining different perspectives on the epidemic and the response is key, for example, to assess gender equity and age-specific differences in coverage, to ensure quality of services for specific subgroups, to review current or long-term performance and to compare population-based and programme-based measures of performance.

Strengthened national HIV surveillance systems involve standardized reporting of individuals with advanced HIV disease. This includes tracking whether individuals had a CD4 count test when recommended and tracking the provision of the recommended package of care for advanced HIV disease. The implementation of recommended screening tools and treatment protocols needs to be monitored to ensure comprehensive care. Mortality data can come from clinics, national death registries and cross-referencing other sources, including verbal autopsy methods. Given the challenges and costs of these measurements, routinely collecting programme data is a valuable way to track how the programme affects the epidemic. Additionally, monitoring helps to direct resources to gaps in care, ensuring that populations and areas with the greatest need receive the necessary support.

With the rapid expansion of digital health information systems, existing HIV information systems can be expanded and linked to routinely capture and track individual data over time. This improves data quality, simplifies reporting and provides actionable insights at the subnational levels. Electronic medical records can support person-centred care and patient monitoring in addition to (and, typically, as the source of) aggregate reporting of service indicator data. National health information systems enable health-care providers to track patient data in real time, facilitating timely and accurate clinical decision support. By integrating clinical decision support tools, health-care providers can make informed decisions about patient care, ensuring that individuals with advanced HIV disease receive the necessary interventions promptly.

Key principles for monitoring advanced HIV disease

Focusing on identifying advanced HIV disease at any stage of interaction with the health-care system is fundamental to effective monitoring. This includes identifying advanced HIV disease at diagnosis, re-engagement or reinitiation of care and if a person experiences treatment failure.

Regularly monitoring CD4 cell counts during follow-up visits helps track disease progression and the effectiveness of treatment. Additionally, monitoring for high viral load, adherence challenges and opportunistic infections provides valuable insights into the patient's health status and the need for tailored care.

A comprehensive list of priority data elements for advanced HIV disease monitoring is essential for tracking longitudinal information over time. This includes data on CD4 cell counts, viral load, adherence and the presence of opportunistic infections. By collecting and analysing these data, health-care providers can identify trends and patterns, enabling them to make informed decisions about patient care and resource allocation.

Minimum dataset for advanced HIV disease monitoring

A minimum dataset containing data elements for monitoring advanced HIV disease is intended to capture the key events in an individual's interaction with the health system related to advanced HIV disease, which can then be used to develop a cascade of advanced HIV disease indicators. The minimum dataset was developed as part of the WHO consolidated guidelines on person-centred HIV strategic information *(220)*. The main purpose is to standardize patient information with a simplified and harmonized set of essential data elements relevant to core patient management and programme monitoring. Standardization also enables programme personnel to compare data across populations, time, geographical areas and settings and provides data for clinical teams to monitor the quality of care longitudinally and along the cascade of HIV services.

Table 12 presents a priority list of data elements for monitoring advanced HIV disease for inclusion in national surveillance systems. These data can be used for understanding who is developing advanced HIV disease and where to better direct resources. Advanced HIV disease indicators based on these data elements will be shared through strategic information guidance in due course.

Key client categories in people with advanced HIV disease:

- people newly diagnosed with HIV;
- people re-diagnosed with HIV (those who have tested HIV-positive in the past but have not received ART);
- people reinitiating ART after a period of treatment interruption; and
- people who experience HIV treatment failure.

Table 12. Minimum dataset of critical data elements for inclusion in national health information systems for monitoring advanced HIV disease

Area	Data elements
Diagnosis of advanced HIV disease	HIV test date
	HIV test result
	Baseline CD4 test date
	Baseline CD4 test result
	Clinical stage at start of ART
Advanced HIV disease package of care	ART start date
	Co-trimoxazole prophylaxis start date
	TB screening date
	TB screening result
	TB diagnostic test category
	TB diagnostic test date
	Date of TB diagnosis
	TB treatment start date
	TB treatment completion date
	Eligible for TB preventive treatment
	TB preventive treatment start date
	TB preventive treatment status
	Cryptococcal disease diagnostic test date
	Cryptococcal disease diagnostic test result
	Cryptococcal disease diagnostic test category
	Date of start of fluconazole prophylaxis
	Date started cryptococcal disease treatment induction regimen

