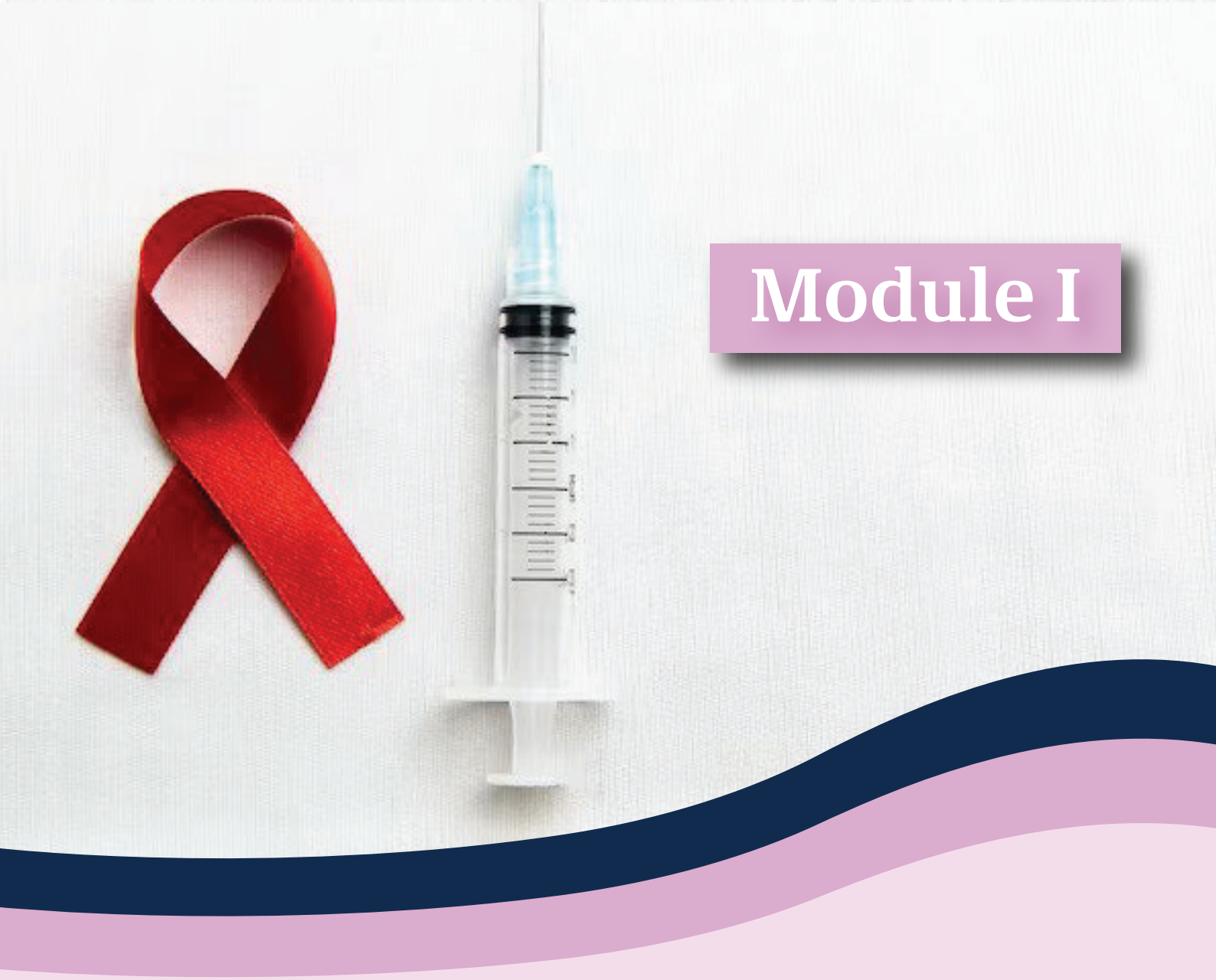
# Module on Advances in HIV management



## Module I

# Management of the HIV-positive person with advanced disease.

# Content

# Introduction

In 2015, WHO recommended that all people living with HIV start ART irrespective of clinical or immune status. Most national guidelines have adopted this recommendation. However, despite this progress, up to half the people living with HIV continue to present to care with advanced HIV disease.

