Prevalence, Characteristics, Management, and Outcome of Pulmonary Tuberculosis in HIV-Infected Children in the TREAT Asia Pediatric HIV Observational Database (TApHOD)

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Abstract

A multicenter, retrospective, observational study was conducted to determine prevalence, characteristics, management, and outcome of pulmonary tuberculosis (PTB) in Asian HIV-infected children in the TREAT Asia Pediatric HIV Observational Database (TApHOD). Data on PTB episodes diagnosed during the period between 12 months before antiretroviral therapy (ART) initiation and December 31, 2009 were extracted. A total of 2678 HIV-infected children were included in TApHOD over a 13-year period; 457 developed PTB, giving a period prevalence of 17.1% (range 5.7–33.0% per country). There were a total of 484 PTB episodes; 27 children had 2 episodes each. There were 21 deaths (4.3%). One third of episodes ($n = 175/484$) occurred after ART initiation at a median of 14.1 months (interquartile range [IQR] 2.5–28.8 months). The median (IQR) CD4+ values were 9.0% (3.0–16.0%) and 183.5 (37.8–525.0) cells/mm³ when PTB was diagnosed. Most episodes ($n = 424/436$, 97.3%) had abnormal radiographic findings compatible with PTB, whereas half ($n = 267/484$, 55.2%) presented with clinical characteristics of PTB. One third of those tested ($n = 42/122$, 34.4%) had bacteriological evidence of PTB. Of the 156 episodes (32.2%) that were accompanied with extrapulmonary TB, pleuritis was the most common manifestation (81.4%). After treatment completion, most episodes ($n = 396/484$, 81.9%) were recorded as having positive outcomes (cured, treatment completed and child well, and improvement). The prevalence of PTB among Asian HIV-infected children in our cohort was high. Children with persistent immunosuppression remain vulnerable to PTB even after ART initiation.

Introduction

TUBERCULOSIS (TB) HAS BECOME a major public health concern worldwide with the greatest burden in sub-Saharan Africa and Asia.¹ The pandemic of HIV causing AIDS

is the major contributor in increasing the incidence and mortality of TB.² Approximately one third of people living with HIV are co-infected with TB.³ Most of them live in resource-limited countries, especially in sub-Saharan Africa and Asia, with the highest point prevalences being 78% and 15%, respectively.⁴

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TB is the most common opportunistic infection in HIV-infected individuals, and a major cause of death.² Because of the progressive suppression of cell-mediated immunity in HIV-infected patients, their immune systems cannot limit the multiplication and dissemination of *Mycobacterium tuberculosis* after primary infection, increasing the risk of multifocal TB disease.² Moreover, HIV increases the vulnerability to both new infection and reinfection, the likelihood of reactivation, and the progress from latent TB infection to active disease.^{5,6} An earlier study demonstrated that HIV-infected individuals co-infected with TB have a 5–15% annual risk and a 50–60% lifetime risk of developing TB disease compared with HIV-uninfected individuals, who have only a 10% lifetime risk.³

HIV-infected children, especially those with low CD4+ cell counts, demonstrate greater morbidity from TB than do HIV-uninfected children, because of atypical manifestations, increased tendency for extrapulmonary TB (EPTB) and disseminated TB,^{7,8} rapid disease progression,⁹ and suboptimal treatment responses.^{10–14} The mortality among HIV-infected children co-infected with TB ranges from 20% to 35%.^{11–14} When compared with HIV-uninfected children, HIV-infected children have a six-times higher risk of TB-related death.^{9,15}

Antiretroviral therapy (ART) has become increasingly available in Asia since 2002, but <50% of children in the region who were eligible for treatment in 2011 received it.¹⁶ There was a study showing that the incidence of TB is decreased by twofold among HIV-infected children receiving ART in sub-Saharan Africa.¹⁷ However, adherence to treatment in HIV-infected individuals co-infected with TB remains a serious challenge in such region.^{18,19} Family support, which was widely documented as a tool for increasing adherence,^{18,20,21} may have negative impact depending upon the patient's interpretation of the support givers' motives.²² This finding could be an issue in Asian regions as well. To date, there are limited published data regarding outcomes of pediatric co-infection in Asian countries. This study aimed to determine the prevalence, characteristics, diagnosis, management, and outcomes of pulmonary TB (PTB) in HIV-infected children in a regional observational cohort in Asia.

