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Tuberculosis in HIV-infected children in Europe, Thailand and Brazil: paediatric TB-HIV EuroCoord study

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SUMMARY

SETTING: Centres participating in the Paediatric European Network for Treatment of AIDS (PENTA), including Thailand and Brazil.

OBJECTIVE: To describe the incidence, presentation, treatment and treatment outcomes of tuberculosis (TB) in human immunodeficiency virus (HIV) infected children.

DESIGN: Observational study of TB diagnosed in HIV-infected children in 2011–2013.

RESULTS: Of 4265 children aged <16 years, 127 (3%) were diagnosed with TB: 6 (5%) in Western Europe, 80 (63%) in Eastern Europe, 27 (21%) in Thailand and 14 (11%) in Brazil, with estimated TB incidence rates of respectively 239, 982, 1633 and 2551 per 100 000 person-years (py). The majority (94%) had acquired HIV perinatally. The median age at TB diagnosis was 6.8 years (interquartile range 3.0–11.5). Over half (52%) had advanced/severe World Health Organization stage immunodeficiency; 67 (53%) were not on antiretroviral therapy (ART) at TB diagnosis. Preventive antituberculosis treatment was given to 23% ($n=23$) of 102 children diagnosed with HIV before TB. Eleven children had unfavourable TB outcomes: 4 died, 5 did not complete treatment, 1 had recurrent TB and 1 had an unknown outcome. In univariable analysis, previous diagnosis of acquired immune-deficiency syndrome, not being virologically suppressed on ART at TB diagnosis and region (Brazil) were significantly associated with unfavourable TB outcomes.

CONCLUSION: Most TB cases were from countries with high TB prevalence. The majority (91%) had favourable outcomes. Universal ART and TB prophylaxis may reduce missed opportunities for TB prevention.

KEY WORDS: HIV-TB coinfection; children; observational study

IN 2014, THERE WERE AN ESTIMATED 9.6 million new cases of tuberculosis (TB) globally, including 1 million children. TB is the leading cause of mortality and morbidity in people living with the human immunodeficiency virus (HIV), and in 2015 TB caused 55 000 deaths in HIV-infected children, comprising 40% of all TB-related childhood deaths.[1] The highest burden of coinfection occurs in sub-Saharan Africa, with 3–47% of HIV-infected children reported to have TB in different cohorts.[2–5]

Although antiretroviral therapy (ART) substantially reduces TB incidence in HIV-infected children,[2,4–7] it may not completely restore functional immune response against the disease, and other environmental TB risk factors remain in this population. In the ART era, TB incidence remains higher in HIV-infected children than in non-infected children or the general paediatric population, regardless of setting.[3,5,8,9] TB diagnosis is difficult in children with HIV infection due to overlapping clinical presentations and frequent

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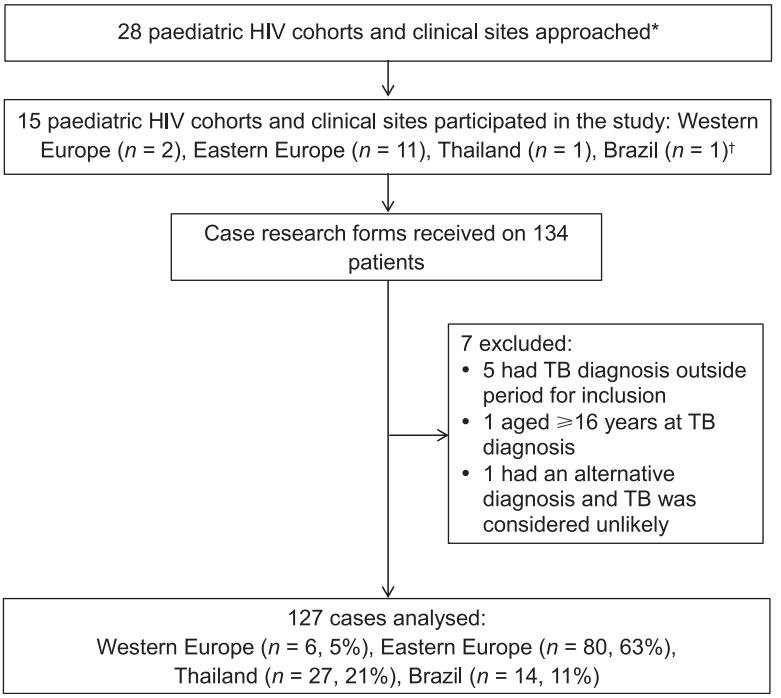

Figure Flow chart of TB cases identified within PENTA cohort collaboration and included in the study. * Twelve European cohorts and clinical sites (in Belgium, France, Denmark, Germany, Greece, Italy, Netherlands, Portugal, Sweden, Switzerland, Poland and Romania) did not have TB cases eligible for the study; the cohort in Argentina did not participate for other reasons.† Cohorts and clinical sites that participated in the study: Cohort of the Spanish Paediatric HIV Network (CoRISPE; Spain); Collaborative HIV Paediatric Study (CHIPS; United Kingdom and Ireland); Riga East University Hospital (Latvia); Republican Hospital of Infectious Diseases, St Petersburg City AIDS Centre and Irkutsk AIDS Centre (Russia); Kryvyi Rih, Donetsk, Kyiv, Mariupol, Mykolaiv, Odessa, Simferopol AIDS Centres (Ukraine); Program for HIV Prevention and Treatment (PHPT; Thailand), Instituto de Infectologia Emilio Ribas cohort, São Paolo, SP, (Brazil). HIV = human immunodeficiency virus; TB = tuberculosis; PENTA = Paediatric European Network for Treatment of AIDS. *N* = number of cohorts and clinical sites; *n* = number of patients.

