TECHNICAL BRIEF — JULY 2020

PACKAGE OF CARE FOR CHILDREN AND ADOLESCENTS WITH ADVANCED HIV DISEASE: **STOP AIDS**

World Health Organization

CLINTON HEALTH ACCESS INITIATIVE

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Innovation in Global Health

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Package of care for children and adolescents with advanced HIV disease: stop AIDS. Technical brief

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ABBREVIATIONS

BCG   Bacille Calmette-Guérin

DTG   dolutegravir

EFV   efavirenz

E   ethambutol

H   isoniazid

HPV   human papillomavirus

LF-LAM   lateral flow urine lipoarabinomannan

LPV/r   lopinavir/ritonavir

R   rifampicin

TB   tuberculosis

Z   pyrazinamide

ACKNOWLEDGEMENTS

BACKGROUND

The major causes of morbidity and mortality among children living with HIV in low- and middle-income countries are pneumonia (including *Pneumocystis* pneumonia), tuberculosis (TB), bloodstream infections, diarrhoeal disease and severe acute malnutrition *(1,2)*. In addition, for adolescents living with HIV, adult-type opportunistic infections also occur, including cryptococcal meningitis *(3,4)*. WHO published guidelines on the management of advanced HIV disease in 2017, promoting a package of interventions to prevent, identify and treat HIV-associated infections among people with advanced HIV disease *(5)*. This publication builds on the 2017 guidelines and highlights existing WHO recommendations and implementation considerations that are relevant to the care of children and adolescents with advanced HIV disease. It is therefore not meant to be a comprehensive review of all severe comorbidities that affect children living with HIV. In addition, many of the interventions described here are also relevant for children and adolescents living with HIV who do not have advanced disease.

Current WHO guidelines on managing advanced HIV disease

In 2017, WHO published guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy *(5)*. **Advanced HIV disease is defined as WHO stage 3 or 4 or a CD4 cell count <200 cells/mm³ for children five years or older.**

All children younger than five years are considered to have advanced disease *(5)*. This is based on the rationale that most children younger than five years usually present for care with advanced immunosuppression, younger children have an increased risk of disease progression and mortality regardless of clinical and immune condition and that varying age-dependent CD4 cell count definitions for advanced immunosuppression among children younger than five years make definitions based on CD4 cell count difficult to implement in programmatic settings.

Although children younger than five years are defined as having advanced disease at presentation, those who have been receiving antiretroviral therapy for more than one year and who are clinically stable should not be considered to have advanced disease and should be eligible for multi-month dispensing *(6)*.

Children and adolescents who had previously initiated antiretroviral therapy and are re-engaging with care after a period of antiretroviral therapy interruption are also considered as having advanced HIV disease and should be offered the advanced HIV disease package of care as well as counselling targeted at adherence and retention in care *(5)*.

The 2017 guidelines focus on providing an enhanced package of prophylactic, diagnostic and therapeutic interventions for those starting antiretroviral therapy with advanced HIV disease. Most of the data informing these guidelines are from adults in two trials (REMSTART and REALITY) that evaluated packages of interventions to reduce mortality among people presenting with advanced HIV disease *(7,8)*. REMSTART only enrolled participants older than 18 years. In the REALITY trial, only 4% of the participants (72 of 1805) were 5–17 years old and received the same package of prophylactic interventions as the adult group. No child had cryptococcal disease, and one child had oral candidiasis at enrolment. One child reportedly died from probable bacterial pneumonia *(7)*.

Evidence on the management of advanced HIV disease specifically related to children is limited, and no randomized controlled trials on packages of interventions have involved children younger than five years.

The main interventions known to reduce morbidity and mortality among children living with HIV can be summarized as **S**creen, **T**reat, **O**ptimize and **P**revent AIDS (**STOP AIDS**, Box 1, Table 1). In addition to the components specified below, 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.

Box 1. Screen, Treat, Optimize and Prevent AIDS

Screen[a]

TB
- Screen for TB using a clinical algorithm[b] followed by X-ray when indicated and if available
- Use the following diagnostic tests to confirm TB as applicable:[c]
  - Rapid molecular diagnostic (Xpert® MTB/RIF or Ultra) on (induced) sputum, stool, gastric aspirate or nasopharyngeal aspirate or other extrapulmonary samples if relevant
  - Lateral flow urine lipoarabinomannan (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
- Height-for-age
- Mid-upper arm circumference among children 2–5 years old

Treat

TB, severe pneumonia, severe bacterial infections, cryptococcal meningitis and **severe acute malnutrition** according to WHO guidelines

Optimize

Rapid antiretroviral therapy start – within seven days with optimal regimens[e]

Antiretroviral therapy counselling

Prevent

Bacterial infections and *Pneumocystis* pneumonia
- Co-trimoxazole prophylaxis

TB
- TB preventive treatment

Cryptococcal meningitis among adolescents
- Fluconazole pre-emptive therapy

Vaccinations
- Pneumococcal vaccine
- Human papillomavirus
- Measles
- BCG

Screen

Prevent   STOP AIDS   Treat

Optimize

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[a] Screening refers to screening and diagnostics throughout this publication.
[b] See Fig. 3 in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (9)*.
[c] A negative test result does not exclude TB in children living with HIV in whom there is a strong clinical suspicion of TB.
[d] See Table 2 and the text for recommendations.
[e] Unless TB or cryptococcal disease is diagnosed *(10)*.