Patients and Methods

Study population

The TREAT Asia Pediatric HIV Observational Database (TApHOD) is a longitudinal, observational cohort study of infants and children living with HIV in the Asia region. The study is coordinated by TREAT Asia/amfAR (Bangkok, Thailand) with data management support from the Kirby Institute for infection and immunity in society (Sydney, Australia). Data collection methods have been described elsewhere.²³ Briefly, participating sites collect demographic, treatment, and clinical data as part of the routine clinical care of HIV patients, and transfer them to the Kirby Institute every 6 months for further analysis. TApHOD clinical sites are primarily public tertiary care hospitals based in urban settings in Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam. Of 17 data-contributing clinical programs, 10 participated in this TB sub-study. Institutional Review Board approval was obtained at all participating clinical sites, and the coordinating and data management centers.

Data collection

This was a multicenter retrospective study. All subjects <18 years of age in the cohort during the study period were assessed for a previous history of PTB. The retrospective review for each child covered the period between 12 months prior to his/her ART initiation and December 31, 2009. Children with PTB episode(s) with or without EPTB that occurred during the specified period were included in the analysis. Children with EPTB alone were not included in this study because of the small number of bacteriologically or pathologically confirmed cases. Demographic data, HIV clinical staging, ART, PTB characteristic features, methods for diagnosis, laboratory results, management, and outcomes until TB treatment completion or death were assessed and recorded. De-identified data were entered into a standardized Microsoft Access file and submitted to investigators at the Chiang Mai University site for data cleaning, linkage to the main database, and analysis.

Definitions and classifications

PTB was defined as TB disease that involved lung parenchyma with or without other organ involvement.²⁴ The characteristic features of PTB were divided into five groups as follows. Group 1, based on *clinical characteristics*, where a child presented with a persistent cough and/or other constitutional symptoms, including but not limited to prolonged fever, night sweats, weight loss, failure to thrive, or other organ-specific symptoms (e.g., abdominal pain) for >2 weeks; Group 2, based on *bacteriological evidence of PTB*, where a child had positive acid-fast bacilli (AFB) sputum smear(s) and/or positive TB culture and/or positive polymerase chain reaction (PCR); Group 3, based on *abnormal radiographic/imaging findings of PTB*, where single or multiple diagnostic imaging studies (e.g., radiographs, computerized tomography [CT], magnetic resonance imaging [MRI], ultrasound) were consistent with PTB; Group 4, based on *positive tuberculin skin test (TST)*, with skin induration of ≥5 mm in diameter after purified protein derivative (PPD) test; and Group 5, based on *immune reconstitution syndrome (IRIS)*, where the PTB episode was recorded within the first 6 months after ART initiation in a child who demonstrated immunological and/or virological recovery.²⁴

The diagnosis of each PTB episode was modified from the World Health Organization (WHO) 2003 guidelines²⁵ as follows: (A) *suspected case of PTB*, where a child presented with Group 1 clinical features only; (B) *probable case of PTB*, where a child was diagnosed by a clinician using Group 1 characteristic features together with characteristic features in at least one of the three other groups (Group 3 to Group 5); and (C) *confirmed case of PTB*, where a child had a positive bacteriological evidence of PTB (Group 2).