HIV-related respiratory comorbidities. Furthermore, confirmation of TB is challenging because of the paucibacillary nature of the disease and difficulties in obtaining specimens in children; diagnosis is therefore often presumptive, complicating effective management.

Successful anti-tuberculosis treatment (ATT) outcomes in HIV-infected children vary across settings, ranging from 69% to 88%.[2,10,11] Concomitant ATT may compromise HIV virological control due to drug interactions between rifamycins and some antiretrovirals, leading to longer time to viral load (VL) suppression and higher resistance mutation rates.[12–14]

Data on TB in children living with HIV in high- and middle-income settings in the combination ART era are scarce. Our aim was to describe incidence, clinical presentation, treatment and treatment outcomes of TB in HIV-infected children in the cohorts and clinical sites collaborating in the Paediatric European Network for Treatment of AIDS (PENTA), including Thailand and Brazil.

MATERIALS AND METHODS

The Paediatric TB-HIV Observational Study was established as part of EuroCoord, an EU-funded network of excellence on enhancing clinical and epidemiological HIV research in Europe through cohort collaboration (http://www.eurocoord.net). Of 28 multicentre cohorts and clinical sites approached, 15 cohorts/sites collaborating within PENTA (http://penta-id.org/hiv.html) participated (Figure). HIV-infected children (aged <16 years) diagnosed with TB within a 3-year period, from 1 January 2011 to 31 December 2013, at the time of TB diagnosis were included. Patients were followed up for 2 years from TB diagnosis.

Anonymised patient data were collected on standardised forms by collaborating physicians. Variables included sociodemographics, history of TB contact, growth measurements, HIV Centers for Disease Control and Prevention (CDC) clinical stage before TB diagnosis, clinical site of TB disease, TB diagnostic tests, including radiology, drug susceptibility testing, laboratory tests (CD4 count and percentage,

Table 1 Sociodemographic characteristics and anthropometry at tuberculosis diagnosis

	Western Europe ($N = 6$) *n/N* (%)	Eastern Europe ($N = 80$) *n/N* (%)	Thailand ($N = 27$) *n/N* (%)	Brazil ($N = 14$) *n/N* (%)	Total ($N = 127$) *n/N* (%)
Male	2 (33)	33 (41)	14 (52)	6 (43)	55 (43)
Age, years, median [IQR]	10.9 [2.3–14.0]	5.3 [3.0–9.4]	7.9 [4.3–12.6]	14.2 [3.5–15.0]	6.8 [3.0–11.5]
<5	2 (33)	38 (48)	7 (26)	4 (29)	51 (40)
5–10	0	25 (31)	9 (33)	2 (14)	36 (28)
>10	4 (67)	17 (21)	11 (41)	8 (57)	40 (32)
Ethnicity					
White	0	61 (76)	0	5 (36)	66 (52)
Asian	0	0	27 (100)	0	27 (21)
Hispanic	0	0	0	4 (29)	4 (3)
Black	6 (100)	1 (1)	0	3 (21)	10 (8)
Other	0	18 (23)	0	0	18 (14)
Unknown	0	0	0	2 (14)	2 (2)
Height-for-age *Z*-score <−2	0/3	22/66 (33)	20/26 (77)	2/6 (33)	44/101 (44)
BMI-for-age *Z*-score <−2	0/3	8/66 (12)	7/26 (27)	2/5 (40)	17/100 (17)

IQR = interquartile range; BMI = body mass index.

VL, liver function tests), treatment and TB outcomes. Data collection started in April 2013, with final follow-up in December 2015. Individual cohorts followed their local ethics approval procedures for collaborative observational studies.

Definitions

TB was categorised as confirmed or clinically diagnosed.[15] Confirmed cases were verified by the isolation of *Mycobacterium tuberculosis* complex using culture and/or molecular tests or identification of acid-fast bacilli by microscopy in the absence of positive cultures for non-tuberculous mycobacteria. Immunological evidence of *M. tuberculosis* infection included positive tuberculin skin test (TST) and/or interferon-gamma release assays (IGRAs). Clinical forms of TB were categorised into pulmonary, extra-pulmonary, and both pulmonary and extra-pulmonary; TB disease was classified as severe and non-severe.[16] We adapted the consensus adult TB-immune reconstitution inflammatory syndrome (IRIS) case definition for paediatric use.[17] TB-IRIS was defined as a new TB diagnosis or worsening of TB without alternative explanation following initiation, reintroduction or change in ART and evidence of either 1) a more than two-fold rise in CD4 count, 2) a reduction in VL of >0.5 $\log_{10}$, or 3) weight gain or other signs of clinical improvement in response to ART. ATT outcomes were classified as cured, treatment completed, treatment not completed, TB recurrence, TB-related death, TB-unrelated death and outcome not known. Time of viral suppression was defined at the midpoint of the first VL ⩽400 copies/ml and the preceding measurement. Height-for-age and body mass index (BMI) *Z*-scores were used to assess stunting and wasting, respectively.[18]

Statistical analysis

TB incidence per 100 000 py was calculated as the reported number of incident TB cases in the participating cohorts in the 3-year study period divided by the number of children at risk (estimated as 3*number of children under follow-up at the end of 2013). Characteristics of children were compared according to TB outcome using Fisher's exact test for categorical variables and Wilcoxon's rank-sum test for continuous variables. Adjusted analysis was not possible due to the small sample size. Statistical analyses were conducted using Stata v. 14.0 (StataCorp, College Station, TX, USA).