Table 1. Screening, diagnosis and prevention components of the package of care for children and adolescents with advanced HIV disease

Intervention	Component	<5 years	5–9 years	10–19 years
Screening and diagnosis	Screen for TB using clinical algorithm followed by X-ray when indicated and if available Xpert® MTB/RIF or Xpert® Ultra assay as the first test (Induced or expectorated) sputum, gastric aspirate, stool or nasopharyngeal aspirate or other extrapulmonary specimens (induced or expectorated)	Yes	Yes	Yes
	LF-LAM assay[a]	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] See Box 2 *(11,12)*.

[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 antiretroviral therapy for 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). When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to 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). Screening and primary prophylaxis are not recommended for children younger than 10 years, given the low incidence of cryptococcal meningitis in this age group *(13)*.

SCREEN

Tuberculosis

The incidence of TB in a cohort of children living with HIV in Uganda and Zimbabwe ranged from 1.2 to 8.8 per 100 child-years, and an estimated 15% of children starting antiretroviral therapy in sub-Saharan Africa develop TB *(14,15)*. Although antiretroviral therapy reduces children's risk of TB infection, its full protective potential is only evident 1–2 years after starting antiretroviral therapy *(8)*. TB is especially common in the first three months after starting antiretroviral therapy *(16)*.

Careful history (including contact history) and examination should be performed for all children and adolescents with HIV to screen for TB. Common symptoms and signs include: coughing for more than two weeks; daily fever that characteristically exceeds 38.0°C (night sweats are uncommon in children); anorexia and associated wasting or failure to thrive during the past 3–6 months, or having lost >10% of body weight; listlessness; and peripheral lymphadenopathy (typically unilateral, enlarged, non-painful, rubbery lymph node) *(9,17)*. Clinical

screening remains problematic, since children living with HIV commonly have symptoms and signs that overlap with TB. Clinical screening should be followed by an X-ray if indicated and feasible.

The 2017 advanced HIV disease guidelines *(5)* recommended the LF-LAM assay for use among children with advanced HIV disease. This recommendation was based on adult data, despite previous studies indicating that LF-LAM has poor sensitivity and specificity among children and adolescents living with HIV (18).

The LF-LAM guidelines from 2019 replace the recommendations from the 2017 advanced HIV disease guidelines and are listed in Box 2 *(11,12)*.

Using culture as the reference standard, studies have shown that the sensitivity of Xpert MTB/RIF for pulmonary TB is 2–3 times higher than that of smear microscopy when testing induced sputum, nasopharyngeal aspirates or gastric aspirate lavages *(19–21)*. WHO recommends rapid molecular TB diagnostics such as Xpert MTB/RIF and Xpert Ultra for children and adolescents. Xpert Ultra has increased sensitivity *(22–24)*. Emerging evidence also indicates the diagnostic value of Xpert testing employing stool specimens, and WHO now recommends this *(25)*. Countries should try to increase capacity to collect non-sputum samples, such as gastric aspirate, lymph node aspirate and stool depending on the level of resources. However, given the low sensitivity of microbiological

Box 2. Recommendations from the LF-LAM guidelines from 2019 *(11,12)*

For inpatient settings
WHO strongly recommends using LF-LAM to assist in diagnosing active TB among children and adolescents living with HIV
- with signs and symptoms of TB (pulmonary and/or extrapulmonary)
- with advanced HIV disease or who are seriously ill[a]
- regardless of signs and symptoms of TB and with a CD4 count <200 cells/ mm^3

For outpatient settings
WHO suggests using LF-LAM to assist in diagnosing active TB among children and adolescents living with HIV
- with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill[a]
- regardless of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm^3

WHO recommends against using LF-LAM to assist in diagnosing active TB among children and adolescents
- without assessing TB symptoms
- without TB symptoms and unknown CD4 cell count or without TB symptoms and the CD4 cell count is greater than or equal to 200 cells/mm^3
- without TB symptoms and with a CD4 cell count of 100–200 cells/mm^3

These recommendations are based on generalization of data from adults, while acknowledging very limited data for children and adolescents.

