Diagnostic and Management Challenges for Childhood Tuberculosis in the Era of HIV

B. J. Marais, S. M. Graham, M. F. Cotton, and N. Beyers

1Desmond Tutu TB Centre, Ukwanda Centre for Rural Health and the Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa; 2Malawi-Liverpool-Wellcome Trust Programme of Tropical Clinical Research and 3Department of Paediatrics, College of Medicine, University of Malawi, Blantyre, Malawi

The diagnosis and management of childhood tuberculosis (TB) pose substantial challenges in the era of the human immunodeficiency virus (HIV) epidemic. The highest TB incidences and HIV infection prevalences are recorded in sub-Saharan Africa, and, as a consequence, children in this region bear the greatest burden of TB/HIV infection. The tuberculin skin test (TST), which is the standard marker of Mycobacterium tuberculosis infection in immunocompetent children, has poor sensitivity when used in HIV-infected children. Novel T cell assays may offer higher sensitivity and specificity than the TST, but these tests still fail to make the crucial distinction between latent M. tuberculosis infection and active disease and are limited by cost considerations. Symptom-based diagnostic approaches are less helpful in HIV-infected children, because of the difficulty of differentiating TB-related symptoms from those caused by other HIV-associated conditions. Knowing the HIV infection status of all children with suspected TB is helpful because it improves clinical management. HIV-infected children are at increased risk of developing active disease after TB exposure/infection, which justifies the use of isoniazid preventive therapy once active TB has been excluded. The higher mortality and relapse rates noted among HIV-infected children with active TB who are receiving standard TB treatment highlight the need for further research to define optimal treatment regimens. HIV-infected children should also receive appropriate supportive care, including cotrimoxazole prophylaxis, and antiretroviral therapy, if indicated. Despite the difficulties experienced in resource-limited countries, the management of children with TB/HIV infection could be vastly improved by better implementation of readily available interventions.

The highest tuberculosis (TB) incidences occur in sub-Saharan Africa, where the TB epidemic is fueled by poverty [1], war [2], and, in particular, the human immunodeficiency virus (HIV) epidemic [3–5]. Children in this area carry a huge burden of TB disease, which is rarely appreciated because of diagnostic difficulties and poor record keeping. The present article provides an overview of childhood TB in the era of HIV and focuses, in particular, on the most important diagnostic and management challenges.

EPIDEMIOLOGIC PROFILE

Of the ~8.3 million new TB cases diagnosed globally in 2000, it is estimated that 884,019 (11%) occurred among children, with the highest burden noted in areas of endemicity [6–9]. Childhood TB reflects recent transmission, and, therefore, the burden of childhood TB provides an accurate measure of the level of TB control achieved in a particular community [10, 11]. A survey conducted in Cape Town, South Africa, in...
dicated that 13.7% of cases entered into the TB register were found among children <13 years of age; after validation of the TB diagnosis, the corrected incidence of childhood TB in this community was calculated to be 407 cases/100,000 population/year [7].

Because children rarely develop sputum smear–positive TB, they often are excluded from recording and reporting practices in areas of endemicity, where, in an effort to contain the epidemic, TB control efforts are primarily focused on the most-infectious cases. Recent guidelines from the World Health Organization (WHO) made 2 important recommendations regarding recording and reporting practices: national TB programs should report HIV-related information for all individuals with TB [12], as well as information on TB in children [13]. Following these recommendations should provide important data for future monitoring and evaluation purposes, although the uncertainty of a TB diagnosis will remain a problem, particularly in HIV-infected children.

The incidence of TB is low among HIV-infected children living in areas where the TB epidemic is well controlled, such as the United States [14]. In the early stages of the HIV epidemic, evidence was conflicting, with there being uncertainty as to how common TB was among HIV-infected children. Initial autopsy studies indicated that TB was uncommon among HIV-infected children [15], whereas clinical studies reported a high prevalence of HIV among children with TB diagnosed, primarily using clinical and radiologic criteria [16, 17]. More recent autopsy studies involving large numbers of children with confirmed TB in Zambia, Ethiopia, and South Africa demonstrated high rates of TB-related morbidity and mortality among HIV-infected children [18–20], with an estimated 20-fold increase in the TB incidence noted among HIV-infected children, compared with that noted among HIV-uninfected children [21]. In a recent prospective study conducted in the Western Cape, 23.4 cases of active TB were recorded per 100 HIV-infected children per year [22]. The high TB incidence among HIV-infected children may be explained by (1) an increased risk of TB exposure and/or (2) an increased risk of progression to active disease after infection.