RESULTS

Of 4265 children aged <16 years under follow-up, 127 (3%) were diagnosed with TB between 2011 and 2013. The proportions of children with TB were respectively 1%, 3%, 5% and 8% for participating cohorts in Western Europe, Eastern Europe, Thailand and Brazil; the estimated TB incidence rates were respectively 239, 982, 1633 and 2551/100 000 py.

Sociodemographic characteristics and anthropometry at TB diagnosis are presented in Table 1. The median age at diagnosis was 6.8 years, with 51 (40%) children aged <5 years. Children in Eastern Europe were significantly younger than elsewhere ($P = 0.0050$, comparing median age). Of 119 children with available data, 115 were residing in their country of origin.

HIV characteristics and ART at the time of TB diagnosis are presented in Table 2. The majority of the children had been infected perinatally (94%) and were diagnosed with TB after HIV (80%). In Thailand, children were more immunocompromised than in other regions ($P < 0.0001$, comparing none/mild and advanced/severe immunological stage); and in Brazil, more children had a CDC stage C event before TB diagnosis than elsewhere ($P = 0.0003$). Of those children not on ART at TB diagnosis ($n = 67$), 93% initiated/restarted ART at a median of 1.8 months

Table 2 HIV characteristics at TB diagnosis

	Western Europe (*N* = 6) *n/N* (%)	Eastern Europe (*N* = 80) *n/N* (%)	Thailand (*N* = 27) *n/N* (%)	Brazil (*N* = 14) *n/N* (%)	Total (*N* = 127) *n/N* (%)
Mode of HIV infection					
Perinatal infection	5 (83)	77 (96)	25 (93)	12 (86)	119 (94)
Blood transfusion	1 (17)	0	0	0	1 (1)
Unknown	0	3 (4)	2 (7)	2 (14)	7 (6)
Age at HIV diagnosis, years, median [IQR]	6.8 [1.2–13.9]	1.3 [0.2–5.1]	7.2 [4.2–10.3]	4.4 [1.4–8.3]	2.7 [0.5–7.2]
Timing of HIV-TB diagnosis					
Diagnosed with TB and HIV within ± 7 days	1 (17)	4 (5)	5 (19)	0	10 (8)
Diagnosed with TB >7 days before HIV	1 (17)	8 (10)	5 (19)	1 (7)	15 (12)
Time from TB to HIV, months, median [IQR]	0.7	0.9 [0.5–1.4]	2.1 [0.5–11.0]	0.9	0.9 [0.5–2.1]
Diagnosed with TB >7 days after HIV	4 (67)	68 (85)	17 (63)	13 (93)	102 (80)
Time from HIV to TB, months, median [IQR]	6.5 [1.7–60.4]	35.2 [11.1–68.7]	2.1 [1.4–19.3]	38.7 [16.2–108.9]	33.4 [6.9–66.8]
WHO immunological stage					
None/mild	5/6 (83)	44/77 (57)	3/24 (13)	6/14 (43)	58/121 (48)
Advanced/severe	1/6 (17)	33/77 (43)	21/24 (88)	8/14 (57)	63/121 (52)
CD4% (*n* = 6, 77, 23, 13, 119), median [IQR]	32 [17–43]	26 [14–35]	10 [5–17]	18 [15–29]	18 [15–29]
CD4 count, cells/μl, age ⩾5 years, median [IQR]	(*n* = 4) 594 [233–909]	(*n* = 41) 397 [202–654]	(*n* = 17) 54 [30–119]	(*n* = 10) 269 [138–469]	(*n* = 72) 275 [56–564]
Viral load, $\log_{10}$	(*n* = 6) 4.5 [2.0–4.9]	(*n* = 63) 4.1 [2.2–5.5]	(*n* = 4) 4.3 [3.3–5.4]	(*n* = 11) 2.3 [1.7–4.9]	(*n* = 84) 4.1 [1.9–5.2]
CDC clinical Stage C before TB diagnosis	1/6 (17)	16/69 (23)	9/27 (33)	11/14 (79)	37/116 (32)
Off ART/ART naïve at TB diagnosis*	4 (67)	40 (50)	21 (78)	2 (14)	67 (53)
Restarted/initiated ART by end of follow-up†	4	37	20	1	62
Time to ART restart/initiation, months, median [IQR]	2.2 [0.6–4.7]	1.5 [0.8–3.2]	2.1 [0.9–4.3]	4.8	1.8 [0.8–3.9]
On ART at TB diagnosis	2 (33)	40 (50)	6 (22)	12 (86)	60 (47)
Any TB-related ART modification‡	0	4	0	1	5
Summary of ART during ATT§					
Boosted PI-based	1 (17)	40 (50)	3 (11)	8 (57)	52 (41)
EFV-based	0	17 (21)	13 (48)	3 (21)	33 (26)
Nevaripine-based	1 (17)	5 (6)	8 (30)	0	14 (11)
3NRTI	0	5 (6)	0	0	5 (4)
Other	3 (50)	9 (11)	0	2 (14)	14 (11)
No ART while on ATT	1 (17)	4 (5)	3 (11)	1 (7)	9 (7)

* Including 15 children diagnosed with HIV after TB, and 3 who had previously initiated ART but were off ART at TB diagnosis.
† Including 5 children who initiated ART after completing ATT.
‡ Defined as switching from boosted PI to EFV-based/3NRTI regimen, or addition of ritonavir to existing PI in period 7 days before or during ATT.
§ Of 27 children aged <3 years on ART, 14 received PI-based regimens, 7 NNRTI-based regimens, and the rest had other regimens.
HIV = human immunodeficiency virus; TB = tuberculosis; IQR = interquartile range; WHO = World Health Organization; CDC = Centers for Disease Control and Prevention; ART = antiretroviral therapy; ATT = anti-tuberculosis treatment; PI = protease inhibitors; EFV = efavirenz; NRTI = nucleotide reverse transcriptase inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors.