Table 13. Summary table of important drug–drug interactions in treatments recommended by WHO for people living with HIV

	Protease inhibitors			Non-nucleoside reverse-transcriptase inhibitors and integrase strand-transfer inhibitors				Nucleoside reverse-transcriptase inhibitors		
	1	2	3	4	5	6	7	8	9	10
Anti-infective drugs										
Amphotericin B[a]	↔	↔	↔	↔ ♥	↔	↔	↔	↔	↔ a	↔ b
Fluconazole	↔ c d	↔	↔ c d	↔ ♥	⇑ 100%	⇑ d	↔	⇑	⇑	⇑ 74% e
Itraconazole	↑ ⇑ d f	↑ ⇑ f	↑ ⇑ d f	↓ 39% ♥	↓ 61%	⇑ d	↔	⇑	⇑	↔
Rifampicin	⇓ 72% g	⇓ 57%	⇓ 75% h	⇓ 26% i	⇓ 58%	⇓	⇓ 54% j	⇓ k	⇓ 12%	⇓ 47%
Rifapentine	⇓	⇓	⇓	⇓	⇓	⇓	⇓ l	⇓ k	↔	↔
Flucytosine	↔	↔	↔	↔	↔	↔	↔	⇓	↔	↔ b
Cytotoxic drugs										
Bleomycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Daunorubicin	↔ m	↔	↔ m	↔ m ♥	↔	↔ m	↔	↔	↔	↔ n
Doxorubicin[a]	↔ m	↔	↔ m	↔ m ♥	↔	↔ m	↔	↔	↔	↔ b
Etoposide	↑↓ o	↑↓ o	↑↓ o	↓	↓	↔	↔	↔	↔	↔ n
Gemcitabine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ n
Paclitaxel	↑	↑	↑	↑	↔	⇓	⇓	↔	↔	↔ n
Vinblastine	↑	↑	↑	↓	↓	⇓	↔	↔	↔	↔ b
Vincristine	↑	↑	↑	↓	↓	↔	↔	↔	↔	↔ b
Vinorelbine	↑	↑	↑	↓	↓	↔	↔	↔	↔	↔

For additional drug–drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, see http://www.hiv-druginteractions.org (University of Liverpool, United Kingdom).

Drugs legend

1 Atazanavir + ritonavir
2 Darunavir + ritonavir
3 Lopinavir + ritonavir
4 Efavirenz
5 Nevirapine
6 Cabotegravir + rilpivirine
7 Dolutegravir
8 Tenofovir alafenamide
9 Tenofovir disoproxil fumarate
10 Zidovudine

Colour legend

No clinically significant interaction expected

These drugs should not be co administered

Potential clinically significant interaction likely to require additional monitoring, alteration of drug dosage or timing of administration

Potential interaction likely to be of weak intensity. Additional action or monitoring or dosage adjustment is unlikely to be required

Legend

↔ No significant effect
↑ Potential increased exposure of the co-administered drug or active metabolite
↓ Potential decreased exposure of the co-administered drug or active metabolite
⇑ Potential increased exposure to antiretroviral drug
⇓ Potential decreased exposure to antiretroviral drug

a Interactions also apply to liposomal or pegylated liposomal formulations.

Numbers refer to effect on the area under the curve as observed in drug–drug interaction studies.Cabotegravir + rilpivirine: pharmacokinetic interactions shown are mostly with rilpirivine; QT interactions shown are with rilpirivine. Efavirenz: pharmacokinetic interaction data from studies performed with efavirenz 600 mg once daily.