WHO defines advanced HIV disease for adults and adolescents (and children five years and older) as having a CD4 cell count of less than 200 cells/mm or WHO clinical stage 3 or 4 disease. All children younger than five years living with HIV are considered to have advanced HIV disease.

Children older than two years who have been receiving ART for more than one year and are clinically stable should not be considered to have advanced disease and should be eligible for multi month ART dispensing.

Advanced HIV disease includes people presenting to care for the first time following an HIV diagnosis and people who have treatment failure and consequent decline in CD4 cell count. Individuals who had previously initiated ART and are re-engaging with care after a period of ART interruption should be assessed for advanced HIV disease and should be offered the advanced HIV disease package as appropriate.

People presenting with advanced HIV disease are at high risk of death, even after starting ART, with the risk increasing with decreasing CD4 cell count, especially with CD4 cell count <100cells/mm. Advanced HIV disease is also associated with increased health-care costs, increased risk of opportunistic infections, immune reconstitution inflammatory syndrome, incomplete immune reconstitution, higher viral reservoirs, higher inflammation, increased risk of AIDS-related and non-AIDS-related comorbidities, use of more health-care services and more frequent monitoring needs.

# Causes of Morbidity and Mortality Among Adults with Advanced Hiv Disease

Leading causes of mortality among adults with advanced HIV disease globally include TB, severe bacterial infections, cryptococcal disease, histoplasmosis, toxoplasmosis and Pneumocystis jirovecii pneumonia. Other invasive fungal infections have been recently estimated as contributing significantly to the number of people dying from AIDS-related causes.

## TB

TB is the leading cause of morbidity and mortality among people living with HIV. In 2019, an estimated 1.2 million (range, 1.1 million–1.3 million) HIV-negative people died from TB (a reduction from 1.7 million in 2000), and an additional 208 000 HIV-positive people died from TB (range, 177 000–242 000) (a reduction from over 678 000 in 2000). TB also remains a leading cause of HIV-associated hospitalization among adults and children living with HIV worldwide.

## Severe bacterial infections

People with advanced HIV disease frequently have severe bacterial infections, including bloodstream, respiratory, central nervous system and gastrointestinal infections. The burden of mortality and morbidity attributable to severe bacterial infections is poorly characterized, largely because appropriate diagnostic testing facilities are lacking. Severe bacterial infections are estimated to cause more than one third of the hospitalizations among adults and children living with HIV worldwide.

## Invasive fungal infections

## Cryptococcal disease

By far the most common presentation of Cryptococcal disease is cryptococcal meningitis, which accounts for an estimated 15% of all people dying from AIDS-related causes globally, three quarters of which are in sub-Saharan Africa. Less common presentations of cryptococcal disease include pulmonary disease, skin, lymph node and bone involvement. Cryptococcal disease is less common among young children than among adults.

## Histoplasmosis

Histoplasmosis is a fungal disease mostly reported in the WHO Region of the Americas, but it has also been reported in countries in Asia and Africa. Histoplasmosis is highly endemic in some regions of Central and South America and is a major opportunistic infection among people living with HIV. Thousands of people living with HIV with advanced disease are estimated to die from histoplasmosis each year.

A major concern about histoplasmosis is misdiagnosing it as TB and the high frequency of co-occurrence (about 20%) because of lack of rapid and accurate diagnosis.

## Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii pneumonia is a leading cause of mortality among hospitalized adults (13%) and children (29%) living with HIV. However, the global burden of morbidity and mortality attributable to P. jirovecii pneumonia is poorly characterized because appropriate diagnostic testing facilities are lacking in most settings.

## Toxoplasmosis

Cerebral toxoplasmosis is the most frequent cause of expansive brain lesions among adults living with HIV not receiving co-trimoxazole. Toxoplasmosis is a common protozoan infection among people with HIV, with the prevalence of coinfection especially high in sub-Saharan Africa (45%), Latin America and the Caribbean (49%) and North Africa and the Middle East (61%).People with latent toxoplasmosis infection are at risk of developing cerebral toxoplasmosis when their CD4 count falls below 200 cells/mm.

## Other important fungal infections

Fungal infections other than those caused by Cryptococcus species and P. jirovecii, notably histoplasmosis and talaromycosis, are associated with advanced HIV disease in specific geographical areas.

