# HIV-Associated Tuberculosis in Adolescents

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Children and adolescents living with HIV continue to be impacted disproportionately by tuberculosis as compared to peers without HIV. HIV can impact tuberculosis (TB) screening and diagnosis by altering screening and diagnostic test performance and can complicate prevention and treatment strategies due to drug–drug interactions. Post-tuberculosis lung disease is an underappreciated phenomenon in children and adolescents, but is more commonly observed in children and adolescents with HIV-associated tuberculosis.

CALHIV tuberculosis HIV child adolescent

## 1. Emerging Epidemiology on Tuberculosis (TB) Risk and Outcomes in High-HIV/TB Burden Settings

The epidemiology of HIV-associated tuberculosis (TB) in children and adolescents continues to evolve along with advances in HIV care guidelines [1]. Despite the widespread introduction of antiretroviral therapy (ART), children and adolescents living with human immunodeficiency virus infection (CALHIV) remains at high risk for HIV associated TB even in cohorts with normal CD4 counts and viral suppression. This ongoing risk was demonstrated in two South African studies. The first demonstrated that adolescents with perinatally acquired HIV had a TB incidence of 2.2/100 person years (PY) (95% confidence interval (CI) 1.6 to 3.1) compared to adolescents without HIV with a TB incidence of 0.3/100 PY (95% CI 0.04 to 2.2); these observations suggest an incidence rate ratio (IRR) of 7.4 (95% CI 1.01 to 53.6) [2]. Although the cohort's median CD4 count was 713 cells/$m^3$ and 76% had a viral load of <40 copies/mL, CALHIV with a CD4 count <500 cells/$m^3$ and a viral load above 1000 copies/mL had an increased risk of TB disease.

Evidence from other African settings also demonstrated the persistent risk of HIV-associated TB despite ART. In a cohort of CALHIV in Ethiopia, ART only reduced the hazard ratio of TB by 36% [3]. The TB incidence rate was 7.7 per 100 person years (95% CI, 6.3–9.2) in CALHIV on ART, similar to 8.2 per 100 person years (95% CI 6.8–9.8) in ART naïve CALHIV. A similar increased risk was observed in a cohort of infants in Kenya were observed in infants with HIV (adjusted hazards ratio (aHR) 4.71 (2.13–10.4) [4]. In a cohort of CALHIV observed in 6 sub-Saharan African countries, increases in ART were associated with declines in TB period prevalence but even with ART coverage nearing 100%, CALHIV still developed TB at approximately 2 per 100 person years [5].

This evidence aligns with data from a recent systematic review indicating that HIV remains a strong risk factor for incident and prevalent TB in children following close TB exposure [6]. Notably, the evidence demonstrates that most cases of TB occurred in the 3 months following exposure. Hence, there is a clear need to develop systems that

rapidly identify CALHIV and those who can benefit from tuberculosis preventive therapy (TPT). As multi-month prescribing for CALHIV is implemented more broadly, programs will need to develop thoughtful screening strategies to identify TB exposure and TB disease early even if children are not presenting on a monthly basis to obtain ARVs.

CALHIV also continue to have worse treatment outcomes than peers without HIV. A South African study compared programmatic TB treatment outcomes in 729,463 children and adolescents with and without HIV and treated for TB between 2004 and 2016 [7]. Although the study demonstrated a decline in the overall case fatality ratio over time, HIV remained a risk factor for mortality (adjusted hazard ratio (aHR) = 5.11 (95% confidence interval 4.71–5.55) even after the initiation of ART. Another study evaluating program data in Kenya (n = 24,214) demonstrated a similar aHR of 4.84 (95% confidence interval 3.59–6.91) among CALHIV not on ART and aHR of 3.69 (95% confidence interval 3.14–4.35) in CALHIV on ART.

Collectively, this data demonstrates that while ART effectively reduces TB risk and improves outcomes among CALHIV in sub-Saharan Africa, the risk remains highly elevated compared to populations without HIV. As a whole, these findings may reflect the persistently high force of TB infection in these settings, as data from low burden settings suggests a more significant decline in HIV-associated TB attributable to ART uptake [8]. This persistent risk of incident TB coupled with an elevated risk of mortality from HIV-associated TB indicates the ongoing need for novel TB screening, diagnostic and preventive strategies for CALHIV. This ongoing risk in CALHIV on ART is unfortunately exacerbated by the high proportion, nearly 50%, of children still not accessing ART globally [9].

