TITLE PAGE

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

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Running head: TB-HIV in children: Europe, Thailand, Brazil

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

SUMMARY

Setting: Centers participating in the Paediatric European Network for Treatment of AIDS (PENTA) including Thailand and Brazil.

Objective: To describe 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 anti-tuberculosis 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 supressed 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.

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

INTRODUCTION

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 HIV-related respiratory comorbidities. Furthermore, confirmation of TB is challenging because of the paucibacillary nature of 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 (Fig 1). 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 two 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, 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 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 (IGRA). Clinical forms of TB were categorised into pulmonary, extra-pulmonary, and both pulmonary and extrapulmonary; 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 three 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 in Stata v14.0 (Stata Corp, College Station, TX, USA).

RESULTS

Of 4,265 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%) aged <5 years. Children in Eastern Europe were significantly younger than those 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 1.8 months (interquartile range [IQR] 0.8-3.9). Children who developed TB on ART (n=60) had their TB diagnosis 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 for treatment failure during ATT. Of the 51 ART-naïve children who started ART while on ATT and 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 preventative 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 cases 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 positive IGRA or TST >5 mm.

Of 23 children who underwent drug susceptibility resistance testing, five (4 in Eastern Europe, 1 in Western Europe) had drug-resistant *M.tuberculosis*: 1 had resistance to INH, 1 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 non-TB related cause (severe HIV encephalopathy) 18 months after completing ATT. None of 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 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 than those in Europe at TB diagnosis, 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[26], 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, co-trimoxazole 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 the settings with 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 which showed 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 HIV burden countries,[2,3,31] we showed a high proportion of severe forms of TB (39%) including severe extrapulmonary TB (27%). In contrast, studies in general paediatric populations reported severe extrapulmonary forms only in 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 TB treatment 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 implementation of the WHO guidelines, and stewardship of anti-tuberculous 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.

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 less than 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 supressed 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 were more likely to have a previous AIDS diagnosis than other children). The proportion of TB-related deaths (1.6%) is relatively low compared to 3.3-11.7% in the literature.[2,4,7,10,11] This may reflect the health status of our cases with nearly half had no/mild immunodeficiency and less than a third had AIDS.

This study has 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. Over-diagnosis of TB was possible as most of our cases were presumptive. Our incidence rates were estimated based on cohort/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 generalizable to the whole country as differences in HIV and TB epidemiology and healthcare provision likely exist.

CONCLUSION

TB incidence appears to be higher in HIV-infected children than in the general population from the same countries. Intensifying 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 sub-optimal and should be addressed. Despite differences in management, most children had good outcomes.

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Authors' contributions:

AT, AJ and CT designed the study. AT, RM designed the case research forms, which were critically appraised and improved by AJ, CT. AJ, RG wrote the analysis plan. The study was coordinated by AT, MDN, SC, GR, AV and JC. EC undertook the analysis, supervised by RG. AT drafted the paper with input from CT, EC, AJ and RG. AT, SC, MDN, AV, NP, SS, VR, GK, EY, MM, NB, SK, PR and SA participated in data collection. All authors contributed to the revision of the manuscript and approved the final version.

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459 **Table 1** Socio-demographic characteristics and anthropometry at TB diagnosis

	Western Europe (N=6)	**Eastern Europe (N=80)**	**Thailand (N=27)**	**Brazil (N=14)**	**Overall (N=127)**
	n (%) or median (interquartile range, IQR)				
Male	2 (33)	33 (41)	14 (52)	6 (43)	55 (43)
Age (years)	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)
Age (years)					
<5 years	2 (33)	38 (48)	7 (26)	4 (29)	51 (40)
5-10 years	0	25 (31)	9 (33)	2 (14)	36 (28)
>10 years	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 (n=3, 66, 26, 6, 101)	0	22 (33)	20 (77)	2 (33)	44 (44)
BMI-for-age z-score <-2 (n=3, 66, 26, 5, 100)	0	8 (12)	7 (27)	2 (40)	17 (17)

460

461

Table 2 HIV characteristics at TB diagnosis

	Western Europe (N=6)	Eastern Europe (N=80)	Thailand (N=27)	Brazil (N=14)	Overall (N=127)
	n (%) or median (interquartile range, IQR)				
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)	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 & HIV within ±7d	1 (17)	4 (5)	5 (19)	0	10 (8)
Diagnosed with TB >7d before HIV	1 (17)	8 (10)	5 (19)	1 (7)	15 (12)
Time from TB to HIV (months)	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 >7d after HIV	4 (67)	68 (85)	17 (63)	13 (93)	102 (80)
Time from HIV to TB (months)	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 (n=6, 77, 24, 14, 121)					
None/Mild	5 (83)	44 (57)	3 (13)	6 (43)	58 (48)
Advanced/Severe	1 (17)	33 (43)	21 (88)	8 (57)	63 (52)
CD4% (n=6, 77, 23, 13, 119)	32 (17, 43)	26 (14, 35)	10 (5, 17)	18 (15, 29)	18 (15, 29)
CD4 count (cells/μL), age ≥5 years (n=4, 41, 17, 10, 72)	594 (233, 909)	397 (202, 654)	54 (30, 119)	269 (138, 469)	275 (56, 564)
Viral load (log_{10}) (n=6, 63, 4, 11, 84)	4.5 (2.0, 4.9)	4.1 (2.2, 5.5)	4.3 (3.3, 5.4)	2.3 (1.7, 4.9)	4.1 (1.9, 5.2)
CDC clinical stage C prior to TB diagnosis (n=6, 69, 27, 14, 116)	1 (17)	16 (23)	9 (33)	11 (79)	37 (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)	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)
Efavirenz-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 children who had previously initiated ART but were off ART at TB diagnosis.