(interquartile range [IQR] 0.8–3.9). Children who developed TB on ART ($n = 60$) had their TB diagnosed at a median 29.7 months (IQR 6.1–55.0) after ART initiation, and 51% (23/45) of those with available results had VL ⩽400 copies/ml. Five patients had conventional substitutions to avoid or minimise drug interactions with rifampicin (RMP) following TB diagnosis; 12 had a change of ART due to toxicity and 23 due to treatment failure during ATT. Of the 51 ART-naïve children who started ART while on ATT and who had measurements available, 48 (94%) achieved VL ⩽400 copies/ml in the first 12 months. Of those on ART at TB diagnosis with measurements available, 3/21 were not virologically suppressed at the end of ATT and after 12 months on ART.

TB characteristics are presented in Table 3. Overall, 59 (46%) children had a history of TB contact. Eight children had a history of previous TB, of whom 2 were cured, 5 completed treatment and 1 had an unknown outcome; 3 children had completed treatment for previous TB within 2 years of the current episode, suggesting possible relapse. The use of preventive ATT was reported in 23% ($n = 23$) of the 102 children who were diagnosed with HIV before TB: 18 received isoniazid (INH) preventive treatment (IPT), 4 received INH and pyrazinamide, and 1 received INH and ethambutol (EMB).

Overall, 97 (76%) children had mycobacterial culture and/or molecular tests sent; 35 (28%) were confirmed based on culture or polymerase chain reaction, increasing to 48 (38%) confirmed based on any test; the proportion with confirmed TB was lowest in Thailand (Table 3). Of the 111 (87%) children with immunological tests for tuberculous infection, 4 underwent IGRA, 101 underwent TST and 6 underwent both IGRA and TST. Of those tested, 46 (41%) had evidence of tuberculous infection based on a positive IGRA or TST >5 mm.

Of 23 children who underwent drug susceptibility

Table 3 Characteristics of current TB

	Western Europe ($N = 6$) *n* (%)	Eastern Europe ($N = 80$) *n* (%)	Thailand ($N = 27$) *n* (%)	Brazil ($N = 14$) *n* (%)	Total ($N = 127$) *n* (%)
History of TB contact	3 (50)	44 (55)	11 (41)	1 (7)	59 (46)
History of previous TB	1 (17)	4 (5)	0	3 (21)	8 (6)
Case definition					
Confirmed*	3 (50)	29 (36)	7 (26)	9 (64)	48 (38)
Clinically diagnosed	3 (50)	51 (64)	20 (74)	5 (36)	79 (62)
Clinical presentation					
PTB only	3 (50)	38 (48)	18 (67)	7 (50)	66 (52)
EPTB only†	3 (50)	22 (28)	6 (22)	5 (36)	36 (28)
Lymph nodes	1	16	5	1	23
Spine/bone/joints	1	0	0	0	1
Gastrointestinal	0	2	1	0	3
Genitourinary tract	0	0	0	1	1
Miliary	0	8	1	3	12
Other	2	1	0	0	3
PTB and EPTB†	0	20 (25)	3 (11)	2 (14)	25 (20)
Pleura	0	1	0	0	1
Lymph nodes	0	14	3	0	17
Spine/bone/joints	0	0	0	1	1
CNS/meningitis	0	3	0	0	3
Gastrointestinal	0	2	0	0	2
Skin	0	0	1	0	1
Genitourinary tract	0	1	0	0	1
Other	0	7	0	1	8
Severe TB	3 (50)	28 (35)	11 (41)	8 (57)	50 (39)
Any clinical symptoms present	6 (100)	68 (85)	26 (96)	13 (93)	113 (89)

* Based on culture, molecular tests, microscopy or histology.
† Children may have >1 site of TB summarised.
TB = tuberculosis; PTB = pulmonary TB; EPTB = extra-pulmonary TB; CNS = central nervous system.

testing, 5 (4 in Eastern Europe, 1 in Western Europe) had drug-resistant *M. tuberculosis*: 1 had resistance to INH, one to INH plus EMB, 3 had multidrug-resistant TB (MDR-TB, defined as resistance to at least INH and RMP) (2 with resistance to INH and RMP, and 1 with resistance to INH, RMP, EMB, streptomycin [SM], kanamycin and capreomycin, i.e., pre-extensively drug-resistant TB). A further four children in Eastern Europe had presumed MDR-TB based on the DST pattern of the source case.

Most (89%) children were symptomatic at presentation, with cough, fever and weight loss in respectively 61%, 54% and 30%; 17% ($n = 18$) of the 104 children had symptoms for >3 months. The most common clinical presentation was pulmonary TB alone, and overall one third of children had severe forms of TB. There were no geographic differences in the proportion with severe TB ($P = 0.4091$) and no age differences in children with severe and non-severe TB (median age for severe and non-severe TB 7.4 years, IQR 3.0–13.1 and 6.4, IQR 3.4–10.7, respectively; $P = 0.4241$). TB-IRIS was reported in seven cases at a median of 2.3 months after ART initiation (IQR 1.1–8.8); all had newly diagnosed TB.

Details of ATT are presented in Table 4. In 118 children treated for suspected drug-susceptible TB, 90% started rifamycin-based treatment, with 9% receiving rifabutin and 2% rifapentin (RPT). Overall, SM was used in 25 (20%) children; almost all ($n = 24$) were from Eastern Europe, including 21 children who had TB for the first time. The use of less than three second-line ATT drugs in the initial regimen without documented or suspected TB resistance was reported in one fifth of treated children, most frequently in Eastern Europe ($P = 0.0093$). The overall median duration of ATT among those with drug-susceptible TB was 9.5 months (IQR 7.8–12.4); children in Brazil received the shortest treatment ($P = 0.0013$). ATT was generally well tolerated, with only one child experiencing a grade 3 alanine transaminase/aspartate transaminase elevation.

