The burden of morbidity and mortality associated with HIV infection has decreased over the past decade as access to antiretroviral therapy (ART) has increased. Nevertheless, around 1 in 3 people living with HIV (PLHIV) present to care with advanced HIV disease. This proportion is higher in low and middle-income countries. Additionally, a growing number of PLHIV are returning to care with advanced HIV disease following a period of treatment interruption.

People with advanced HIV disease are at high risk of death from serious opportunistic infections even after starting ART, with this risk increasing with decreasing CD4 cell count. The most common causes of death among adults are tuberculosis (TB), severe bacterial infections, and cryptococcal meningitis, the latter being less common among children.

1. Most children <5 years old with HIV present for care with advanced immunosuppression and have a high-risk of disease progression and mortality regardless of their clinical and immune condition. Furthermore, the varying age-dependent CD4 cell count definitions for advanced immunosuppression among children <5 years old render the general advanced HIV disease definition difficult to implement in programmatic settings.

Package of care interventions for Advanced HIV Disease

WHO recommends a defined package of care interventions, which includes screening, treatment and prophylaxis for major opportunistic infections, rapid initiation of antiretroviral therapy (ART) and intensified treatment adherence support, for people presenting or representing to care with advanced HIV disease to reduce HIV associated morbidity and mortality.

Several large randomized trials have shown that providing a package of care interventions can reduce morbidity and mortality associated with advanced HIV disease. The individual components contained within the package of care interventions are already recommended by WHO and are brought together in a standardized and simplified, package of HIV priority interventions.

CD4 cell count testing remains essential in order to identify people with advanced HIV disease so that actions can be taken to reduce the risk of death from serious opportunistic infections.

WHO recommendation

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation, and intensified adherence support should be offered to everyone presenting with advanced HIV disease (strong recommendation, moderate-quality evidence).
# Table 1: Diagnosis and prophylaxis components of package of care interventions for advanced HIV disease

<table>
<thead>
<tr>
<th>AREAS FOR THE PACKAGE</th>
<th>INTERVENTION</th>
<th>CD4 CELL COUNT</th>
<th>ADULTS AND ADOLESCENTS</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening and diagnosis</strong></td>
<td>Sputum Xpert MTB/RIF as first test for TB diagnosis in symptomatic patients</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Urine LF-LAM* for TB diagnosis in patients with symptoms and signs of TB</td>
<td>≤100 cells/mm(^3) Or at any CD4 cell count value if seriously ill</td>
<td>Yes</td>
<td>Yes**</td>
</tr>
<tr>
<td></td>
<td>Cryptococcal antigen (CrAg) screening***</td>
<td>≤100 cells/mm(^3) ****</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤200 cells/mm(^3)****</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prophylaxis and pre-emptive treatment</strong></td>
<td>Co-trimoxazole prophylaxis</td>
<td>≤350 cells/mm(^3) or WHO clinical stage 3 or 4 event. Any CD4 cell count value in settings with high prevalence of malaria and/or severe bacterial infections</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>TB preventive treatment(^{i})</td>
<td>Any</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td></td>
<td>Fluconazole pre-emptive therapy for CrAg-positive patients without evidence of meningitis</td>
<td>≤200 cells/mm(^3)****</td>
<td>Yes</td>
<td>Not applicable (Screening not advised)</td>
</tr>
<tr>
<td><strong>ART initiation</strong></td>
<td>Rapid ART initiation</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Defer ART initiation if clinical signs and symptoms are suggestive of TB or cryptococcal meningitis</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Adapted adherence support</strong></td>
<td>Tailored counselling to ensure optimal adherence to advance disease care package, including home visits if feasible</td>
<td>&lt; 200 cells/mm(^3)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Urine LF-LAM: lateral flow urine lipoarabinomannan assay.
** Limited data for children
***CrAg screening and pre-emptive therapy is strongly recommended at CD4 <100 cells/mm\(^3\) and conditionally recommended at CD4 >100 cells/mm\(^3\) and
****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) and may be considered at a higher CD4 cell count threshold of < 200 cells/mm\(^3\) (conditional recommendation; moderate-certainty evidence).
\(^{i}\) Co-trimoxazole, isoniazid and pyridoxine are now available as a fixed-dose combination tablet.
\(^{\#}\) For children <12 months of age, only those with a history of TB contact should receive TB preventive treatment if the evaluation shows no active TB disease.
Cryptococcal disease in people with advanced HIV disease.