Exposure. The TB/HIV epidemic has important consequences that affect, in a number of ways, the risk of TB developing in children. The HIV epidemic has caused a marked increase in the incidence of sputum smear–positive TB and a decrease in the peak age prevalence, so that the highest incidence of infectious TB cases now occurs among young adults (age, 20–35 years) [23, 24], who often are parents of young children. Furthermore, the high prevalence of TB and HIV infection among adults in their reproductive years implies that children are at risk for both TB and HIV infection and that HIV-infected children are more likely to be exposed to TB than are HIV-uninfected children.

The overall effect of HIV on TB transmission within communities remains uncertain. Among South African gold miners, the prevalence of HIV infection had a much bigger influence on TB incidence than on the point prevalence of TB, suggesting that the incident cases (more likely to be HIV-infected individuals who present early) contribute less to the overall transmission of TB than do the prevalent cases (more likely to be HIV-uninfected individuals who present late). Prevalent cases may remain undetected for prolonged periods, during which time they actively contribute to TB transmission within the community [25]. Even though HIV-infected adults more often have sputum smear–negative TB, they still pose a considerable risk of transmission (table 1). In addition, reports from Tanzania and Botswana indicate that many HIV-infected adults have sputum smear–positive TB and/or receive a TB diagnosis only after having had symptomatic disease for a considerable period of time, contradicting the observations made in gold miners where more active disease surveillance is practiced. This indicates that HIV-infected patients with TB make a considerable contribution to TB transmission in endemic areas [29, 30].

After TB exposure, the TST is generally used to diagnose M. tuberculosis infection, but it has important limitations:

1. Conversion may be delayed for up to 3 months after infection [10].
2. There is an inability to indicate when primary infection occurred or to register reinfection [31].
3. There is poor sensitivity in immunocompromised children [32].
4. There is reduced specificity because of environmental mycobacteria and cross-reaction with bacille Calmette-Guérin (BCG), although this is less of a confounding factor in countries where TB is endemic and where BCG is given during the neonatal period [33].

Disease. The most important determinants of a child’s risk of developing TB after primary infection are age, with the highest risk occurring in children with an immature immune system (children <3 years of age), and the immune status of the child [10]. The comparative risk of an HIV-infected child developing TB is mainly influenced by the degree of immunocompromise and/or the severity of HIV disease. In a prospective study from Côte d’Ivoire, the risk of TB was 4 times higher in children with a CD4 cell percentage of <15% than in children with a CD4 cell percentage of ≥15%, and it was 3 times higher when the plasma HIV RNA level at baseline was >5 × 10 log10 copies/mL [34].

DIAGNOSIS

Diagnosis of childhood TB presents a major challenge, because bacteriologic confirmation is rarely achieved [35]. Sputum smear microscopy is often the only diagnostic test available, but positive findings are noted for <10%–15% of children with
From TB infection to active disease, by age group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pulmonary Disease</th>
<th>Disseminated (miliary) disease or TBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>50</td>
<td>10–20</td>
</tr>
<tr>
<td>1 to &lt;2 years</td>
<td>75–80</td>
<td>10–20</td>
</tr>
<tr>
<td>2 to &lt;5 years</td>
<td>95</td>
<td>2</td>
</tr>
<tr>
<td>5 to &lt;10 years</td>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>≥10 years</td>
<td>80–90</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

NOTE. TBM, tuberculous meningitis.

a The risks of infection, in the absence of treatment of the index case, were derived from the prechemotherapy literature [28]. The risk is best quantified for household exposure; however, in countries where there is a high burden of TB infection, the majority of transmissions of TB infection may occur outside the household [27, 28].

b The majority of infection occurs within the first 3 months of the onset of symptoms in the index case.

c With pulmonary TB diagnosed by culture or chest radiography.

d Risk estimates were based on the natural history of TB in children; more recent studies suggest that immunocompromised children experience a risk similar to that noted for very young (defined by a immature immune system) children (age, <2 years) [10]. The risk of disease progression is quantified after primary infection; little is known about the risk associated with reinfection.