The site of TB disease was defined as (1) *PTB*, which referred to disease involving the lung parenchyma only; and (2) *PTB with EPTB*, which referred to disease involving both the lung parenchyma and other organs/sites such as the pleura, lymph nodes, gastrointestinal tract, genitourinary tract, skin, joints, bone, or meninges, according to WHO 2008 guidelines.²⁴ Additionally, PTB was classified as smear-positive PTB, when one or more initial sputum smear examinations were positive for AFB by microscopy; and smear-negative PTB, where a case of PTB did not meet the above definition of smear-positive PTB.²⁴

The category of each episode at diagnosis was classified according to WHO 2008 guidelines²⁴ as (1) *new diagnosis*, when a child had never had treatment for PTB or when he/she had taken anti-TB drugs for <1 month; (2) *relapse*, when a child had previously been treated for TB, had been declared cured or treatment had been completed, and was again diagnosed with bacteriologically positive TB; (3) *treatment after failure*, when a child was started on a re-treatment regimen after previous treatment had failed; (4) *treatment after default*, when a child returned to treatment with positive bacteriology, following interruption of treatment for ≥ 2 months; and (5) *transfer in*, when a child had been transferred from another TB register to continue treatment in a different area.

The outcome of each PTB episode was assessed at the end of PTB treatment and was characterized using modified WHO 2008 guidelines²⁴ as (1) *cure*, where there was good clinical response to treatment and follow-up cultures/smears were negative for an episode of bacteriologically confirmed TB; (2) *treatment completed and child well*, where there was good clinical response to treatment for an episode that did not have bacteriological confirmation, or where follow-up cultures/smears were not available; (3) *improvement*, where some symptoms persisted but the child was assessed as clinically better than at the time of TB diagnosis; (4) *no improvement*, where the original symptoms persisted or worsened; (5) *death*, where a child died from any cause during the course of treatment; (6) *defaulted*, where treatment was interrupted for ≥ 2 consecutive months; and (7) *transferred out*, where the child was transferred to a health facility in another clinical management site and for whom the treatment outcomes were not known. Children who were within the *cure*, *treatment completed and child well*, and *improvement* categories were defined as having positive outcomes, and children who were categorized as having had *no improvement* or *death* were defined as having negative outcomes.

Adverse events (AE) of anti-TB drugs resulting in the modification or discontinuation of PTB treatment are identified according to WHO 2003 guidelines.²⁵ The severity of

AEs was classified according to the United States National Institutes of Health Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version 1.0).²⁶

Statistical analysis

Data on PTB episodes were analyzed using Stata software, version 12.0 (StataCorp LP, College Station, TX). Demographic characteristics were reported as medians (IQR) or proportions, as appropriate. The comparison of characteristics between children who had PTB before ART initiation (pre-ART) and those who had PTB after ART initiation (post-ART) were performed using χ^2 or Fisher's exact tests for categorical data, and Mann-Whitney *U* test for continuous data. A *p* value of <0.05 was considered statistically significant.

Results

Prevalence of PTB

During the 13 year period (May 1997 to December 2009), a total of 2678 HIV-infected children were enrolled in TAPHOD, of whom 457 children developed PTB, giving an overall period prevalence of 17.1%. The prevalence of PTB for each participating country was 31.9% (*n*=131/411) for India, 33.0% (*n*=57/175) for Indonesia, 14.1% (*n*=252/1,794) for Thailand, and 5.7% (*n*=13/248) for Malaysia.

Demographic characteristics of the study population

Four hundred and fifty-seven children contributed 484 PTB episodes; 430 children had one episode, and 27 children had 2 episodes (Table 1). The median age of children at the time of PTB diagnosis was 6.4 (IQR 3.7–8.8) years, with a female-to-male ratio close to 1. The majority of children (94.8%) had advanced HIV disease by WHO stage at the time of PTB diagnosis; 175 (36.2%) episodes were in those who had already initiated ART by the time of PTB diagnosis. In these children, the median time from ART commencement to PTB diagnosis

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF HIV-INFECTED CHILDREN CO-INFECTED WITH PULMONARY TUBERCULOSIS, STRATIFIED BY PRE-ART AND POST-ART EPISODES