Talaromycosis (formerly known as penicilliosis) is a systemic mycosis that is endemic to many countries in South-East Asia, including parts of China and India, and is a leading cause of HIV-associated mortality, especially among individuals with a CD4 cell count <100 cells/mm. Untreated disseminated infection is usually fatal, and even when appropriate therapy is provided mortality rates among hospitalized people are up to 30%.

Emergomycosis and other dimorphic fungal pathogens are emerging around the world. The emergence of novel species, such as Emergomyces africanus, is adding challenges to the clinical care of immunocompromised people, including those with advanced HIV disease. Lack of knowledge about diagnosis, treatment and care are key aspects for further work.

## Cytomegalovirus disease

Cytomegalovirus infection is a systemic viral infection that usually manifests as cytomegalovirusretinitis among severely immunocompromised people; the reported prevalence of cytomegalovirus retinitis is highest in Asia and appears to be low in Africa.

## Wasting syndrome and malnutrition

Malnutrition and wasting are an important cause of hospitalization, responsible for 3% of hospitalizations overall, rising to 12% in the WHO African Region. Nutritional assessment (anthropometry and clinical and dietary assessment), counselling and support should be an integral component of HIV care and conducted at enrolment in care and monitored across the care continuum. Children with advanced HIV disease commonly present with malnutrition.

## Assessing advanced HIV disease

CD4 cell count is the best indicator of disease stage and immediate risk of death and thus should be used to identify people with advanced HIV disease. If access to CD4 count is limited or unavailable, WHO staging should be used. For children from five years of age, adolescents and adults, advanced HIV disease is defined as the presence of a CD4 cell count <200 cells/mm or WHO clinical stage 3 or 4. All children younger than five years (who are not already receiving ART and clinically stable) are considered to have advanced HIV disease.

Everyone entering or re-entering care should receive a CD4 test at treatment baseline and as clinically indicated for people who are severely ill, clinically unstable or have advanced HIV disease. A person receiving ART is considered clinically stable based on the following criteria: receiving ART for at least six months, no current illnesses, good understanding of life long adherence and evidence of treatment success within the past six months (such as all viral load measurements <1000 copies/mL).

CD4 cell count testing can be performed using a variety of technologies, including laboratory-based CD4 analysers, point-of-care technologies, and device-free semi-quantitative rapid tests. Many countries have one or more of these options already available from previous investments made when CD4 cell count was used to set priorities among people living with HIV initiating ART. It is suggested that countries map their CD4 network and identify the best technologies and potential mix useful for their context, considering testing volume needs, health-care facility distribution and key characteristics of each assay, such as time to obtain results, throughput and costs. Although same-day point-of-care CD4 cell count testing supported more rapid ART initiation before the "treat all" policy was adopted, the clinical benefits of using same-day point-of-care CD4 cell count testing to more rapidly and effectively identify people living with advanced HIV disease has not yet been studied. However, given the high rates of morbidity and mortality observed among people living with advanced HIV disease, more rapidly identifying people with advanced HIV disease and providing the advanced HIV disease package of care are likely to improve outcomes. To support rapid and, ideally, same-day identification, several technologies are available, both with and without devices. As with any diagnostic assay, careful consideration should be given to human resource requirements, quality assurance and service and maintenance (if device-based). Lack of same-day availability of CD4 count results should not be a barrier to initiating ART on the same day.

In settings with limited or no access to laboratory-based CD4 cell count and available point-of-care CD4, it may be considered acceptable for use in the context of the advanced HIV disease package, noting the limitation that a point-of-care test is unable to differentiate between an individual who has a CD4 cell count of less than 100 cells/mm and a cell count between 100 and 200 cells/mm.

# Providing a Package of Care

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.

## Recommendation (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).*
Source: *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy.*

Rationale for this recommendation

The rationale for this recommendation is based on two randomized controlled trials: REMSTART and REALITY.

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 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 CD4counts <100 cells/mm in Kenya, Malawi, Uganda and Zimbabwe. All underwent screening for active TB at enrolment and then were 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.

The enhanced prophylaxis package at the time of ART initiation reduced mortality by 27% (from12.2% to 8.9%) over 24 weeks. Mortality from Cryptococcus species declined considerably, from1.5% 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.

## Implementation considerations

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. To support treatment adherence, shorter regimens for TB preventive treatment are recommended. Identifying suitable screening tools for use is also an important research gap.

Table 1: summarizes the specific components of the package of interventions that should be offered to people presenting with advanced HIV disease. For 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 lipo arabinomannan assay (LF-LAM).

