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.

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.

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/mm^3. 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).