Demographic characteristics ^a	Pre-ART episodes, n (%)	Post-ART episodes, n (%)	Total, n (%)	p Value
Total	309 (100)	175 (100)	484 (100)	
Age (years), median (IQR)	5.8 (3.3–8.4)	7.63 (4.9–9.5)	6.4 (3.6–8.8)	<0.01
Male sex	162 (52.4)	86 (49.1)	248 (51.2)	0.49
WHO clinical stage	309	174	483	<0.01
Stage 1	2 (0.7)	1 (0.6)	3 (0.6)	
Stage 2	14 (4.5)	8 (4.6)	22 (4.6)	
Stage 3	268 (86.7)	122 (70.1)	390 (80.7)	
Stage 4	25 (8.1)	43 (24.7)	68 (14.1)	
CD4+ values				
Number tested	114	127	241	
Percentage, median (IQR)	10.5 (4.3–16.7)	8.0 (2.4–16.0)	9.0 (3.0–16.0)	0.23
Cell count (cells/mm ³), median (IQR)	259.0 (55.0–581.3)	136.5 (27.0–480.0)	183.50 (37.8–525.0)	0.03
Plasma HIV-1 RNA				
Number tested	11	29	40	
Copies/mL, median (IQR)	466,344 (52,400–1,272,922)	5,870 (87–212,500)	24,650 (114–429,200)	0.02

^aAt the time of pulmonary tuberculosis diagnosis.

ART, antiretroviral therapy; IQR, interquartile range; WHO, World Health Organization.

was 14.1 (IQR 2.5–28.8) months. The regimens of ART included nevirapine-based ($n=60$, 12.4%), efavirenz-based ($n=86$, 17.8%), protease inhibitor (PI)-based ($n=13$, 2.7%), double-boosted PIs ($n=2$, 0.4%), and other regimens ($n=13$, 2.7%). Table 1 shows differences in the baseline demographic characteristics between those who were diagnosed with PTB pre- and post-ART. Children with PTB after ART commencement were older ($p<0.01$), and had more severe HIV disease (WHO clinical stage 4; $p<0.01$), lower baseline CD4+ cell counts ($p=0.03$), and lower baseline plasma HIV-1 RNA levels at the time of PTB diagnosis ($p=0.02$).

Characteristics of PTB

Among 484 PTB episodes, 42 (8.7%) were confirmed cases of PTB, 401 (82.8%) were probable cases of PTB, and 41 (8.5%) were suspected cases of PTB (Table 2). The most common characteristic was having abnormal radiographic/imaging findings compatible with PTB (97.3%), whereas 267 episodes (55.2%) had clinical characteristics of PTB, which varied between pre-ART episodes and post-ART episodes (49.2% vs.

65.1%, $p<0.01$). Bacteriological investigations were performed for 122 episodes, of which 42 (34.4%) had positive AFB sputum smears; 3 also had positive PCR for TB, and 2 had positive *M. tuberculosis* cultures. Of 99 episodes in which a TST was performed, 16 (16.2%) had a documented positive test. Five out of 175 post-ART episodes (2.9%) were cases of IRIS.

EPTB accompanied PTB in 156 episodes (32.2%). The top three reported sites for extrapulmonary involvement were the pleura (81.4%), lymph nodes, or lymphatic system (7.7%), or the disease was disseminated or miliary (5.1%). Post-ART episodes were, less frequently, pleuritis (69.9% vs. 88.0%, $p<0.01$), and, more frequently, lymphadenitis or lymphatic system infection (17.9% vs. 2.0%, $p<0.01$) when compared with pre-ART episodes. Drug susceptibility testing was done for one episode, which showed a susceptible TB strain. Thirty-nine (8.8%) episodes were in patients with a previous history of TB diagnosis. Of the 241 episodes in which history of contact with a TB patient within 12 months prior to the diagnosis was available, 83 (34.4%) patients reported a prior TB contact; 78 contacts (94.0%) were family members.