[a] A seriously ill child is defined as having any of the following danger signs: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; and repeated vomiting. Other clinical conditions such as body temperature ≥39°C and age-defined tachycardia and/or tachypnoea can be considered based on clinical judgement.

diagnosis among children, the ability for clinicians to diagnose TB based on clinical and radiological evidence remains critical.

Cryptococcal disease

In contrast to adults, cryptococcal disease is rare, especially among children younger than five years of age. In a laboratory-based survey performed in South Africa, the incidence of cryptococcal disease was estimated to be 47 per 100 000 children living with HIV in 2007 *(26)*, and within two trial cohorts of children living with HIV, no cases of cryptococcal disease were reported for children younger than five years *(27)*. Screening for cryptococcal antigen and pre-emptive therapy is therefore only recommended for adolescents.

Useful resources

Rapid communication: molecular assays as initial tests for the diagnosis of tuberculosis and rifampicin resistance. Geneva: World Health Organization; 2020 (https://www.who.int/tb/publications/2020/rapid-communications-molecular-assays/en).

Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 (https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en).

TREAT

Tuberculosis

Treatment for drug-sensitive TB among children comprises a four-drug regimen that includes rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E). A child-friendly, fixed-dose combination, dispersible tablet of RHZ is available and can be taken with a 100-mg child friendly formulation of E (intensive-phase treatment). In addition, there is a child-friendly, dispersible fixed-dose combination of RH for the continuation phase of treatment. All these formulations are available through the Global Drug Facility and should be implemented to alleviate the pill burden among children coinfected with HIV. Drug–drug interactions between rifampicin and Lopinavir/ritonavir (LPV/r) need to be taken into account and antiretroviral therapy adjusted accordingly, using a super-boosting strategy or double-dose LPV/r depending on age and ability to swallow medication *(10)*. Drug–drug interactions between rifampicin and dolutegravir (DTG) can also be adjusted for by double-dosing DTG (children >25 kg) *(28)*.

Severe pneumonia

In studies of severe pneumonia among children living with HIV, the most common bacterial pathogens isolated were predominantly *Streptococcus pneumoniae* and *Staphylococcus aureus*, pathogens that may be effectively covered by commonly available and recommended antibacterial medications *(29)*. The severity of illness and need for hospitalization should be classified according to the WHO integrated management of childhood illness algorithms *(30)*.

The use of intravenous or oral co-trimoxazole, 5 mg of trimethoprim and 25 mg of sulfamethoxazole per kg per dose, every six hours for 21 days, reduces mortality from *Pneumocystis* pneumonia among young infants with HIV *(31)*. The early use of steroids in infants with a clinical diagnosis of *Pneumocystis* pneumonia in addition to co-trimoxazole therapy significantly reduced in-hospital mortality and mortality at six months after discharge in a study in Malawi *(32)*. In addition, cytomegalovirus coinfection may play an important role in mortality *(33,34)*. The EMPIRICAL trial (https://penta-id.org/hiv/empirical) is studying the empirical use of ganciclovir for children living with HIV with severe pneumonia.

The current recommendation is to treat all infants living with HIV with severe pneumonia empirically with co-trimoxazole and the antibiotics recommended in WHO guidelines because of the high prevalence of *Pneumocystis* pneumonia in this age group *(29)*. For children between one and five years old, the recommendation is to use antibiotics recommended in WHO guidelines and not cotrimoxazole due to the lower prevalence of PCP in this age group *(29)*.

Severe bacterial infections

High rates of bacteraemia have been described in children starting antiretroviral therapy, especially within the first three months of treatment *(35,36)*. A recent study of 82 children with malnutrition admitted to a tertiary hospital in Durban, South Africa showed that 6% of admission blood cultures were positive. Community-associated infections were primarily

Streptococcus or *Staphylococcus*. Health care-associated infections were predominantly gram-negative (39 of 43, 91%). No pathogen was specifically associated with mortality *(37)*. *Salmonella* is also a common cause of bacteraemia among children living with HIV *(38)*. Treatment should be provided according to current WHO guidelines and tailored according to age, suspicion of meningitis and blood and cerebrospinal fluid culture if available.

Cryptococcal meningitis

Guidelines for cryptococcal meningitis treatment have been revised, and 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 children living with HIV. Further recommendations are available in the 2018 WHO guidelines *(13)*.

Malnutrition

Severe acute malnutrition is common at HIV diagnosis and carries a high risk of mortality. The availability of malnutrition treatment programmes and commodities, including ready-to-use therapeutic food where appropriate, can be considered as essential components of HIV treatment programmes for children.