## Clinical considerations

The role of presumptive treatment in managing cryptococcal disease and histoplasmosis as well as preventive therapy for TB, P. jirovecii pneumonia and bacterial infections should be considered in settings in which access to diagnostic tests is limited and people present with typical or possible signs and symptoms (especially when accompanied by clinical signs indicating severe illness). 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 conditions, such as body temperature ≥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. 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.

| | Intervention | CD4 cell count | Adults | Adolescents | Children <10 years |
|---|---|---|---|---|---|
| **Screening and diagnosis** | Screening tools for TB disease for adults and adolescents: WHO-recommended four-symptom screen, chest X-ray, C-reactive protein, WHO-recommended molecular rapid diagnostic test for TB, alone or in combination<br>Screening tools for TB disease among children: symptom screening for children living with HIV | Any | Yes | Yes | Yes<br>(symptom screen only) |
| | WHO-recommended molecular rapid diagnostics as the first test for pulmonary TB diagnosis among those who screen positive for TB and investigations for extrapulmonary TB as applicable; chest X-ray may also be used to support investigations | Any | Yes | Yes | Yes |
| | LF-LAM to assist TB diagnosis among people with symptoms and signs of TB | ≤200 cells/mm$^3$ (inpatient)<br>≤100 cells/mm$^3$ (outpatient)<br>Or any CD4 count with symptoms or if seriously ill | Yes | Yes | Yes |
| | Cryptococcal antigen screening | Recommended for <100 cells/mm$^3$ and considered for 200 cells/mm$^3$ | Yes | Yes | No |
| **Prophylaxis and pre-emptive treatment** | Co-trimoxazole prophylaxis | <350 cells/mm$^3$ or clinical stage 3 or 4<br>Any CD4 count in settings with high prevalence of malaria or severe bacterial infections | Yes | Yes | Yes<br>For criteria, see Chapter 6 |
| | TB preventive treatment[a] | Any | Yes | Yes | Yes |
| | Fluconazole pre-emptive therapy for cryptococcal antigen–positive people without evidence of meningitis | <100 cells/mm$^3$ | Yes | Yes | Not applicable (screening not advised) |
| ART initiation | Rapid ART initiation[b] | Any | Yes | Yes | Yes |
| | Defer initiation if clinical symptoms suggest meningitis (TB or cryptococcal) | Any | Yes | Yes | Yes |
| **Adapted adherence support** | Tailored counselling to ensure optimal adherence to the advanced HIV disease package, including home visits if feasible | <200 cells/mm$^3$ | Yes | Yes | Yes |

a TB preventive treatment should be provided in accordance with current WHO guidance (27).

b People receiving a positive WHO four-symptom screen should initiate ART while being evaluated for TB if clinical signs and symptoms of meningitis are absent.

# Overview of clinical management of cryptococcal disease

Cryptococcal disease is one of the most important opportunistic infections among people living with advanced HIV disease and is a major contributor to mortality. Cryptococcusneoformans, the causative agent of cryptococcal disease, is present in the environment worldwide. Exposure occurs through inhalation.

In 2018, WHO published Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children.

Early diagnosis and treatment of cryptococcal meningitis is key to reducing mortality from cryptococcal disease. Health-care professionals should have a low threshold for suspecting cryptococcal meningitis among people with advanced HIV disease. Countries should give priority to reliable access to rapid diagnostic cryptococcal antigen assays, preferably lateral flow assays, for use in CSF, serum, plasma or whole blood.

Of importance, immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and ART initiation should be deferred 4–6 weeks from the initiation of antifungal treatment.

Box 2 summarizes the recommendations, which are all based on evidence reviewed by the Guideline Development Group.

## Box 5.1Summary of recommendations (2018)

## Diagnosis of 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).*

The following diagnostic approaches are recommended, according to the context.
Settings with ready access to and no contraindication for lumbar puncture
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

*(strong recommendation, moderate-certainty evidence for adults and adolescents).*

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).*

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

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).*

If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured: prompt referral for further investigation and treatment as appropriate

*(strong recommendation, moderate-certainty evidence for adults and adolescents).*

## Prevention and screening

*Overarching principle*

Screening for 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 aged 10 years or older presenting with advanced HIV disease.