Eleven (9%) children had unfavourable ATT outcomes. Two children died during initial ATT: both were severely immunocompromised; one died 2 weeks and the other 4 months after TB diagnosis, the latter had TB-IRIS. Five children interrupted ATT and did not complete it, and one was transferred out with no data on TB outcome. Of the children remaining in follow-up, two had TB recurrence, of whom one subsequently died from a systemic infection. One additional child from Eastern Europe died of a non-TB-related cause (severe HIV encephalopathy) 18 months after completing ATT. None of the children with unfavourable outcomes had suspected or confirmed TB resistance.

In unadjusted analysis (Table 5), children from Brazil, those not virologically suppressed on ART and those with a previous CDC stage C event had a

Table 4 ATT, toxicity and treatment outcomes

	Western Europe (*N* = 6) *n/N* (%)	Eastern Europe (*N* = 80) *n/N* (%)	Thailand (*N* = 27) *n/N* (%)	Brazil (*N* = 14) *n/N* (%)	Total (*N* = 127) *n/N* (%)
Initial treatment regimen (drug-susceptible TB only)					
Rifamycin included in ATT	5/5 (100)	62/72 (86)	25/27 (93)	14/14 (100)	106/118 (90)
Rifamycin not included in ATT	0/5	10/72 (14)	2/27 (7)	0/14	12/118 (10)
Streptomycin use	0	24 (30)	1 (4)	0	25 (20)
Use of ⩽3 second-line ATT drugs with no confirmed/suspected resistance	0	20 (25)	4 (15)	0	24 (19)
Treatment duration of drug-susceptible TB* (*n* = 5, 65, 26, 8, 104), median [IQR]	8.9 [6.1–12.0]	9.6 [8.0–12.0]	12.2 [8.9–13.2]	6.6 [6.2–7.2]	9.5 [7.8–12.4]
Any drug discontinued for any toxicity	1 (17)	6 (8)	4 (15)	0	11 (9)
Any drug discontinued for hepatotoxicity	0	2 (3)	2 (7)	0	4 (3)
Any elevated ALT/AST on treatment (*n* = 5, 66, 24, 11, 106)					
Grade 1 (50–99 IU/l)	2/5 (40)	18/66 (27)	5/24 (26)	3/11 (27)	28/106 (29)
Grade 2 (100–199 IU/l)	0/5	6/66 (9)	4/24 (17)	0/11	10/106 (9)
Grade 3 (⩾200 IU/l)	0/5	0/66	1/24 (4)	0/11	1/106 (1)
Outcome					
Cure	1 (17)	41 (51)	3 (11)	5 (36)	50 (39)
Treatment completed†	5 (83)	34 (43)	23 (85)	4 (29)	66 (52)
Treatment not completed	0	2 (3)	0	3 (21)	5 (4)
Recurrence of TB: survived	0	0	1 (4)	0	1 (1)
Died: TB-related	0	2 (3)	0	0	2 (2)
Died: not TB-related‡	0	1 (1)	0	1(7)	2(2)
Not known	0	0	0	1 (7)	1 (1)

* Including only participants with completed treatment.
† One child from Thailand interrupted treatment for 5 months after 4 months of treatment before restarting and completing treatment, and was assigned to treatment completed.
‡ One child from Brazil had TB recurrence and died later of non-specified systemic infection and was assigned to non-TB-related deaths.
ATT = anti-tuberculosis treatment; TB = tuberculosis; IQR = interquartile range; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IU = international unit.

significantly increased probability of an unfavourable TB outcome. Although a greater proportion of children with an unfavourable outcome had advanced/severe World Health Organization (WHO) stage at TB diagnosis, this was not statistically significant.

DISCUSSION

In this study, we evaluated TB in HIV-infected children followed in cohorts/clinical sites in high- and middle-income countries. Estimated TB incidence rates indicate that incident TB in this population is substantially higher than in the general population in the same countries.[1,19,20] The younger age of the TB cases in Eastern Europe may reflect the more recent HIV epidemic there. Children with TB living in Thailand or Brazil tended to have more severe HIV disease at TB diagnosis than those in Europe, possibly due to suboptimal access to care for populations most at risk of HIV and TB.

For most TB cases in our study, the HIV diagnosis came first. IPT in known HIV-infected children was underutilised (reported in only 23% children), and represents a missed opportunity for TB prevention. IPT was effective in preventing TB in HIV-infected children in sub-Saharan Africa,[3,21,22] and is also an effective adjunct to early ART for TB prevention in adults;[23] however, its role in unexposed children has been debated.[3,24] The WHO recommends 6 months of post-exposure IPT for all HIV-infected children and pre-exposure IPT for children aged >1 year,[25] although IPT implementation has been unacceptably slow in most countries.[1] Increased pill burden, perceived negative effect on ART adherence, exaggerated fear of developing resistance, poor integration between vertical HIV and TB systems and insufficient training among health professionals may be barriers for implementation that need to be addressed. A recently developed fixed-dose formulation of INH, cotrimoxazole and B6[26] may improve coverage among older children. Other simplified approaches, such as preventive treatment with once-weekly RPT and INH, are promising[27] and need further study in HIV-infected children on ART. In settings of high INH resistance such as Eastern Europe,[28] the efficacy of IPT and other preventive treatment regimens needs further evaluation.