Useful resources

WHO, UNICEF. Statement on the use of child-friendly fixed-dose combinations for the treatment of TB in children. Geneva: World Health Organization; 2017 (https://www.who.int/tb/publications/ChildTbStatementfixed-dose combinations/en)

Pneumonia and bloodstream infections: Integrated management of childhood illness for high HIV settings. Geneva: World Health Organization; 2008 (https://apps.who.int/iris/handle/10665/44010).

Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 (https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en).

Nutrition for HIV-infected infants and children (Chapter 14). In: Antiretroviral therapy of HIV infection in infants and children: towards universal access: recommendations for a public health approach – 2010 revision. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/bitstream/handle/10665/164255/9789241599801_eng.pdf;jsessionid=26591810CC4A1EB29C4F4B9BD9B9522F?sequence=1).

Guideline: updates on the management of severe acute malnutrition in infants and children. Geneva: World Health Organization; 2020 (https://www.who.int/publications-detail-redirect/9789241506328).

OPTIMIZE

In a randomized trial from South Africa, young children living with HIV (median age 23 months) with severe acute malnutrition were randomized to receive antiretroviral therapy within 14 days of admission or for antiretroviral therapy to be delayed until nutritional recovery (and after two weeks; median time 23 days) *(39)*. The results suggested that a short delay in antiretroviral therapy initiation during early treatment of acute malnutrition resulted in improved immune recovery, led to more rapid viral suppression and improved anthropometric measures *(39)*. In another randomized trial from Kenya, hospitalized children with HIV (median age 23 months), of which almost half had severe acute malnutrition, were randomized to initiating antiretroviral therapy within 48 hours versus after 7–14 days. The treatment arms did not differ in mortality, and the authors concluded that rapid treatment is safe and that prompt initiation of antiretroviral therapy is essential to reduce the very high mortality observed overall, with 21% of children dying during six months of follow-up *(40)*. Overall, although rapid antiretroviral therapy initiation within seven days of diagnosis is a priority, especially for children older than five years, children who present with severe acute malnutrition or TB or other illnesses that require hospitalization need to be stabilized first. However, **initiating antiretroviral therapy 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 antiretroviral therapy. Similarly, ensuring linkage to the facility where the child will receive ongoing HIV care upon discharge is critical.**

Counselling and support

Additional counselling and support are needed with earlier antiretroviral therapy initiation. Counselling tools have been updated to reflect newer optimal regimens and formulations. Adolescents generally face challenges in adhering to medication, and adolescent-friendly services, including enhanced adherence counselling, adolescent peer counsellors and support groups, may be especially valuable.

Useful resources

Update of recommendations on first- and second-line antiretroviral regimens: policy brief. Geneva: World Health Organization; 2019 (https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en).

Pediatric ARV counseling cards and job aids [website with toolkits]. New York: ICAP at Columbia University Mailman School of Public Health; 2020 (https://icap.columbia.edu/tools_resources/pediatric-arv-counseling-cards-and-job-aids).

PREVENT

Preventing TB, *Pneumocystis* pneumonia, bacterial infections and cryptococcal disease

Tuberculosis

TB preventive treatment has been shown to reduce morbidity and mortality among children living with HIV one year and older even if they do not have a known TB contact *(41)*. Despite this, TB preventive treatment has not yet been fully implemented as part of comprehensive HIV care for children and adolescents *(42)*. TB preventive treatment is currently not recommended for infants living with HIV younger than 12 months of age unless they have a known TB contact *(43)*. This recommendation is based on evidence showing that TB preventive treatment did not improve TB- free survival for infants living with HIV *(43)*. Nevertheless, these infants are at the highest risk of progression to severe TB disease, and the source case is often difficult to identify. For adults living with HIV, shorter TB preventive treatment regimens are now recommended (for example, three months of once-weekly isoniazid and rifapentine (3HP) and one month of daily isoniazid and rifapentine (1HP)); this is currently being studied among children.

■ Six months of daily isoniazid is the regimen of choice for children living with HIV, especially those younger than five years, preferably using the dispersible formulation of isoniazid 100 mg. Pyridoxine (vitamin B6) should be added to isoniazid to prevent peripheral neuropathy.

■ A shorter regimen of three months of daily rifampicin and isoniazid (RH) can be used for children who are receiving antiretroviral therapy with no drug–drug interaction with rifampicin (such as efavirenz (EFV)-based ART) using the child-friendly dual-drug fixed-dose combination (rifampicin and isoniazid 75 and 50 mg) for children weighing up to 25 kg.

■ Weekly rifapentine and isoniazid for three months (3HP) could be used from two years of age for children who are receiving antiretroviral therapy with no drug–drug interaction with rifapentine (such as EFV-based ART), although no child-friendly formulation exists.