TABLE 2. FINDINGS IN HIV-INFECTED CHILDREN CO-INFECTED WITH PULMONARY TUBERCULOSIS, STRATIFIED BY PRE-ART AND POST-ART EPISODES

Findings	Pre-ART episodes, n (%)	Post-ART episodes, n (%)	Total, n (%)	p Value
Case definition	309	175	484	0.22
Confirmed	24 (7.8)	17 (9.7)	42 (8.7)	
Probable	254 (82.2)	148 (84.6)	401 (82.8)	
Suspected	31 (10.0)	10 (5.7)	41 (8.5)	
Characteristics features				
Clinical characteristics of PTB	153/309 (49.2)	114/175 (65.1)	267/484 (55.2)	<0.01
Bacteriologic evidence of PTB ^a	24/78 (30.8)	17/45 (37.8)	42/122 (34.4)	0.27
Abnormal radiographic/imaging findings of PTB	265 (98.2)	159/166 (95.8)	424/436 (97.3)	0.14
Positive tuberculin skin test	5/29 (17.2)	11/70 (15.7)	16/99 (16.2)	0.85
Immune reconstitution syndrome	0 (0)	5/175 (2.9)	5/484 (1.0)	0.01
Site of tuberculosis	309	175	484	0.94
PTB only	209 (67.6)	119 (68.0)	328 (67.8)	
PTB with EPTB	100 (32.4)	56 (32.0)	156 (32.2)	
Type of PTB	92	30	122	0.27
PTB, smear-positive	29 (31.5)	13 (43.3)	42 (34.4)	
PTB, smear-negative	63 (68.5)	17 (56.7)	80 (65.6)	
Type of EPTB ^b	100	56	156	
Pleuritis	88 (88.0)	39 (69.6)	127 (81.4)	<0.01
Lymphadenitis/lymphatic system infection	2 (2.0)	10 (17.9)	12 (7.7)	<0.01
Gastrointestinal tract infection/peritonitis	5 (5.0)	2 (3.6)	7 (4.5)	1.00
Meningitis/CNS infection	2 (2.0)	0 (0)	2 (1.3)	0.54
Disseminated/miliary	3 (3.0)	5 (8.9)	8 (5.1)	0.14
Previous history of TB diagnosis	18/277 (6.5)	21/164 (12.8)	39/441 (8.8)	0.04
Contact with TB patient (within 12 months before PTB diagnosis)	43/122 (35.3)	40/119 (33.6)	83/241 (34.4)	0.89
Index case	43	40	83	0.15
Family member	42 (97.7)	36 (90.0)	78 (94.0)	
Neighborhood/community	0 (0)	4 (10.0)	4 (4.8)	
No definite index case	1 (2.3)	0 (0)	1 (1.2)	
Receiving TB prophylaxis regimen	4/303 (1.3)	11/172 (6.4)	15/475 (3.2)	<0.01

^aBacteriologic evidence of PTB: positive acid-fast bacilli sputum smears only (37); positive sputum smears plus positive PCR (3); positive sputum smears plus positive *M. tuberculosis* cultures (2).

^bExtrapulmonary TB in children who were primarily infected in the lungs.

ART, antiretroviral therapy; CNS, central nervous system; EPTB, extrapulmonary tuberculosis; PTB, pulmonary tuberculosis.

Treatment and outcomes

Anti-TB drugs were initiated in 447 episodes (92.4%). The other 37 episodes (7.6%) were untreated or treated with unknown regimens. After treatment completion, 15 (3.1%) of episodes were recorded as *cured*, 361 (74.6%) were recorded as *treatment completed and child well*, and 20 (4.2%) were recorded as *improvement*. During the study period, there were 21 deaths (4.3%). Among 12 deaths occurring after ART initiation, 9 (75.0%) involved patients who died within the first 6 months of ART (median 2.9 months, range 0.6–5.8 months). Overall, 2 (9.5%) were caused by PTB, 14 (66.7%) were from other causes, and the causes of death in the remaining 5 (23.8%) were unknown (Table 3). There were 53 adverse events related to anti-TB drugs reported during the study period. These included fever ($n=11$, 2.3%), skin reaction ($n=10$, 2.1%; one grade 4 Stevens–Johnson Syndrome), nausea/vomiting ($n=7$, 1.5%), aspartate aminotransferase elevation ($n=6$, 1.2%), allergic reaction ($n=6$, 1.2%), alanine aminotransferase elevation ($n=5$, 1.0%), and others ($n=8$, 1.7%).