Two thirds of study cases had clinically diagnosed TB, similar to other paediatric TB studies.[29] This underscores the importance of initiating ATT without laboratory confirmation in the presence of symptoms suggestive of TB and the need for better diagnostics. Unlike natural history studies that have shown that young children have higher risk of severe TB disease,[30] we found no age difference in severe and non-severe disease, possibly because HIV-related immunodeficiency progresses with age in untreated children and ART does not fully restore immune function. In line with other studies from high TB and

Table 5 Anti-tuberculosis treatment outcomes

	Favourable outcome* ($N = 116$) *n* (%)	Unfavourable outcome ($N = 11$) *n* (%)	*P* value
Age at TB diagnosis, years, median [IQR]	6.7 [3.0–11.3]	11.1 [5.4–15.4]	0.1071
Region			0.0099
Western Europe	6 (100)	0	
Eastern Europe	75 (94)	5 (6)	
Thailand	26 (96)	1 (4)	
Brazil	9 (64)	5 (36)	
Sex			0.7556
Male	51 (93)	4 (7)	
Female	65 (90)	7 (10)	
ART/virological suppression status at TB diagnosis			
ART-naïve	64 (100)	0	
ART-experienced	52 (83)	11 (17)	
VL⩽400 copies/ml	22 (96)	1 (4)	0.0429†
VL>400 copies/ml	16 (70)	7 (30)	
Unknown VL	14 (82)	3 (18)	
WHO immunological stage at TB diagnosis			0.0978
None/mild	56 (97)	2 (3)	
Advanced/severe	55 (87)	8 (13)	
CDC stage prior to TB diagnosis			0.0356
N/A/B	75 (95)	4 (5)	
C	30 (81)	7 (19)	
Severity of TB			0.3398
Severe	44 (88)	6 (12)	
Not severe	72 (94)	5 (6)	
Mode of diagnosis			0.3296
Confirmed	42 (88)	6 (13)	
Clinically diagnosed	74 (94)	5 (6)	
TB-IRIS			0.1129
Yes	5 (71)	2 (29)	
No	111 (93)	9 (8)	
Any resistance/suspected resistance?			1.0000
Yes	9 (100)	0	
No	107 (91)	11 (9)	

* Favourable clinical outcomes are cure and treatment completed.
† Comparison of ART-experienced children with VL ⩽400 vs. VL>400 copies/ml.
TB = tuberculosis; IQR = interquartile range; ART = antiretroviral treatment; VL = viral load; WHO = World Health Organization; CDC = Centers for Disease Control and Prevention; TB-IRIS = TB-associated immune reconstitution inflammatory syndrome.

HIV burden countries,[2,3,31] we showed a high proportion of severe forms of TB (39%), including severe extra-pulmonary TB (27%). In contrast, studies in general paediatric populations reported severe extra-pulmonary forms in only 10–15% of all cases.[32,33]

Our study highlights different management practices in paediatric TB across the regions, including more SM use and suboptimal use of second-line drugs in Eastern Europe. SM is injected intramuscularly due to poor oral absorption, has high toxicity and limited additional efficacy when added to first-line ATT, and is therefore not recommended.[34] Use of less than three second-line drugs in high MDR-TB burden settings also raises concern as it provides suboptimal activity of the empiric ATT regimen[35] and may propagate further resistance. Such practices should be discouraged and addressed through training of paediatric TB and HIV clinicians in the region, expanding international collaboration, audits and studies on the implementation of WHO guidelines, and stewardship of anti-tuberculosis drugs. Government commitment to allocate sufficient budget and dedicated personnel for the monitoring and evaluation of collaborative TB-HIV activities is necessary for the successful implementation of WHO guidance.[36]

RMP has significant drug interactions with protease inhibitors (PIs) and nevirapine. RMP-based ATT was associated with virological failure and resistance in children on PI-based ART.[12,14] Good HIV outcomes were previously reported for efavirenz (EFV) based ART.[13,35] Although only a quarter of our cases received EFV-based ART, the overall rate of virologically non-suppressed children was <10%. Favourable outcomes were achieved in 92% of children, slightly higher than the 69–88% reported elsewhere.[2,10,11] Previous acquired immune-deficiency syndrome (AIDS) diagnosis, not being virologically suppressed at TB diagnosis and region (Brazil) were associated with unfavourable TB outcomes. However, as small numbers precluded adjusted analyses,

these results should be interpreted with caution, as they are subject to confounding (e.g., children from Brazil were older and more likely to have a previous AIDS diagnosis than other children). The proportion of TB-related deaths (1.6%) is relatively low compared to the 3.3–11.7% reported in the literature.[2,4,7,10,11] This may reflect the health status of our cases, as nearly half had no/mild immunodeficiency and less than a third had AIDS.

The study had a number of limitations, including an observational design, with inherent limitations such as incomplete data and possible underreporting of cases. However, we distributed reminders to report all children with suspected TB, regardless of follow-up status. Overdiagnosis of TB was possible, as most of our cases were presumptive. Our incidence rates were estimated based on cohort or clinic size, and should be interpreted with caution. Finally, as we did not have national coverage in each country, except for the United Kingdom, the results may not be generalisable to the whole country, as differences in HIV and TB epidemiology and health care provision likely exist.

In conclusion, TB incidence appears to be higher in HIV-infected children than in the general population in the same countries. Intensifying the use of preventive treatment in the studied cohorts and universal ART initiation in all HIV-infected children would reduce missed opportunities to prevent TB in HIV-infected children. Some prescribing practices in Eastern Europe are suboptimal and should be addressed. Despite differences in management, most children had good outcomes.