■ Daily rifapentine and isoniazid for one month (1HP) has only been studied among children

Table 2. TB preventive therapy options and their drug-drug interaction with antiretrovirals used in children and adolescents with HIV

TB preventive treatment regimen	LPVr	EFV	DTG
6H	No	No	No
3RH	Yes	No	Yes
3HP	Yes	Being studied but no major DDI expected	Being studied
1HP	Yes	Being studied but no major DDI expected	Being studied

LPV/r: lopinavir/ritonavir; EFV: efavirenz; DTG: dolutegravir; 6H: six months of daily isoniazid; 3RH: three months of daily rifampicin and isoniazid; 3HP: three months of weekly isoniazid and rifapentine; 1HP: one month of daily isoniazid and rifapentine.

older than 12 years, and thus 1HP can be used for adolescents who are receiving antiretroviral therapy with no drug–drug interaction with rifapentine.

PCP and other infections

Co-trimoxazole
Studies done in South Africa and Zambia in the era before antiretroviral therapy showed a high prevalence of *Pneumocystis* pneumonia, with infants younger than six months being especially vulnerable regardless of CD4 cell count *(44,45)*. Despite improved access to antiretroviral therapy, *Pneumocystis* pneumonia remains a common cause of hospitalization because of undiagnosed HIV among infants. Cotrimoxazole has been shown to prevent *Pneumocystis* pneumonia, bacterial infections, toxoplasmosis and malaria in endemic regions *(46)*. Children in Uganda and Zimbabwe were randomized to

continue or stop co-trimoxazole after receiving antiretroviral therapy for a median of 2.1 years; continued therapy did not prevent death but did reduce hospitalization from malaria and other infections *(47)*. The recommendation of the 2017 advanced HIV disease guidelines *(5)* is to start co-trimoxazole prophylaxis for all infants, children and adolescents with advanced HIV disease and to continue co-trimoxazole after initiating antiretroviral therapy in areas with a high prevalence of malaria and/or bacterial infections and to discontinue for children who live in areas with a low prevalence of malaria and/or bacterial infections and are clinically stable and/or have suppressed viral loads while receiving antiretroviral therapy for at least six months and have a CD4 cell count >350 cells/mm^3.

Azithromycin
Azithromycin was given as part of the intervention package in the REALITY trial, but the trial had few children participating, and any observed mortality reduction could not be attributed to azithromycin *(7)*. Another trial in three countries in Africa showed that mass administration of azithromycin prophylaxis to children reduced mortality, although this effect was mainly driven by a reduction in mortality in one country *(48)*. WHO guidelines are being developed to guide mass administration of azithromycin to children 1–11 months old. More research is needed on using azithromycin for children living with HIV.

Cryptococcal meningitis
Screening and primary prophylaxis are not recommended for children younger than 10 years, given the low incidence of cryptococcal meningitis in this age group. Children older than 10 years (that is, adolescents in accordance with the WHO definition of adolescents being 10–19 years old) and CD4 count <100 cells/mm^3 should be screened with blood (serum or plasma or whole blood) cryptococcal antigen and, if positive, given fluconazole as suggested in the guidelines. In settings where cryptococcal

Table 3. Prophylactic doses of drugs for children based on weight bands: daily administration

Drug	Recommended daily dose	Formulation	Dosing						
			3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–29.9 kg	>30 kg
Co-trimoxazole	Trimethoprim 5–10 mg/kg per day	Suspension (200 mg of sulfamethoxazole and 40 mg of trimethoprim per 5 mL)	2.5 mL	5 mL	5 mL	10 mL	10 mL	–	–
		Tablets (dispersible) 100/20 mg	1	2	2	4	4	–	–
		Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	2	2
		Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	1	1
Isoniazid	10–15 mg/kg per day (maximum 300 mg)	100 mg (scored, dispersible)	0.5	1	1.5	2	3	3	3
		300 mg	–	–	–	–	1	1	1
Isoniazid, co-trimoxazole and vitamin B6	Isoniazid: 10–15 mg/kg per day (maximum 300 mg)	300/960/25 mg	–	–	–	0.5	0.5	1	1
Fluconazole	6 mg/kg per day (maximum 200 mg)	100 mg	–	0.5	1	1	1	2	2

antigen is not available, primary fluconazole prophylaxis may be offered to adolescents with CD4 count <100 cells/mm³. Table 2 includes fluconazole dosing. Adolescents who have a positive cryptococcal antigen on blood specimen should be screened for signs of meningitis and have a lumbar puncture if possible for cerebrospinal fluid cryptococcal antigen.

Vaccinations

The WHO 2017 advanced HIV disease guidelines *(5)* highlighted the importance of vaccination in preventing severe disease among people living with HIV. Several other important vaccines were specifically recommended, including meningococcal, polio, rotavirus and yellow fever; however, this publication focuses on immunizations for the vaccine-preventable infections that are most significant to children living with HIV: TB, human papillomavirus (HPV) measles and pneumococcus.