Cryptococcal meningitis is a major cause of morbidity and mortality in PLHIV with advanced disease, accounting for an estimated 15% of all HIV-related deaths globally, three quarters of which are in sub-Saharan Africa. Mortality from cryptococcal meningitis is highest in low and middle-income countries. High cost and limited access to first-line antifungal drugs as well as limited access to rapid diagnostic assays and lumbar puncture are major contributors to this high mortality.

In March 2018 WHO released updated guidelines: Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. These guidelines include recommendations on the following areas:

- the optimal approach to diagnosing cryptococcal meningitis
- strategies for preventing invasive cryptococcal disease through cryptococcal antigen screening and pre-emptive fluconazole therapy (consistent with the WHO recommended package for advanced HIV disease) and
- treating cryptococcal meningitis with combination antifungal therapy regimens.

WHO Recommendations: treatment of cryptococcal meningitis

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 and fluconazole is the preferred option for treating cryptococcal meningitis among people living with HIV (strong recommendation, moderate-certainty evidence for adults, low-certainty evidence for children and adolescents).

The following induction regimens are recommended as alternative options:

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

Consolidation

Fluconazole (400–800 mg daily, 6–12 mg/kg/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, 6 mg/kg/day for adolescents and children) is recommended for the maintenance phase (strong recommendation, high-certainty evidence).

Note: A minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management can be provided to minimize treatment toxicity during induction phase with Amphotericin B containing regimens2 and fluconazole.

Implementation of the package of care for advanced HIV disease.

The package of care for people with advanced HIV disease should be offered at both hospitals and at decentralised primary care clinics and peripheral sites. Successful implementation of the simplified package of interventions requires that countries improve access to diagnostics and medicines, and increase knowledge and awareness of health-care providers in the management of opportunistic infections.

Access to diagnosis

Since early diagnosis is key to reducing mortality from opportunistic infection, countries need to ensure reliable availability of diagnostic assays in the package. CD4 cell count is essential to identify those who have advanced HIV disease and who should be offered the package of care. Access to cryptococcal antigen testing, LF-LAM testing and Xpert® MTB/RIF is also required as these are key components of the package. As these diagnostic tests are available as point of care assays (CD4, CrAg, LF-LAM and Xpert® MTB/RIF), it can facilitate task shifting by nurses and other mid-level healthcare workers, and expanded access of the package of interventions at decentralised primary care clinics and peripheral sites.

Access to medicines

Access to co-trimoxazole, TB preventative treatment, and fluconazole is required for the implementation of the package of care both in hospitals and at decentralised primary care clinics and peripheral sites. A fixed-dose combination of isoniazid, pyridoxine and co-trimoxazole is now available and has been added to the WHO List of Essential Medicines: http://www.who.int/medicines/publications/essentialmedicines/en/

For patients identified as having a serious opportunistic infection such as TB or cryptococcal meningitis, access to anti-TB medication and antifungal therapy, including amphotericin B (ideally in liposomal form) and fluconazole is essential. The induction regimen given priority by WHO, based on the best-performing arms in the ACTA trial, contains fluconazole as well as amphotericin B. The combination fluconazole and fluconazole induction regimen is an alternative regimen if amphotericin B is not available. These two fluconazole-containing regimens can potentially reduce mortality by half compared with using fluconazole mono-therapy. Amphotericin B, fluconazole and fluconazole are included in the WHO Model List of Essential Medicines.

2. Liposomal amphotericin B is preferred over amphotericin B deoxycholate, since liposomal amphotericin B has demonstrated equivalent efficacy and better safety compared with the conventional form of amphotericin B deoxycholate.
CRITICAL ENABLERS OF IMPLEMENTING THE PACKAGE OF CARE FOR ADVANCED HIV DISEASE AND THE TREATMENT OF CRYPTOCOCCAL MENINGITIS

1. Incorporating commodities in the advanced HIV disease package into routine national forecasting and quantification plans and national tenders.

2. Ensuring national registration of all cryptococcal meningitis medicines and including them in national essential medicine lists (amphotericin B, flucytosine and fluconazole are now included in WHO Model List of Essential Medicines).

3. Support price reduction strategies, increased competition, and increased funding availability.

4. Coordinating funding, procurement and tenders across major funders to increase market predictability, improve economies of scale, and minimize price volatility.

5. Supporting routine use of the advanced HIV disease package both in hospitals and at decentralised primary care clinics and peripheral sites by facilitating task-shifting to nurses and other mid-level healthcare workers.