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References

1 World Health Organization. Global tuberculosis report, 2015. WHO/HTM/TB/2015.22. Geneva, Switzerland: WHO, 2015.
2 Walters E, Cotton M F, Rabie H, Schaaf H S, Walters L O, Marais B J. Clinical presentation and outcome of tuberculosis in human immunodeficiency virus infected children on antiretroviral therapy. BMC Pediatr 2008; 8: 1.
3 Madhi S A, Nachman S, Violari A, et al. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. N Engl J Med 2011; 365: 21–31.
4 Abuogi L L, Mwachari C, Leslie H H, et al. Impact of expanded antiretroviral use on incidence and prevalence of tuberculosis in children with HIV in Kenya. Int J Tuberc Lung Dis 2013; 17: 1291–1297.
5 Auld A F, Tuho M Z, Ekra K A, et al. Tuberculosis in human immunodeficiency virus-infected children starting antiretroviral therapy in Cote d'Ivoire. Int J Tuberc Lung Dis 2014; 18: 381–387.
6 Violari A, Cotton M F, Gibb D M, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med 2008; 359: 2233–2244.
7 Mu W, Zhao Y, Sun X, et al. Incidence and associated factors of pulmonary tuberculosis in HIV-infected children after highly active antiretroviral therapy (HAART) in China: a retrospective study. AIDS Care 2014; 26: 1127–1135.
8 Dangor Z, Izu A, Hillier K, et al. Impact of the antiretroviral treatment program on the burden of hospitalization for culture-confirmed tuberculosis in South African children: a time-series analysis. Pediatr Infect Dis J 2013; 32: 972–977.
9 Turkova A, Chappell E, Judd A, et al; Collaborative HIV Paediatric Study (CHIPS) Steering Committee. Prevalence, incidence, and associated risk factors of tuberculosis in children with HIV living in the UK and Ireland (CHIPS): a cohort study. Lancet HIV 2015; 2: e530–539.
10 Sudjaritruk T, Maleesatharn A, Prasitsuebsai W, et al. Prevalence, characteristics, management, and outcome of pulmonary tuberculosis in HIV-infected children in the TREAT Asia pediatric HIV Observational Database (TApHOD). AIDS Patient Care STDS 2013; 27: 649–656.
11 Dos Santos Dias E, do Prado T N, da Silva Guimarães A L, et al. Childhood tuberculosis and human immunodeficiency virus status in Brazil: a hierarchical analysis. Int J Tuberc Lung Dis 2015; 19: 1305–1311.
12 Zanoni B C, Phungula T, Zanoni H M, France H, Feeney M E. Impact of tuberculosis cotreatment on viral suppression rates among HIV-positive children initiating HAART. AIDS 2011; 25: 49–55.
13 van Dijk J H, Sutcliffe C G, Hamangaba F, Bositis C, Watson D C, Moss W J. Effectiveness of efavirenz-based regimens in young HIV-infected children treated for tuberculosis: a treatment option for resource-limited settings. PLOS ONE 2013; 8: e55111.
14 Meyers T, Sawry S, Wong J Y, et al. Virologic failure among children taking lopinavir/ritonavir-containing first-line antiretroviral therapy in South Africa. Pediatr Infect Dis J 2015; 34: 175–179.
15 World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014). WHO/HTM/TB/2013.2. Geneva, Switzerland: WHO, 2014.
16 Wiseman C A, Gie R P, Starke J R, at al. A proposed comprehensive classification of tuberculosis disease severity in children. Pediatr Infect Dis J 2012; 31: 347–352.
17 Meintjes G, Lawn S D, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis 2008; 8: 516–523.
18 World Health Organization. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva, Switzerland: WHO, 2006. http: //www.who.int/childgrowth/standards/Technical_report.pdf?ua=1 Accessed July 2016.
19 European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2015. Stockholm, Sweden: ECDC, 2015. http://ecdc.europa.eu/en/publications/Publications/tuberculosis-surveillance-monitoring-Europe-2015.pdf Accessed July 2016.

* The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2016/00000020/00000011/art00007

20 Lolekha R, Anuwatnonthakate A, Nateniyom S, et al. Childhood TB epidemiology and treatment outcomes in Thailand: a TB active surveillance network, 2004 to 2006. BMC Infect Dis 2008; 8: 94.
21 Zar H J, Cotton M F, Strauss S, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. BMJ 2007; 334: 136.
22 Frigati L J, Kranzer K, Cotton M F, Schaaf H S, Lombard C J, Zar H J. The impact of isoniazid preventive therapy and antiretroviral therapy on tuberculosis in children infected with HIV in a high tuberculosis incidence setting. Thorax 2011; 66: 496–501.
23 TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med 2015; 373: 808–822.
24 Schaaf H S, Cotton M F, Boon G P, Jeena P M. Isoniazid preventive therapy in HIV-infected and -uninfected children (0–14 years). S Afr Med J 2013; 103: 714–715.
25 World Health Organization. WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. WHO/HTM/TB/2012.1. Geneva, Switzerland: WHO, 2012.
26 Harries A D, Lawn S D, Suthar A B, Granich R. Benefits of combined preventive therapy with co-trimoxazole and isoniazid in adults living with HIV: time to consider a fixed-dose, single tablet coformulation. Lancet Infect Dis 2015; 15: 1492–1496.
27 Villarino M E, Scott N A, Weis S E, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr 2015; 169: 247–255.
28 Jenkins H E, Zignol M, Cohen T. Quantifying the burden and trends of isoniazid resistant tuberculosis, 1994–2009. PLOS ONE 2011; 6: e22927.
29 Nicol M P, Zar H J. New specimens and laboratory diagnostics for childhood pulmonary TB: progress and prospects. Paediatr Respir Rev 2011; 12: 16–21.
30 Marais B J. Tuberculosis in children. J Paediatr Child Health 2014; 50: 759–767.
31 Palme I B, Gudetta B, Bruchfeld J, Muhe L, Giesecke J. Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. Pediatr Infect Dis J 2002; 21: 1053–1061.
32 Teo S S, Alfaham M, Evans M R, et al. Epidemiology of childhood tuberculosis in the United Kingdom and Republic of Ireland. Arch Dis Child 2009; 94: 263–267.
33 Hatleberg C I, Prahl J B, Rasmussen J N, et al. A review of paediatric tuberculosis in Denmark: 10-year trend, 2000–2009. Eur Respir J 2014; 43: 863–871.
34 World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. WHO/HTM/TB/2014.03. Geneva, Switzerland: WHO, 2014.
35 Efsen A M, Schultze A, Post F A, et al. Major challenges in clinical management of TB/HIV coinfected patients in Eastern Europe compared with Western Europe and Latin America. PLOS ONE 2015; 10: e0145380.
36 World Health Organization. A guide to monitoring and evaluation for collaborative TB/HIV activities: 2015 revision. WHO/HTM/TB/2015.02. Geneva, Switzerland: WHO, 2015.