*Recommendations*

Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease are recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 count <100 cells/mm

*(strong recommendation, moderate-certainty evidence).*

This may be considered at a higher CD4 cell count threshold of <200 cells/mm

*(conditional recommendation, moderate-certainty evidence).*

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 India ink or CSF cryptococcal antigen assay to exclude active cryptococcal disease. India ink has low sensitivity, and a negative result on India ink should be confirmed by CSF cryptococcal antigen testing.

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 <100cells/mm

*(strong recommendation, moderate-certainty evidence).*

This may be considered at a higher CD4 cell count threshold of <200 cells/mm

*(conditional recommendation, moderate-certainty evidence).*

## Treatment

*Induction*

The following is recommended as the preferred induction regimen.
For adults, adolescents and children, a short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) is the preferred option for treating cryptococcal meningitis among people living with HIV *(strong recommendation, moderate-certainty evidence for adults).*

The following induction regimens are recommended as alternative options.

Two weeks 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).*

Two weeks of amphotericin B deoxycholate (1.0 mg/kg per day) + fluconazole (1200mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) *(strong recommendation, moderate-certainty evidence).*

*Consolidation*

Fluconazole (400–800 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).*

*Maintenance (or secondary prophylaxis)*

Fluconazole (200 mg daily for adults or 6 mg/kg per day for adolescents and children) is recommended for the maintenance phase *(strong recommendation, high-certainty evidence).*

## Using adjunctive systemic corticosteroids in treating cryptococcal meningitis

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).*

**Timing of ART** 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).*

The Southern African HIV Clinicians' Society recommends starting ART two weeks after starting fluconazole, and consideration is being given to starting ART immediately if lumbar puncture excludes cryptococcal meningitis among people who test positive for whole-blood cryptococcal antigen.

The Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children also set out good practice principles (Table 2).

## Preventing, monitoring and managing amphotericin B toxicity.

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

## 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.

## Managing raised intracranial pressure.

Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient 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. For people with persistent symptoms of intracranial pressure, repeat daily therapeutic lumbar puncture (with measurement of CSF opening pressure where available) and CSF drainage, if required, are recommended until the symptoms resolve or the opening pressure is normal for at least two days.

## 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.

## Managing treatment failure.

For people who present with cryptococcal meningitis relapse, the following steps are recommended: start or restart induction treatment according to there commendations 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.
Paradoxical cryptococcal immune reconstitution inflammatory syndrome occurs among 10–50%of people with cryptococcal disease initiating ART and is associated with high mortality. The median time to onset in reported cohort studies is 1–10 months but typically is 3–12weeks after initiating ART.

Raised intracranial pressure is a common feature of cryptococcal immune reconstitution inflammatory syndrome and an important contributor to high mortality (58). Multiple repeat lumbar puncture may be necessary. Optimizing antifungal therapy and reinduction with anamphotericin-based regimen are important if suboptimal antifungal treatment is considered to contribute to developing immune reconstitution inflammatory syndrome.

**Table 2:** Scenarios for cryptococcal diagnostic testing.

| Cryptococcal diagnostic testing scenarios | Preferred clinical approach |
|---|---|
| Settings with ready access to lumbar puncture and cryptococcal antigen testing | Perform lumbar puncture and rapid cryptococcal antigen testing and obtain results within 24 hours. Initiate treatment for cryptococcal meningitis if positive before starting ART |
| Settings with ready access to lumbar puncture but no cryptococcal antigen testing | Perform lumbar puncture and cerebrospinal fluid India ink staining, and initiate treatment for cryptococcal disease if positive before starting ART. ART should be delayed 4–6 weeks in accordance with WHO recommendations |
| Settings with ready access to lumbar puncture but it is clinically contraindicated and cryptococcal antigen testing is available | Perform rapid plasma, serum or whole-blood cryptococcal antigen assay. If the cryptococcal antigen test is positive, initiate pre-emptive antifungal therapy in accordance with WHO recommendations |
| Settings with ready access to lumbar puncture but it is clinically contraindicated and no cryptococcal antigen testing is available | Immediate referral for further management |
| No signs and symptoms of meningitis, cryptococcal antigen testing is not available and CD4 count is 100–200 cells/$mm^3$; or if point-of-care CD4 cell count is <200 cells/$mm^3$[a] | Start primary fluconazole prophylaxis in accordance with WHO recommendations |
| No signs and symptoms of meningitis, no cryptococcal antigen testing and no CD4 cell testing available | Clinical assessment and WHO staging to facilitate decision for management, consider referral for further management if unclear |

a In settings in which a semiquantitative CD4 lateral flow assay is the only tool available to diagnose advanced HIV disease, the application of cryptococcal antigen and TB-LAM screening for everyone screening positive (CD4 <200 cells/$mm^3$) may be appropriate if alternative testing would imply delays or reduced coverage.