Comments

a Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent. If co-administration is unavoidable, monitor renal function closely.

b Potential increased risk of zidovudine adverse reactions.

c Electrocardiographic monitoring is recommended.

d Caution as both drugs can induce QT interval prolongation.

e Routine zidovudine dose modification not required but monitor for potential zidovudine toxicity.

f The daily dose of itraconazole should not exceed 200 mg with boosted antiretroviral drugs.

g The pharmacokinetic interaction can be overcome by doubling the atazanavir + ritonavir dose (300/100 mg twice daily).

h If no other option, use ritonavir 400 mg twice daily or double dose lopinavir + ritonavir.

i Efavirenz 600 mg once daily should be used in the presence of rifampicin; in the absence of rifampicin, efavirenz can be used at 400 mg or 600 mg once daily.

j A dose adjustment of dolutegravir to 50 mg twice daily is recommended for treatment-naive or integrase strand-transfer inhibitor–naive people. This dose adjustment should be maintained for two weeks after stopping rifampicin as the inducing effect persists after discontinuation of a strong inducer. Alternatives to rifampicin should be used where possible for integrase strand-transfer inhibitor–experienced people with certain integrase strand-transfer inhibitor–associated resistance substitutions or clinically suspected integrase strand-transfer inhibitor resistance.

k Rifamycins decrease tenofovir alafenamide exposure when given 25 mg. However, the intracellular tenofovir diphosphate (active entity) concentrations are likely to be higher than those observed with tenofovir disoproxil fumarate even without rifampicin, suggesting that using tenofovir alafenamide 25 mg once daily may be acceptable.

l Based on dolutegravir interactions studies with rifabutin and rifampicin, consider administering dolutegravir at 50 mg twice daily in the presence of rifapentine. This dose adjustment should be maintained for two weeks after stopping rifapentine since the inducing effect persists after discontinuation of a strong inducer.

m Daunorubicin and doxorubicin may induce cardiac toxicity including arrhythmias and/or non-specific electrocardiographic abnormalities; caution is warranted in presence of other drugs with potential effects on PR and QT intervals.

n Potential increased risk of additive myelosuppression and haematological toxicity. If concomitant treatment is necessary, extra care should be taken in monitoring haematological parameters.

o It is difficult to predict: etoposide exposure could potentially increase (inhibition of CYP3A4) or decrease (induction of UGT1A1). Close monitoring of etoposide-induced toxicity and efficacy is recommended. Reduce dose if clinically necessary or consider selecting an alternate non-cytochrome 450–inhibiting ART regimen.

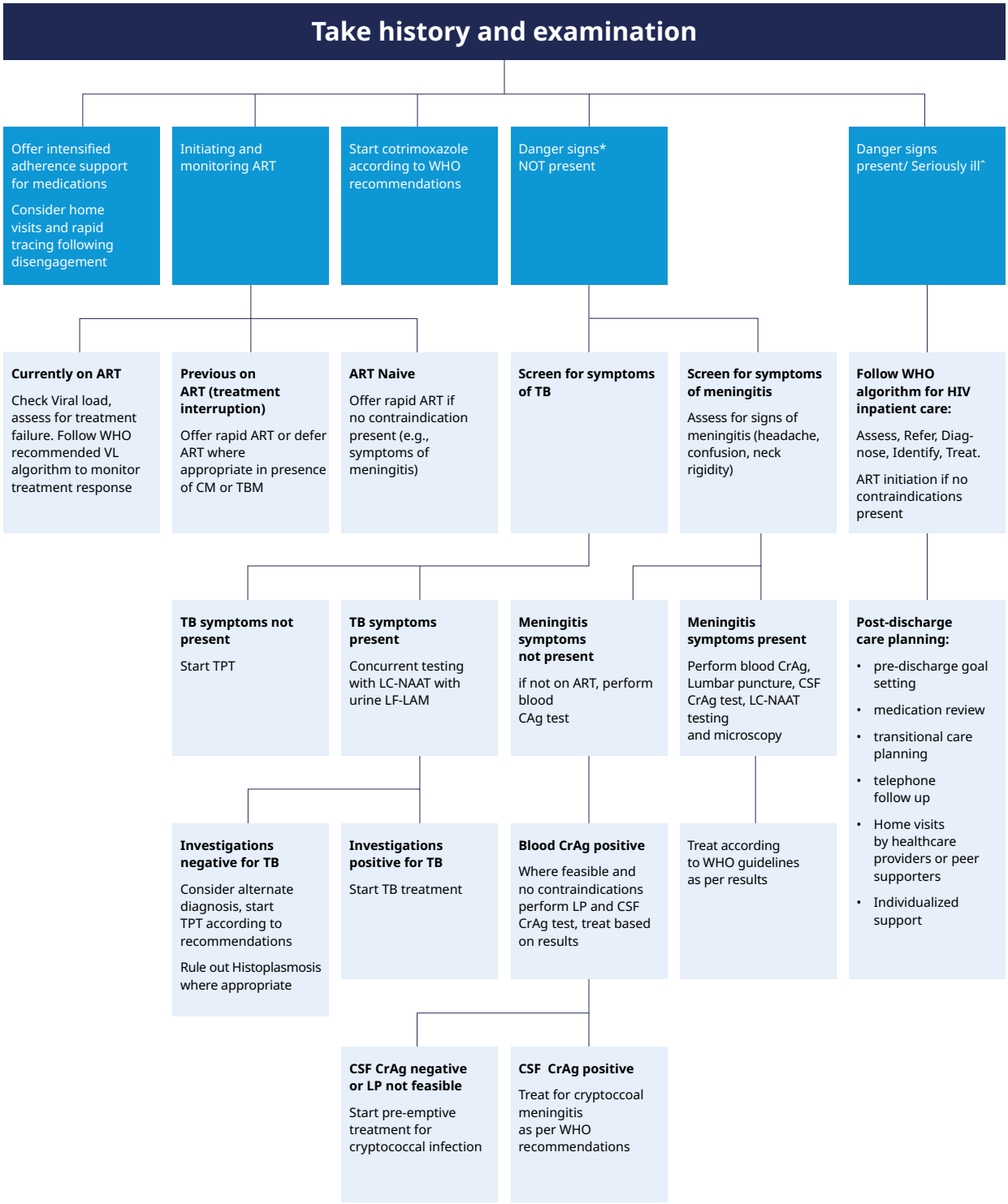
♥ Efavirenz prolonged the QT interval above the regulatory threshold of concern in homozygous carriers of the CYP2B6*6/*6 allele (516T variant). Co-administration with a drug with a known risk of torsades de pointe is contraindicated in the efavirenz European label.