Discussion

Our finding of a 17.1% period prevalence (range 5.7–33.0% per country) within this regional cohort affirms the high burden of HIV/TB co-infection among HIV-infected children living in low- and middle-income countries in Asia. However, this rate was higher than the mean point prevalence of HIV/TB co-infection of 4.4% (range 0.2–15.0%) in Asian countries reported by WHO in 2011.⁴ The prevalence of PTB found in this study might not directly reflect the prevalence in the region, as our participating study sites are tertiary care referral hospitals. Most PTB cases were diagnosed as probable, where they were diagnosed by a clinician without positive bacteriological evidence. The reasons for the limited number of confirmed cases of PTB included the difficulties of obtaining an adequate sample of sputum, omitting to submit sputum for TB culture in a patient with a negative AFB smear, and the lack of access to appropriate laboratory testing. Additionally, some patients were treated with anti-TB drugs by primary care clinicians before referral to the participating study sites, reducing the potential yield of positive cultures or smears. The routine sputum submission for TB culture, even if a patient has a

negative AFB smear, and/or the repeat of a negative TST after few months, could raise the number of confirmed PTB cases.

In our study, most PTB episodes were diagnosed pre-ART initiation. Similar to other studies,^{17,27} the number of pre-ART PTB episodes was nearly twice the number of post-ART episodes. Walters et al. reported a fivefold reduction in the number of TB episodes after ART (84.7% vs. 15.3%). The TB incidence rate was also reduced from 53.3 per 100 person-years during the 9 months pre-ART initiation to 6.4 per 100 person-years during post-ART follow-up period (odds ratio [OR] 16.6; 95% confidence interval [CI] 12.5–22.4).²⁷ Similarly, Edmonds et al. showed a twofold reduction in the number of post-ART TB episodes (32.8% vs. 16.9%) and a reduction of TB incidence rate from 20.4 per 100 person-years in HIV-infected children who did not receive ART to 10.2 per 100 person-years in children who did.¹⁷

The majority of children were at an advanced stage of HIV disease at the time of their PTB diagnoses by both clinical and immunological criteria. The finding that CD4+ cell counts at the time of PTB diagnosis, even in cases with prolonged ART, were significantly lower than the CD4+ cell counts in pre-ART PTB episodes was consistent with other data on the association between severe immunosuppression with TB disease. This finding is also similar to other studies, which show that even after several months of ART, the risk of developing TB disease in those with concomitant HIV remains higher than that in the HIV-uninfected population, suggesting that patients remain at risk of TB until immune restoration is optimized.^{28,29}

Approximately one-third of our children had a known TB contact history with an index case within 12 months prior to TB diagnosis, mostly with their family members. This finding is similar to that for those uninfected with HIV, where family members are the most common source of infection.³⁰ Very few children in our study received TB prophylaxis; reflecting the inconsistent uptake of the WHO recommendation to screen all HIV-infected children for active TB disease and to offer isoniazid prophylaxis to those suspected of having latent TB³¹ in our cohort. The recommendation for INH preventive therapy (IPT) among HIV-infected children remains controversial.^{31,32} Some experts believe that IPT should be recommended for all HIV-infected children >1 year of age, even in the absence of documented exposure to an active TB source case.³¹ However, findings from a recent

TABLE 3. OUTCOMES OF PULMONARY TUBERCULOSIS AMONG HIV-INFECTED CHILDREN, STRATIFIED BY PRE-ART AND POST-ART EPISODES

Outcomes	Pre-ART episodes, n (%)	Post-ART episodes, n (%)	Total, n (%)	p Value
Total	309	175	484	
Positive outcomes				0.39
Cured	6 (2.0)	9 (5.1)	15 (3.1)	
Treatment completed and child well	230 (74.4)	131 (74.9)	361 (74.6)	
Improvement	10 (3.2)	10 (5.7)	20 (4.2)	
Negative outcomes				0.16
No improvement	4 (1.3)	2 (1.1)	6 (1.2)	
Death ^a	9 (2.9)	12 (6.9)	21 (4.3)	
Defaulted	4 (1.3)	1 (0.6)	5 (1.0)	0.65
Transferred out	4 (1.3)	3 (1.7)	7 (1.5)	1.00
Unknown	42 (13.6)	7 (4.0)	49 (10.1)	<0.01