APPENDIX

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RESUME

CONTEXTE : Les centres participant au Réseau des pédiatres européens pour le traitement du syndrome de l'immunodéficience acquise (PENTA), incluant la Thaïlande et le Brésil.

OBJECTIF : Décrire l'incidence, la présentation, le traitement et l'évolution de la tuberculose (TB) chez les enfants infectés par le virus de l'immunodéficience humaine (VIH).

SCHÉMA : Etude d'observation de la TB diagnostiquée chez des enfants infectés par le VIH en 2011–2013.

RÉSULTATS : Sur 4265 enfants âgés de moins de 16 ans, 127 (3%) ont eu un diagnostic de TB : 6 (5%) en Europe de l'Ouest, 80 (63%) en Europe de l'Est, 27 (21%) en Thaïlande et 14 (11%) au Brésil, soit un taux d'incidence estimée de la TB de 239, 982, 1633 et 2551 par 100 000 années-personnes, respectivement. La majorité (94%) avait acquis le VIH en période périnatale. L'âge médian lors du diagnostic de TB a été de 6,8 ans (IQR 3,0–11,5). Plus de la moitié des enfants (52%) avait un déficit immunitaire de stade avancé/grave de l'Organisation Mondiale de la Santé ; 67 (53%) enfants n'étaient pas sous traitement antirétroviral (ART) lors du diagnostic de TB. Un traitement préventif de la TB avait été mis en œuvre chez 23% (23/102) des enfants ayant eu un diagnostic de VIH avant la TB. Onze enfants ont eu une évolution défavorable de la TB (4 sont décédés, 5 n'ont pas terminé leur traitement, 1 a eu une rechute de TB, 1 a été perdu de vue). En analyse univariée, un diagnostic préalable de syndrome d'immunodéficience acquise, le fait de n'être pas sous ART lors du diagnostic de TB et la région (Brésil) ont été significativement associés à une évolution défavorable de la TB.

CONCLUSION : De nombreux cas de TB émanaient de pays à prévalence élevée de TB. La majorité (91%) a eu une évolution favorable. La mise en œuvre universelle de l'ART et de la prophylaxie de la TB pourraient réduire les opportunités manquées de prévention de la TB.

RESUMEN

MARCO DE REFERENCIA: Los centros que participan en la Red Europea de Pediatría para el Tratamiento del Sida (PENTA), incluidos centros en Tailandia y el Brasil.

OBJETIVO: Describir la incidencia, la forma de presentación, el tratamiento y el desenlace clínico actuales de la tuberculosis (TB) en los niños infectados por el virus de la inmunodeficiencia humana (VIH).

MÉTODO: Fue este un estudio de observación de niños aquejados de infección por el VIH con diagnóstico de TB del 2011 al 2013.

RESULTADOS: De los 4265 niños menores de 16 años en seguimiento, se diagnosticó la TB en 127 (3%), de los cuales 6 casos en Europa occidental (5%), 80 en Europa oriental (63%), 27 en Tailandia (21%) y 14 en el Brasil (11%); la estimación de las tasas de incidencia fue 239, 982, 1633 y 2551 por 100 000 años-persona, respectivamente. La mayoría de los niños contrajo la infección por el VIH durante el período perinatal (94%). La mediana de la edad en el momento del diagnóstico de TB fue 6,8 años (intervalo intercuartil 3,0–11,5). Más de la mitad de los casos (52%) presentaba inmunodeficiencia avanzada o grave, según la clasificación de la Organización Mundial de la Salud; 67 niños no recibían tratamiento antirretrovírico (ART) en el momento del diagnóstico de TB (53%). El tratamiento preventivo de la TB se administraba a 23% (23/102) de los niños con diagnóstico de infección por el VIH, antes del comienzo de la TB. Once niños presentaron un desenlace desfavorable (4 muertes, 5 tratamientos incompletos, 1 caso de recaída y 1 desenlace desconocido). En el análisis univariante se asociaron de manera significativa con los desenlaces desfavorables de la TB un diagnóstico anterior de síndrome de inmunedeficiencia adquirido, la falta de supresión del virus mediante medicamentos ART en el momento del diagnóstico de TB y la región de procedencia (Brasil).

CONCLUSIÓN: La mayoría de los casos de TB provenía de países con alta prevalencia de esta enfermedad. La mayor parte alcanzó un desenlace favorable (91%). La administración universal del ART y el tratamiento profiláctico de la TB puede reducir las oportunidades desaprovechadas de prevención de la TB.