BCG
- Neonates born to women of unknown HIV status should be vaccinated, since the benefits of BCG vaccination outweigh the risks.

- Neonates with unknown HIV status born to women living with HIV should be vaccinated if no clinical evidence suggests HIV infection, regardless of whether the mother is receiving antiretroviral therapy.

- Neonates with confirmed HIV infection should delay BCG vaccination until antiretroviral therapy has started and they are confirmed to be immunologically stable (CD4 >25%).

Implementation strategies may differ from these recommendations because of the practical challenges of confirming HIV status before routine BCG vaccination is administered. In Kenya and South Africa, for example, BCG is given at birth to all neonates, regardless of HIV status or exposure. Further research is needed to determine the risk of disseminated BCG disease. BCG given to infants living with HIV with early antiretroviral therapy initiation have low risk of developing BCG immune reconstitution inflammatory syndrome *(49)*.

HPV
- As children living with HIV reach adolescence and become sexually active, they are at risk of acquiring HPV infection, with subtypes known to cause cervical or anal cancer.

- Evidence indicates that **adolescent females living with perinatally-acquired HIV** have a higher prevalence of high-risk HPV and abnormal cervical cytology than uninfected adolescents after adjusting for age, sexual history and pregnancy *(50)*.

- The quadrivalent HPV vaccine is safe and highly immunogenic in boys and girls with HIV. WHO recommends a three-dose series (0, 1–2 and 6 months) for females older than

nine years living with HIV rather than the standard two-dose series following studies that showed lower antibody titres after HPV vaccination among women living with HIV than among HIV-uninfected women *(51)*. Vaccination of secondary target populations, such as males, is only recommended if it is feasible, affordable and cost-effective and does not divert resources from vaccinating the primary target population or from effective cervical cancer screening programmes.

Measles

- Vaccination should be routinely administered to potentially susceptible, asymptomatic children living with HIV and should be considered for those who are symptomatic if they are not severely immunosuppressed according to WHO definitions.

- In areas with a high incidence of both HIV infection and measles, the first dose of measles-containing vaccine may be offered at six months followed by two additional doses according to the national immunization schedule up to two years of age.

For those with a low CD4 cell count when first immunized, an additional dose of measles-containing vaccine should be administered when immune reconstitution has been achieved, (when the CD4 cell percentage reaches 20–25%); if CD4 cell count monitoring is not available, children should receive an additional dose of measles vaccine 6–12 months after initiating antiretroviral therapy.

Catch-up pneumococcal conjugate vaccine

- Wherever possible, catch-up vaccination at the time when countries introduce pneumococcal conjugate vaccine should be used to accelerate its impact on disease among children 1–5 years old, especially in settings with a high disease burden and mortality. If the availability of vaccine or of financial resources for catch-up vaccination is limited, the

youngest children (younger than two years) should be given priority to receive catch-up doses of pneumococcal conjugate vaccine because of their higher risk for pneumococcal disease.

- Unvaccinated children aged 1–5 years who are at high risk for pneumococcal infection because of underlying conditions, such as HIV infection or sickle-cell disease, should receive at least two doses separated by at least eight weeks.

- Infants and preterm neonates living with HIV who have received their three primary vaccine doses before 12 months of age may benefit from a booster dose in the second year of life.

- Co-administration with other vaccines for programmatic reasons appears to be acceptable.

Useful resources

BCG vaccines: WHO position paper – February 2018. Geneva: World Health Organization; 2018 (https://www.who.int/immunization/policy/position_papers/bcg/en).

Summary of the WHO position on measles vaccine – April 2017. Geneva: World Health Organization; 2017 (https://www.who.int/immunization/policy/position_papers/WHO_PP_measles_vaccine_summary_2017.pdf?ua=1).

Summary of the WHO position paper on vaccines against human papillomavirus (HPV), May 2017. Geneva: World Health Organization; 2017 (https://www.who.int/immunization/policy/position_papers/pp_hpv_may2017_summary.pdf?ua=1).

Summary of WHO position paper on pneumococcal conjugate vaccines in infants and children under 5 years of age, February 2019. Geneva: World Health Organization; 2019 (https://www.who.int/immunization/policy/position_papers/who_pp_pcv_2019_summary.pdf?ua=1).

Case study — Thyolo District Hospital, Malawi

In October 2018, the Elizabeth Glaser Pediatric AIDS Foundation began supporting the implementation of advanced HIV disease recommendations for children and adolescents (and adults) at Thyolo District Hospital in Malawi. In December 2019, in conjunction with other partners, they supported the Ministry of Health of Malawi in scaling up implementation to 21 sites working on a hub-and-spoke model. A pool of trainers obtained the capacity to carry out training in advanced HIV disease at the various sites.