probable TB [35–37]. The yield from culture of 2–3 gastric aspirate samples obtained during fasting is ~30%–40% [35–37], although higher yields have been reported in cultures performed in children with advanced disease [38]. Alternative methods of sample collection include nasopharyngeal aspiration (which provides a 30% yield vs. the 38% yield noted with gastric aspiration) [39], hypertonic saline–induced sputum collection (with 1 sample providing the same yield provided by 3 gastric aspirate specimens) [36], and the string test (which provides an improved yield, compared with that of sputum induction in adults with sputum smear-negative pulmonary TB) [40]. A recent study from Peru demonstrated that the string test is well tolerated in children as young as 4 years of age [41], but additional studies are needed to establish the feasibility and
The diagnosis of latent TB infection (LTBI) in HIV-infected children is important because of the high risk of disease progression and the well-documented benefits of IPT in adults with LTBI [67, 68]. IPT eradicates existing TB bacilli but does not protect against future reinfection, which probably explains the waning of its beneficial effect after 2–3 years in areas of endemicity. The TST is used to identify LTBI but has greatly reduced sensitivity in HIV-infected children. Therefore, it seems warranted to recommend IPT for any HIV-infected child with significant exposure to an adult with pulmonary TB, irrespective of the child’s age or TST result, once active TB has been considered and excluded.

The effect of providing IPT to all HIV-infected infants in an area where TB is endemic was recently explored in a randomized controlled trial [22]. The placebo arm of the study was discontinued after interim analysis of the first 263 HIV-infected children who were evaluated, 132 (50.2%) of whom had been assigned to receive isoniazid. The mortality rate was significantly lower in the group receiving isoniazid (8.3%) than in the group receiving placebo (16%), according to intent-to-treat analysis (odds ratio [OR], 0.46 [95% confidence interval [CI], 0.22–0.95]). The incidence of confirmed or probable TB was also significantly lower among individuals receiving isoniazid (4.5%) than among those receiving placebo (9.2%; OR, 0.37 [95% CI, 0.14–0.97]), but this did not explain the difference in mortality. A second randomized controlled trial is currently under way to assess the effect of isoniazid prophylaxis on TB and all-cause mortality among infants infected with or exposed to HIV.

There are concerns that IPT may promote the development of drug resistance; therefore, an important prerequisite for IPT is the exclusion of active TB disease. Providing IPT to young children poses a negligible risk, because these children tend to develop paucibacillary disease and contribute little to disease transmission. However, providing IPT to adolescents and adults poses a considerably higher risk, because these individuals frequently develop cavitary disease with high organism loads, increasing the risk of acquiring random drug resistance and transmitting disease within the community. A recent survey (conducted in 2003–2005) from South Africa reported isoniazid resistance in 40 (12.4%) of 323 pediatric TB cultures, which is a significant increase compared with that noted in a previous survey (conducted in 1994–1998) that documented isoniazid resistance in 21 (6.9%) of 306 pediatric TB cultures [69]. This raises concern about the continued efficacy of isoniazid monotherapy and the transmission of drug-resistant TB in areas of endemicity.

**Curative treatment.** The main variables that influence the success of chemotherapy, apart from primary drug resistance, are the bacterial load and the anatomical distribution of bacilli. For treatment purposes, the wide spectrum of pathologic find-
Table 2. Various childhood tuberculosis (TB) disease groups, together with the treatment rationale and current American Thoracic Society (ATS) treatment guidelines applicable to each group.

<table>
<thead>
<tr>
<th>TB disease group</th>
<th>Treatment rationale</th>
<th>ATS treatment guidelinesa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure/LTBI</td>
<td>Preventive therapy</td>
<td>6- to 9-month regimen of INH</td>
</tr>
<tr>
<td>All children ≤5 years of age, including all HIV-infected children</td>
<td>Relatively high risk of disease progression after infection; low organism load</td>
<td></td>
</tr>
<tr>
<td>Active disease</td>
<td>Curative treatment</td>
<td></td>
</tr>
<tr>
<td>Children with sputum smear–negative TB</td>
<td>Low organism load; good drug penetration</td>
<td>2-month regimen of INH, RIF and PZA/4-month regimen of INH and RIF</td>
</tr>
<tr>
<td>Children with sputum smear–positive TB</td>
<td>High organism load; good drug penetration</td>
<td>2-month regimen of INH, RIF, PZA, and ETH/4-month regimen of INH and RIF</td>
</tr>
<tr>
<td>Children with disseminated (miliary) TB</td>
<td>High organism load; variable CNS penetration</td>
<td>2-month regimen of INH, RIF, PZA, and ETH/7- to 10-month regimen of INH and RIF</td>
</tr>
</tbody>
</table>