# Overview of clinical management of histoplasmosis

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. 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.

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.

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.

In 2020, WHO published Guidelines on diagnosing and managing disseminated histoplasmosis among people living with HIV. Box 5.2 summarizes the recommendations, which are all based on evidence reviewed by the Guideline Review Committee.

## Box 2 Summary of recommendations (2020)

## Diagnosis of disseminated histoplasmosis among people living with HIV

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

## Induction therapy

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

As a good 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 maybe 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 *(conditional recommendation, very-low-certainty evidence).*

## Maintenance therapy

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 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 (conditional recommendation, very-low-certainty evidence).

TB therapy for people coinfected 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 *(conditional recommendation, very-low-certainty evidence).*

# Advanced Hiv Disease Among Children and Adolescents

All children younger than five years (who are not already receiving ART and clinically stable) are considered to have advanced disease because evidence shows that 80% of all children initiating ART have severe immunosuppression.

Advanced HIV disease is defined as WHO stage 3 or 4 or a CD4 count <200 cells/mm for children five years or older (the same definition used for adults). All children younger than five years living with HIV are considered as having advanced HIV disease, although those who have been receiving ART for more than one year and are established on ART and older than two years should not be considered to have advanced disease and should be eligible for multi month dispensing.

Children and adolescents who had previously initiated ART and are re-engaging with care after a period of ART interruption should be assessed for advanced HIV disease and should be offered the advanced HIV disease package as appropriate.

## Major causes of morbidity and mortality

The major causes of morbidity and mortality among children living with HIV in low- and middle-income countries are pneumonia (including P. jirovecii pneumonia), TB, blood stream infections, diarrhoeal disease and severe acute malnutrition. No randomized controlled trials have included children to determine the optimal package of care for advanced HIV disease for children. However, the main interventions known to reduce morbidity and mortality among children living with HIV can be summarized as screen, treat, optimize and prevent AIDS.

These recommendations include screening for TB (Table3), severe malnutrition and (for adolescents) cryptococcal meningitis; treatment of TB, severe pneumonia, severe bacterial infections and malnutrition (as well as cryptococcal meningitis); rapid ART unless there are signs of meningitis (as for adults) with appropriate measures to prevent TB disease, pneumococcal disease and other vaccine-preventable diseases. In addition, routine interventions recommended by WHO for children in general such as deworming, malaria prophylaxis, iron and vitamin A supplementation and growth monitoring should all be provided.

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 (Table 1).

The burden of TB is still high among children living with HIV. Table 1 and Box 3 highlight the main recommendations for TB screening. Data on LF-LAM among children is limited and recommendations are largely extrapolated from adults. 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. Drug–drug interactions between rifampicin and LPV/r or DTG need to be considered and ART dosing adjusted accordingly.

Although rapid ART initiation within seven days of diagnosis is a priority, especially for children older than five years, children who require hospitalization for severe acute malnutrition, TB meningitis or other illnesses need to be clinically stabilized first. However, initiating ART is encouraged as part of the child's hospital admission, 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, the start of ART 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.

Prevention of opportunistic infections in advanced HIV disease among children consists mostly of rapid and optimal ART initiation, preventing severe TB disease with BCG and TB preventive treatment (mainly with isoniazid while drug–drug interactions with rifapentine are ruled out),preventing P. jirovecii pneumonia with co-trimoxazole prophylaxis and administering age-appropriate vaccinations and catch-up vaccine administration when indicated (Table 3 and Box 3).DTG need to be considered and ART dosing adjusted accordingly.