All children younger than five years receive a LF-LAM assay. Children older than five years automatically have a cryptococcal antigen test and LF-LAM assay done if their CD4 count is less than 200 cell/mm^3. All children are screened for TB using a symptom-based approach and, if this is positive, they will have a chest X-ray and rapid molecular test.

Children are referred to hubs if they need to have lumbar puncture performed, but most spokes can perform cryptococcal antigen testing, LF-LAM assay and initiate rapid antiretroviral therapy if clinically appropriate.

Challenges include limited knowledge and reluctance in diagnosing and treating TB in children. Tailored training for dealing with children with TB has been implemented to try to resolve this. In addition, there are occasional difficulties in collecting samples, especially urine. The fixed-dose combination of isoniazid/co-trimoxazole and vitamin B6 is also not currently available.

From October 2018 to October 2019 at the initial site, 23 children younger than five years were classified as having advanced HIV disease, and 17 (74%) received six months of isoniazid preventive therapy and co-trimoxazole prophylaxis in accordance with national guidelines. Three children were 5–10 years old and had advanced HIV disease with CD4 <200 cells/mm^3, and they all received co-trimoxazole and six months of isoniazid preventive therapy. All 26 children 0–10 years old were screened with LF-LAM. Six children were treated for TB, and there were no cases of cryptococcal meningitis.

IMPLEMENTATION CONSIDERATIONS

National level

- The recommendations in the 2017 guidelines on advanced HIV disease *(5)* (and other related updated WHO guidelines) need to be adopted in national policy and guidelines.

- It is important to try to align recommendations across multiple guidelines relating not only to HIV (for example, TB and HIV guidelines relating to TB preventive treatment) but also to routine child health and development interventions (vitamin A, deworming and Expanded Programme on Immunization).

- Registration and procurement of the required commodities and medication (especially formulations for children) are vital to implementing services for advanced HIV disease for children and adolescents (see table 4 for pricing for some key AHD commodities).

- Policies and/or standard operating procedures to enable catch-up vaccination outside the Expanded Programme on Immunization schedule for children living with HIV need to be available.

Facility level

- Currently, the advanced HIV disease package is being implemented as a hub-and-spoke model. Further guidance on this is available in the global advanced HIV disease toolkit (http://www.differentiatedcare.org/Resources/Resource-Library/Global-Advanced-HIV-DiseaseToolkit).

- In the context of ongoing and enhanced efforts to ensure task shifting for services for children, all cadres of health-care workers need training for certain components of the package such as screening and enhanced antiretroviral therapy counselling.

- Centres introducing the advanced HIV disease package for children should provide a child-friendly environment.

- Child-specific resources such as a mid-upper arm circumference tape, stadiometer, appropriate scales and expertise in paediatric phlebotomy should be available.

- A specific child-friendly space could be used as an opportunity to educate on early childhood development and sensitization to components of the advanced HIV disease package (https://www.who.int/maternal_child_adolescent/child/nurturing-care-framework/en).

- Ensure an appropriate mix of TB preventive treatment regimens based on the age distribution of children and adolescents. Consider how many children are receiving a regimen based on protease inhibitor or integrase inhibitors, since they will need six months of isoniazid rather than a regimen based on RH, 3HP or 1HP. Anticipate the correct mix of commodities based on age and regimens.

- Protocols for referral up, down and across should be in place: for example. safe administration of amphotericin B may require referral to a centre with a minimum package of preventing, monitoring and managing toxicity.

Health-care providers

- Health-care providers should be sensitized on child-specific issues such as growth monitoring and other routine child health interventions.

- Training and capacity building for staff should be implemented in sites where these recommendations are to be implemented.

- Ensure that the advanced HIV disease package is included in any curriculum of training on HIV related to children or adolescents.

- Uptake of TB screening specific to children is challenging. Ensure appropriate adaptation of existing screening tools for the advanced HIV disease package that focus on the different ways that TB can present in children.

- Limited access to new diagnostics should not prevent clinical diagnosis and treatment. A negative test should not prevent treatment initiation if TB is strongly clinically suspected. Clinical diagnosis will remain necessary for many children.

Laboratory

- Ensure that protocols and standard operating procedures are in place for obtaining and transporting specimens from young children. Training and expertise in paediatric phlebotomy and ordering urine bags, gastric washings, sputum induction and stool collection and processing need to be considered.

- Explore the capacity for antibiotic resistance surveillance to ensure that the optimal first-line treatment for severe bacterial infections is being used.

Monitoring and evaluation

- Monitor the potential toxicity of children receiving TB preventive treatment, co-trimoxazole plus antiretroviral therapy (and potentially fluconazole for adolescents).