NOTE. CNS, central nervous system; ETH, ethambutol; INH, isoniazid; LTBI, latent TB infection; PZA, pyrazinamide; RIF, rifampin.

a See [71].

b Children <3 years of age were at highest risk.

c Irrespective of age.

d Treatment forms part of the directly observed therapy, short course (DOTS) strategy and all curative treatment should be given as directly observed therapy [71].
3. Misdiagnosis of TB in children with HIV-related lung disease, such as lymphocytic interstitial pneumonitis, bronchiectasis, or Kaposi sarcoma [58]
4. The presence of underlying chronic lung disease resulting in poor penetration of drugs into fibrotic or bronchiectatic areas [80]
5. Poor adherence to treatment because of chronic illness or the death of the parent responsible for the child’s treatment
6. Advanced immunosuppression and severe malnutrition

In adults, a large proportion of TB/HIV-related deaths occur during the first couple of months after TB therapy has commenced [5]. The exact reasons for this are not completely understood, but the situation in children seems to be similar to that in adults [9].

Drug interactions. TB is frequently the presenting disease in children with previously undiagnosed HIV infection who may have advanced HIV disease requiring ART. The Centers for Disease Control and Prevention (CDC) has established guidelines for initiating ART in adults presenting with TB and for initiating anti-TB treatment in those already receiving ART. These guidelines are revised on a regular basis (see the relevant CDC Web site for the latest recommendations [83]). No pediatric guidelines are provided, but the main issues (when to initiate ART, drug-drug interactions, overlapping adverse effects, and adherence concerns) are probably similar to the main issues in adults. Because, for both HIV infection and TB, the highest mortality rate is noted among children <1 year of age, most clinicians caring for these very young children would initiate ART within days of the initiation of anti-TB treatment. In older children, in the absence of severe immunosuppression, it is reasonable to complete the anti-TB treatment first, but there is a need for more data to optimally define when to initiate ART in children with TB.

Significant drug interactions occur between the rifamycins, especially rifampin, and some of the nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and/or protease inhibitors (PIs). Rifampin is regarded as being compatible with all nucleoside reverse-transcriptase inhibitors (NRTIs), although it promotes the glucuronidation and elimination of zidovudine. Abacavir, another NRTI that has been used in triple-NRTI regimens, is also eliminated by glucuronidation. Little pharmacokinetic information is available on the interaction of these drugs, but numerous studies are ongoing. Although use of a triple-NRTI regimen is considered to be an option in patients receiving anti-TB treatment, the regimen has not performed well in comparative efficacy studies [84, 85]. Current recommendations are to retain a double-NRTI backbone in combination with efavirenz (a NNRTI) or ritonavir (a PI), because the levels of these 2 drugs are least affected by rifampin. An alternative to PI therapy is to boost lopinavir/ritonavir treatment with additional ritonavir [86].

OTHER HIV-RELATED ISSUES

TS prophylaxis. TS prophylaxis has proven benefit in reducing the risk of *Pneumocystis jiroveci* pneumonia, invasive bacterial infections, and malaria in HIV-infected adults and children [87–90]. A randomized controlled trial of TS prophylaxis in HIV-infected Zambian children of ≥2 years of age showed a significant survival benefit [90]. Routine TS prophylaxis is now recommended by the WHO for all HIV-infected children, including those with TB [91]. TS prophylaxis is also recommended for HIV-exposed infants, because *P. jiroveci* pneumonia is common in that age group [58].