| Intervention | Component | <5 years | 5–9 years | 10–19 years |
|---|---|---|---|---|
| Screening and diagnosis | Systematic screening for TB at each clinic visit using any one of the symptoms of current cough, fever, weight loss, night sweats or close contact with a person with TB for children younger than 10 years | Yes | Yes | Yes |
| | Use C-reactive protein for screening for TB disease additionally | No | No | Yes[a] |
| | Use of chest X-ray for screening for TB disease additionally | May be considered | May be considered | Yes |
| | WHO-recommended rapid diagnostic test, (induced or expectorated) sputum, gastric aspirate, stool or nasopharyngeal aspirate or other Extrapulmonary specimens (induced or expectorated) | Yes | Yes | Yes |
| | Inpatients in HIV wards in which the TB prevalence is >10% use WHO-recommended rapid diagnostic tests | No | No | Yes |
| | LF-LAM assay (73,74) | Yes | Yes | Yes |
| | Cryptococcal antigen screening (specimen: serum, plasma or whole blood) If blood cryptococcal antigen positive or symptomatic, lumbar puncture | No | No | Yes |
| Prevention, prophylaxis and pre-emptive treatment | Pneumococcal conjugate vaccine (catch-up) | Yes | No | No |
| | Co-trimoxazole[b] | Yes | Yes | Yes |
| | TB preventive treatment | Yes | Yes | Yes |
| | Fluconazole pre-emptive therapy for cryptococcal antigen–positive without evidence of meningitis[c] | Not applicable | Not applicable | Yes |

a Depending on the resources available, C-reactive protein, chest X-ray or molecular WHO-recommended rapid diagnostic test may be used in addition to the four-symptom screen to enhance TB screening among adolescents.

b See text for when to discontinue.

c Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive adolescents to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adolescents living with HIV who have a CD4 count <100 cells/mm$^3$ *(strong recommendation, moderate-certainty evidence)* and may be considered at a higher CD4 count threshold of <200 cells/mm$^3$ *(conditional recommendation, moderate-certainty evidence)*. When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adolescents living with HIV who have a CD4 count <100 cells/mm$^3$ *(strong recommendation, moderate-certainty evidence)* and may be considered at a higher CD4 cell count threshold of<200 cells/mm$^3$ *(conditional recommendation, moderate-certainty evidence)*. Screening and primary prophylaxis are not recommended for children younger than 10 years, given the low incidence of cryptococcal meningitis in this age group (34).

**Box 5.3 Screen, Treat, Optimize and Prevent AIDS among children**

| | |
|---|---|
| **Screen**[a] | |
| **TB** | • Screen for TB using available screening tools as indicated[b]<br>• For those who screen positive, use the following diagnostic tests to confirm TB as applicable[c]:<br>– Rapid molecular diagnostic on (induced) sputum, stool, gastric aspirate or nasopharyngeal aspirate or other extrapulmonary samples if relevant<br>– LF-LAM assay[d] |
| **Cryptococcal infection among adolescents** | Serum or plasma or blood cryptococcal antigen screening followed by lumbar puncture if positive or symptomatic |
| **Malnutrition** | • Weight-for-height<br>• Height-for-age<br>• Mid-upper arm circumference among children 2–5 years old |
| **Treat** | |
| **TB, severe pneumonia, severe bacterial infections, cryptococcal meningitis and severe acute malnutrition** | In accordance with WHO guidelines |
| **Optimize** | |

| | |
|---|---|
| **Rapid ART start** | Preferably same-day but no later than seven days after diagnosis with optimal regimens[e] |
| **ART counselling** | In accordance with WHO guidelines |
| **Prevent** | |
| **Bacterial infections and *P. jirovecii* pneumonia** | Co-trimoxazole prophylaxis |
| **TB** | TB preventive treatment |
| **Cryptococcal meningitis among adolescents** | Fluconazole pre-emptive therapy if cryptococcal antigen positive or cryptococcal antigen unavailable |
| **Vaccinations** | • Pneumococcal vaccine<br>• Human papillomavirus<br>• Measles<br>• BCG |

a Screening refers to screening and diagnostics throughout this publication.

b For screening algorithms and screening tools, see *WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment* (28) and *WHO operational handbook on tuberculosis: module 1: prevention: tuberculosis preventive treatment* (75). Screening and diagnosis of TB for adolescents is the same as for adults.

c A negative test result does not exclude TB for children living with HIV for whom there is a strong clinical suspicion of TB.

d *Package of care for children and adolescents with advanced HIV disease: stop AIDS: technical brief* (76).

e Unless TB or cryptococcal meningitis is diagnosed (77).


Screen
Prevent
STOP
AIDS
Treat
Optimize

For the use or a Registered Medical Practitioner or a Hospital or a Laboratory only

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