- Monitoring tools need to be developed for the advanced HIV disease package that are specific to children.

Table 4. Cost implications and considerations for commodities

Medicines (dosage form and pack size)	Reference price excluding transport (USD)	Source[a]
TB and co-trimoxazole preventive therapy in HIV		
Isoniazid, 300-mg tablet, 30	0.75	Global Fund Pooled Procurement Mechanism
Isoniazid, 100-mg tablet, 100[b]	1.29	Global Fund Pooled Procurement Mechanism
Isoniazid, 300-mg tablet, 1000	19.90	Global Fund Pooled Procurement Mechanism
Rifapentine, 150-mg tablet, 24	5.00	Global Fund Pooled Procurement Mechanism
Rifapentine/isoniazid, 300-/300-mg tablet, 36	15.00	Global Fund Pooled Procurement Mechanism
Isoniazid/co-trimoxazole/vitamin B6, 300-/960-/25-mg tablet, 30	1.99	Global Fund Pooled Procurement Mechanism
Co-trimoxazole, 120-mg tablet (dispensed), 100 by 10 blister packs	22.75	USAID Procurement and Supply Management
Cryptococcal disease		
Amphotericin B liposomal, 50 mg for injection, 1 vial	16.25	Global Fund Pooled Procurement Mechanism
Amphotericin deoxycholate, 50 mg, 1 vial	7.13	Global Fund Pooled Procurement Mechanism
Fluconazole, 200-mg capsule, 100	6.20	Global Fund Pooled Procurement Mechanism
Flucytosine, 500-mg tablet, 100	75.00	Global Fund Pooled Procurement Mechanism

Diagnostic tests	Reference price per test excluding transport (USD)	Source
IMMY cryptococcal antigen lateral flow assay	2.50	Global Fund Pooled Procurement Mechanism
VISITECT® CD4 Advanced Disease rapid test	3.98	Global Fund Pooled Procurement Mechanism
TB LAM	3.50	Global Fund Pooled Procurement Mechanism
GeneXpert Xpert® MTB/RIF Assay, 50 cartridges	528.28	USAID Procurement and Supply Management
GeneXpert Xpert® MTB/RIF Ultra Assay, 50 cartridges	499.00	USAID Procurement and Supply Management

[a] Reference pricing from The Global Fund Pooled Procurement Mechanism and USAID Procurement and Supply Management are updated regularly.
[b] The price of child-friendly 100-mg tablets differs.

RESEARCH GAPS

Clinical research

Diagnostics
- Research gaps related to diagnostics in children include the need to develop simplified point-of-care diagnostics for pneumonia, specifically *Pneumocystis* pneumonia and cytomegalovirus disease.

- In addition, the use of rapid molecular tests in stools and other urine LAM assays needs to be further evaluated in children.

Prophylaxis
- Whether there is an optimal package of prophylactic interventions for children living with HIV younger than five years has yet to be determined. This may focus on bacterial infections and specifically on the benefit of azithromycin.

- TB preventive treatment using 3HP and 1HP is currently being studied among younger children. It is especially important to ensure the safe use of rifamycin-containing TB preventive treatment in conjunction with DTG (https://clinicaltrials.gov/ct2/show/NCT03730181 https://www.impaactnetwork.org/studies/IMPAACT2024.asp).

- Research gaps related to prophylaxis include the evaluation of TB preventive treatment among children living with HIV younger than one year.

Treatment
- There is an urgent need to confirm that double-dose DTG will enable therapeutic levels and is safe in children who weigh <25 kg and are co-treated with rifampicin.

- Research gaps related to treatment include the treatment of pneumonia and whether empirical treatment of TB and/or cytomegalovirus should be initiated among children living with HIV who present with severe pneumonia. In addition, the most appropriate timing to initiate antiretroviral therapy during nutritional rehabilitation is also being studied in the EMPIRICAL trial. (EMPIRICAL: https://penta-id.org/hiv/empirical).

- Single-dose liposomal amphotericin B (in addition to flucytosine and fluconazole) is being studied in adults and may have implications for adolescents and older children with cryptococcal meningitis (AMBITION: https://doi.org/10.1186/ISRCTN10248064).

Operational research

- TB diagnosis and prevention is being studied in several countries in Africa in the Catalyzing Pediatric Tuberculosis Innovations programme (https://unitaid.org/assets/Catalyzing-Pediatric-Tuberculosis-Innovations-CaP-TB.pdf). Enhanced early detection of TB is being studied in the TB-Speed study in seven countries in Africa and Asia (https://www.tb-speed.com). A publication on research priorities for children with TB (https://www.treatmentactiongroup.org/publication/research-priorities-for-pediatric-tuberculosis).

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