Immune reconstitution inflammatory syndrome (IRIS). Transient worsening of such symptoms as fever, increasing lymphadenopathy, exacerbation of intracerebral tuberculomas, pleural effusions, and even adult respiratory distress syndrome have been reported after the initiation of ART in severely immunocompromised patients [92–96]. This temporary exacerbation of TB symptoms and signs is mainly ascribed to the effects of immune reconstitution, although a “hypersensitivity” reaction to antigens released by killed TB bacilli may also contribute. It does not indicate treatment failure and usually subsides spontaneously, although severe cases may require treatment with corticosteroids. In a recent prospective survey, IRIS was documented in 19% of 152 Thai children with low CD4 cell percentages (<15%), usually within 4 weeks of initiation of ART. The majority of cases of IRIS were due to atypical mycobacteria. Only 3 of 14 mycobacterial infections were due to *M. tuberculosis*, and 2 were due to BCG [97]. Two recent reports also documented IRIS due to *Mycobacterium bovis* BCG in HIV-infected children in whom ART was initiated [98, 99].

BCG vaccination. BCG offers variable protection in different settings, but it is generally accepted that BCG offers significant protection against disseminated (miliary) disease in young HIV-uninfected children (those <2 years of age) [100–102]. Because of suboptimal immune responses, the protection provided to HIV-infected children by BCG vaccination is uncertain and poses a considerable risk of disseminated BCG disease [103]. In addition, BCG vaccination could theoretically accelerate the progression of HIV disease, as has been suggested by studies of simian immunodeficiency virus–infected macaques [104]. However, whether chronic immune stimulation induces progression of HIV disease in HIV-infected infants is unknown, and active TB does not seem to affect HIV loads to a significant degree [105]. In the absence of a comprehensive risk-benefit analysis, the WHO advises that all asymptomatic HIV-exposed infants in TB-endemic areas should receive BCG vaccination, as well as careful monitoring for the development of BCG-related disease [106].
Other mycobacteria. Clinically relevant disease due to environmental or nontuberculous mycobacteria is well documented in HIV-infected adults, and its clinical impact seems to be underestimated [107–109]. Apart from the documentation of M. bovis disease, there are very limited data available on the prevalence of disease caused by nontuberculous mycobacteria in HIV-infected children. In a report from Côte d’Ivoire, it was noted that 4 HIV-infected children had disease due to Mycobacterium avium—Mycobacterium intracellulare complex [110], but this finding has not been reported in autopsy studies and is likely to be uncommon in HIV-infected children from African countries.

Perinatal infection. In sub-Saharan Africa, many women in their reproductive years have both TB and HIV infection. Maternal TB is a cause of increased maternal mortality [111–115]. Maternal TB [116] and/or HIV infection [117] also has adverse effects on perinatal outcomes, with increased prematurity and low birth weight and increased neonatal mortality rates noted, whereas severe and rapid progression of HIV disease have been reported in neonates with TB and HIV coinfection [118]. In the Western Cape, TB exposure was documented in 77 (10.1%) of 766 HIV-exposed infants who underwent screening tests for enrollment into a prospective study [119].

Except for streptomycin, which may affect the hearing of the infant, first-line TB drugs have few adverse effects during pregnancy. The combination of both anti-TB medication and ART during pregnancy is more complicated, but ART has proven efficacy in reducing the vertical transmission of HIV and is routinely used during pregnancy in many countries. Efavirenz is the only antiretroviral drug with documented teratogenicity, and it should be avoided in the first trimester of pregnancy. Active TB case finding may be considered in all HIV-infected pregnant women presenting for antenatal care, in an attempt to decrease the perinatal risks for mother and infant.

The management of an infant born to a mother who has TB and HIV coinfection is complex; the first principle is to ensure that the mother is receiving optimal treatment and to regard the infant as being at risk for TB, HIV infection, and other congenital infections. Counseling and preventive measures to reduce the risk of transmission of HIV to the infant are needed in addition to appropriate HIV-related care. The possibility of active TB in the infant needs to be considered, and the disease should be treated. If the infant does not have active TB, then IPT is required if the mother is symptomatic or has been receiving anti-TB treatment for <2 months.

CONCLUSION

The major burden of TB in HIV-infected children occurs in areas where both diseases are common in adults. The diagnosis of TB infection and disease in HIV-infected children is particularly difficult. Routine HIV testing is an important part of the diagnostic workup, because knowledge of the HIV infection status of the child will guide clinical management. In addition to IPT or treatment for TB, other interventions, such as cotrimoxazole prophylaxis and ART, can benefit the child with TB/HIV infection. Although there are major diagnostic and therapeutic challenges, particularly in resource-limited countries, the management of children with TB/HIV infection could be vastly improved by better implementation of readily available interventions.

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