^aCauses of death: tuberculosis = 2 (9.5%; both in post-ART period); other causes = 14 (66.7%; 8 in pre-ART period vs. 6 in post-ART period); unknown = 5 (23.8%; 1 in pre-ART period vs. 4 in post-ART period).

ART, antiretroviral therapy.

randomized controlled trial in South Africa³² showed that there was no benefit from IPT, in terms of disease-free survival, among HIV-infected infants without known exposure to an active TB case (TB disease or death; INH group 19.0% vs. placebo group 19.3%; $p = 0.93$).

In our study, approximately half of PTB episodes (55.2%) had classical clinical manifestations of PTB. Similarly, Walters et al. showed that most of their HIV/TB co-infected children presented with weight loss or failure to thrive (65.7%), persistent cough for >2 weeks (36.5%), and intermittent fever for >1 week (31.4%).²⁷ However, these classical presentations were less frequently observed in HIV-infected children than in HIV-uninfected children with definite PTB.³³ This could be explained by the relative inability to develop a full inflammatory reaction to TB infection because of HIV-related immunosuppression.

Only five TB episodes (2.9%) in our study were associated with IRIS. The prevalence of IRIS in our study was lower than has been observed in TB-HIV co-infected adults after ART initiation (11–45%).³⁴ The prevalence of TB-IRIS in HIV-infected children in our study was also much lower than that reported in adults from Asia and Africa (3.2–13.9%),³⁵ and lower than that observed in a previous report on children from Thailand (9% for all mycobacterial organisms).³⁶ It is likely that the low rate seen in our study was related to weaknesses in the passive reporting system, and a lack of definitive clinical and laboratory definitions of TB-IRIS during the time period that most of the children in the study were diagnosed with PTB.

The majority of children in our study had positive clinical outcomes, which is similar to the study by Walters et al., which reported that 94/134 (70.1%) of HIV-infected children with TB had positive outcomes defined as cure (12%), being clinically well (32%), or improved (27%).²⁷ The low incidence of serious adverse events related to anti-TB drugs recorded in our study is similar to those from a systematic review, which demonstrated that serious adverse events are usually rare in children living in both resource-constrained and resource-rich countries.³⁷ Half of the deaths occurred while children were already on ART; the majority within a short time after ART initiation. Although definite causes of deaths could not be identified because of data limitations, it is possible that some may have been related to unreported IRIS.

Our study was limited by its retrospective nature, which was associated with incomplete data and missing records. Most of the study centers are tertiary care referral centers, where patients may have been referred from lower-level hospitals. Tracing back patients' PTB histories or obtaining information about the initial diagnostic evaluations in these cases was difficult. In addition, our cohort included few individual clinical centers in their respective countries. The results reflect care in higher level referral centers, and are not generalizable on a national level. Furthermore, our confirmed PTB cases were diagnosed based on positive bacteriological evidence, which mainly relied on AFB smear positivity. Thus, atypical mycobacteria, especially *Mycobacterium avium intracellulare* (also known as *Mycobacterium avium* complex) which commonly occurs in children with advanced HIV disease and severe immunosuppression, or contaminated staining solution, could give false positive results. Finally, because of the multicenter observational study design, each center may have had different standards for PTB assessments, and some had limited access to advanced laboratory testing for TB diagnosis. This resulted in inconsistencies in the thoroughness of the data.

However, our study helps to inform the regional understanding of the prevalence and outcomes of PTB in HIV-infected children receiving care at pediatric referral centers in the region. The prevalence of PTB within our cohort was high. ART can improve, but may not completely restore, the immune system; therefore, HIV-infected children still remain at higher risk for TB infection even when they are receiving ART.

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