There are additional intersections between TB and COVID-19 to be considered. Adult data suggests that TB and HIV are both associated with an increased risk of mortality from COVID-19. Individuals with TB have a 2.7-fold increased risk of COVID-19 mortality (aHR) 2.7, 95% CI 1.8 to 4.0) [10]. Similarly, PLHIV have a 2.1-fold increased risk of COVID-19 mortality (aHR 2.1, 95% CI 1.7 to 2.7). Data from a single center in South Africa reported that only 2 of 62 children hospitalized in the first 6 months of the pandemic had HIV, but surveillance data also from South Africa reports that 50 of 565 (8.8%) adolescents and children who died from COVID-19 also had HIV [11]. This evidence suggests that CALHIV may be over-represented among COVID-19-related deaths in these age groups.

Global TB notification rates declined from 7.2 to 5.9 million in 2020 [12]. These declines in part reflect COVID-19 induced disruptions in TB health services. Nevertheless, it is unclear if masking and social distancing alter adult and children's risk of *Mycobacterium tuberculosis* infection and subsequent disease. Of note, epidemiological data from South Africa shows that pediatric TB diagnosis increases soon after the peak of the epidemiological curve of influenza; it remains to be seen whether an increase may be observed following the COVID-19 pandemic as well [13]. In addition, patients may seek care later. Care at the clinic may be fragmented and diagnostic procedures be delayed for fear of COVID-19, and health care resources may have shifted to COVID-19. Early program data from South African hospitals demonstrate a reduction in TB case notifications and overall pediatric admissions suggesting a change in health seeking behavior and a weakening of existing TB health systems for TB diagnosis [14]. The long-term impact of COVID-19 on TB and HIV-associated TB in children must be watched closely.

## 2. TB Screening

The probability of TB progression and poor outcomes is higher in CALHIV than their peers without HIV, partly due to diagnostic delays and non-specific presentation. One recommended vital strategy for early TB case detection is systematic TB screening, especially for high-risk groups such as CALHIV. However, evidence to inform the design of pediatric TB screening strategies is limited. As a result, the implementation of TB screening in children remains a challenge and has contributed to the significant gap in TB case detection.

Advances in TB screening approaches for children generally lag behind that of adults due to limited evidence, often leading to the adaptation of evidence-based adult recommendations despite differences in disease characteristics. More recently, the World Health Organization recommended that systematic screening for TB disease be conducted using a symptom screen including any one of current cough, fever, poor weight gain, or close contact with a TB patient among children <10 years who are living with HIV at each care encounter. Any child living with HIV with a positive symptom screen should undergo further diagnostic evaluation [15], but programmatic data from Kenya suggests attendance at pediatric-focused HIV clinics may be associated with a lower likelihood of appropriate diagnostic follow up [16]. Additionally, as this approach misses up to 40% of children with HIV-associated TB, research on new strategies for TB screening in this high-risk population is urgently needed [17].

Advancement in HIV care, including the provision of differentiated service delivery approaches, has created new opportunities to effectively integrate TB screening within routine HIV services and ensure uninterrupted care. Similarly, systematic screening for TB disease should be conducted using a symptom screen including any one of cough, fever or poor weight gain; or chest radiography; or both for children <15 years with TB exposure. The yield of symptom screening is higher among close contacts of TB patients than other risk groups. If available, CXR may be used as a TB screening tool for children <15 years with TB exposure [18]. Direct comparisons of these strategies in CALHIV were not performed. The use of C-reactive protein in TB screening is currently limited to adolescents and adults living with HIV [15]. Commercially available tests of TB infection (TST and IGRA) cannot differentiate between TB infection and disease, may be affected by conditions unrelated to TB infection, and are often inaccessible in TB high-burden settings. Hence, tests of infection have a limited role in TB screening in high-burden settings, particularly among CALHIV.