Table 14. WHO definitions of clinical, immune and viral failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after six months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical conditions except for TB) after six months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections)
Immune failure (adults)	**Adults and adolescents** CD4 count at 250 cells/mm^3 following clinical failure or persistent CD4 cell count below 100 cells/mm^3[a]	Without concomitant or recent infection to cause a transient decline in the CD4 cell count
Immune failure (children)	**Children** *Younger than five years* Persistent CD4 cell count below 200 cells/mm^3 *Older than five years* Persistent CD4 cell count below 100 cells/mm^3	Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with viral failure. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immune failure
Viral failure	Viral load above 1000 copies/mL based on two consecutive viral load measurements three months apart, with adherence support following the first viral load test. ART switch after first viral load >1000 copies/mL for those receiving non-nucleoside reverse-transcriptase inhibitor–based regimens	An individual must be taking ART for six months before it can be determined that a regimen has failed Individuals with viral load >50 and <1000 copies, maintain ART regimen, enhance adherence counselling and repeat viral load testing after three months Consider switch after second viral load >50 and <1000 copies/mL if people are receiving non-nucleoside reverse-transcriptase inhibitor–based ART

a Previous guidelines defined immune failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation.

Advanced HIV disease algorithm



*A seriously ill adult is defined as having any of the following danger signs: respiratory rate ≥30 breaths per minute; heart rate ≥120 beats per minute; or unable to walk unaided. Other clinical condition, such as temperature ≥39°C combined with other signs such as headache, can also be considered based on local epidemiology and clinical judgement. A seriously ill child is defined as having any of the following danger signs: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; repeated vomiting. Other clinical conditions such as temperature ≥39 and age-defined tachycardia and /or tachypnea can be considered based on clinical judgement.

Abbreviations: ART: antiretroviral therapy; CM: cryptococcal meningitis; TB: tuberculosis; TBM: TB meningitis; LC-NAAT: Low-complexity nucleic acid amplification test; LF-LAM: lateral flow- lipoarabinomannan assay; CrAg: cryptococcal antigen test; TPT: TB preventive therapy; CSF: cerebrospinal fluid; LP: lumbar puncture; WHO: World health organisation

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