## 3. Prevention Strategies in the Context of Anti-Retroviral Therapy

The elevated TB risk among CALHIV despite anti-retroviral therapy (ART) indicates the ongoing need for effective and widespread implementation of TB preventive treatment (TPT) in this population. Data on drug–drug interactions between rifamycins and dolutegravir is urgently needed so that CALHIV may also benefit from the increasing availability of shorter TPT treatment regimens. Recent data suggests that 1 month of isoniazid and rifapentine is safe and feasible in children and adolescents two years and above [19]. This data, combined with efficacy data in adults living with HIV suggests that this very short TPT regimen, is appropriate for CALHIV [20].

However, there is limited evidence to inform whether adjustments in dolutegravir dosing are needed in children receiving daily or weekly rifapentine for TPT.

While more data is needed to optimize TPT delivery for CALHIV, existing data on TPT uptake and completion is encouraging. While TPT uptake is more robust in adults than children, rates of TPT adherence and completion have been quite good when evaluated within observational cohorts of CALHIV. Evidence demonstrates that differentiated service delivery models, TPT education, and seamless integration with HIV care are important predictors of TPT completion [21][22][23]. Given persistently high rates of TB disease among CALHIV, TPT scale up is essential and will benefit from shorter TPT regimens, child-friendly formulations, and patient-centered TPT administration integrated within ART to minimize increased burden on patients and health systems.

## 4. Diagnostic Strategies for HIV-Associated TB

The TB case detection gap in CALHIV remains problematic and is exacerbated by the COVID-19 pandemic [12]. However, new developments in diagnostics may reduce this gap. Building on years of work supporting the value of stool and nasopharyngeal aspirates for child TB diagnosis, the WHO now endorses both specimen types for TB diagnosis in CALHIV [24][25]. Stool specimens and nasopharyngeal aspirates have similar sensitivity to respiratory specimens when combined or only slightly lower than respiratory specimens as stand-alone tests. However, as these specimens are easier for nurses to collect and require less equipment, more children, including CALHIV, should be evaluated for TB. Additional implementation science work is urgently needed to evaluate the impact of collecting these non-traditional specimens in CALHIV. New diagnostic approaches will certainly be needed as only a small minority of CALHIV on TB treatment have a confirmation by Xpert [25]. Additionally, there is emerging data for urine as a useful specimen for TB diagnosis with the new SILVAMP-LAM point-of-care assay.

One report from a South African pediatric cohort demonstrated a 24% increase in sensitivity in CALHIV (60%, 95%CI 40.7–76.6 for SILVAMP-LAM vs. 36%, 95%CI, 20.2–55.5 for Alere-LAM) against a microbiologic reference standard [26]. SILVAMP-LAM performed equally well in stored urine specimens from 4 African pediatric TB clinics. Sensitivity was 64.9%, 95% CI 43.7–85.2; positive in 40 of 63 confirmed samples versus 30.7% (95% CI 8.6–61.6; 19 positive of 63 confirmed samples) for Alere-LAM [27]. The specificity was similar for both tests in each study; however, additional data using prospectively collected specimens is needed to confirm these promising results.

While new bacteriological tests are important, they are unlikely to identify all cases of paucibacillary TB in CALHIV. Fortunately, emerging approaches to support clinical diagnosis have great promise. Leveraging data from a diagnostic study of 438 CALHIV, a treatment-decision score was developed based on detailed symptom assessments and radiographic data, including CXR and ultrasound; the resultant score had an AUC of 0.861 with a sensitivity of 88.6% and a specificity of 61.2% compared to a composite tuberculosis diagnosis using the NIH consensus definitions [28]. Although CXR was an important component of the algorithm, many high-risk children with exposure to TB and prolonged TB symptoms, can be diagnosed correctly with this algorithm without a CXR. Further, it is also been highlighted poor agreement between local radiologists, pediatric pulmonologists and pediatric radiologists and limited overall diagnostic accuracy (55.3%) in CALHIV [29]. Hence, while CXR may play a

role in TB screening or diagnosis for CALHIV, new strategies, perhaps including computer aided detection, are needed to increase the accuracy of this important tool. Preliminary data on complementary approaches using monocyte-to-lymphocyte ratios as a diagnostic aid also merits additional exploration [30].

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