§ Including five children who initiated ART after completing ATT.

†Defined as switching from boosted PI to EFV-based/3 NRTI regimen, or addition of RTV to existing PI in period 7 days before or during anti-TB treatment.

^Of 27 children aged <3 years on ART, 14 received PI-based regimens, 7 NNRTI-based, and the rest had other regimens.

ART=antiretroviral therapy. ATT=anti-tuberculosis treatment. CDC=Centers for Disease Control and Prevention. MTCT=mother-to-child transmission. PI=protease inhibitors. NRTI=nucleoside/nucleotide reverse transcriptase inhibitors. VL=viral load

Table 3 Characteristics of current TB

	Western Europe (N=6)	Eastern Europe (N=80)	Thailand (N=27)	Brazil (N=14)	Overall (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					
Pulmonary only	3 (50)	38 (48)	18 (67)	7 (50)	66 (52)
Extrapulmonary 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
Gastro-intestinal	0	2	1	0	3
Genito-urinary tract	0	0	0	1	1
Miliary	0	8	1	3	12
Other	2	1	0	0	3
Pulmonary and extrapulmonary§	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
Gastro-intestinal	0	2	0	0	2
Skin	0	0	1	0	1
Genito-urinary 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.

Table 4 TB treatment, toxicity and treatment outcomes

	Western Europe (N=6)	Eastern Europe (N=80)	Thailand (N=27)	Brazil (N=14)	Overall (N=127)
	n (%) or median (interquartile range, IQR)				
Initial treatment regimen (drug-sensitive TB only) (n=5, 72, 27, 14, 118)					
Rifamycin included in ATT	5 (100)	62 (86)	25 (93)	14 (100)	106 (90)
Rifamycin not included in ATT	0	10 (14)	2 (7)	0	12 (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-sensitive, TB* (months) (n=5, 65, 26, 8, 104)	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 to 99 IU/L)	2 (40)	18 (27)	5 (26)	3 (27)	28 (29)
Grade 2 (100 to 199 IU/L)	0	6 (9)	4 (17)	0	10 (9)
Grade 3 (≥200 IU/L)	0	0	1 (4)	0	1 (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 Brazil had TB recurrence and died later of non-specified systemic infection– assigned to not TB-related deaths.

^ One child from Thailand interrupted treatment for 5 months after 4 months of treatment, before restarting and completing treatment – assigned to treatment completed.

ALT=alanine aminotransferase. AST=aspartate aminotransferase. ARV=antiretroviral drugs. ATT=anti-tuberculosis treatment. MDR-TB=multidrug-resistant tuberculosis.

Table 5 Outcomes of TB

	Favourable Outcome* (N=116)	**Unfavourable outcome (N=11)**	**p-value**
	n (%) or median (IQR)		
Age at TB diagnosis	6.7 (3.0, 11.3)	11.1 (5.4, 15.4)	0.1071
Region			
Western Europe	6 (100)	0	0.0099
Eastern Europe	75 (94)	5 (6)	
Thailand	26 (96)	1 (4)	
Brazil	9 (64)	5 (36)	
Gender			
Male	51 (93)	4 (7)	0.7556
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	*22 (96)*	*1 (4)*	0.0429^
VL>400	*16 (70)*	*7 (30)*	
Unknown VL	*14 (82)*	*3 (18)*	
WHO immunological stage at TB diagnosis			
None/Mild	56 (97)	2 (3)	0.0978
Advanced/Severe	55 (87)	8 (13)	
CDC stage prior to TB diagnosis			
N/A/B	75 (95)	4 (5)	0.0356
C	30 (81)	7 (19)	
Severity of TB			
Severe	44 (88)	6 (12)	0.3398
Not severe	72 (94)	5 (6)	
Mode of diagnosis			
Confirmed	42 (88)	6 (13)	0.3296
Clinically diagnosed	74 (94)	5 (6)	
TB-IRIS			
Yes	5 (71)	2 (29)	0.1129
No	111 (93)	9 (8)	
Any resistance/suspected resistance?			
Yes	9 (100)	0	1.0000
No	107 (91)	11 (9)	

*Favourable clinical outcomes are cure and treatment completed.

^Comparison of ART experienced children with VL ≤400 vs VL>400 c/mL.

ART=antiretroviral treatment. CDC=Centers for Disease Control and Prevention. TB-IRIS=TB-associated immune reconstitution inflammatory syndrome. VL=viral load.

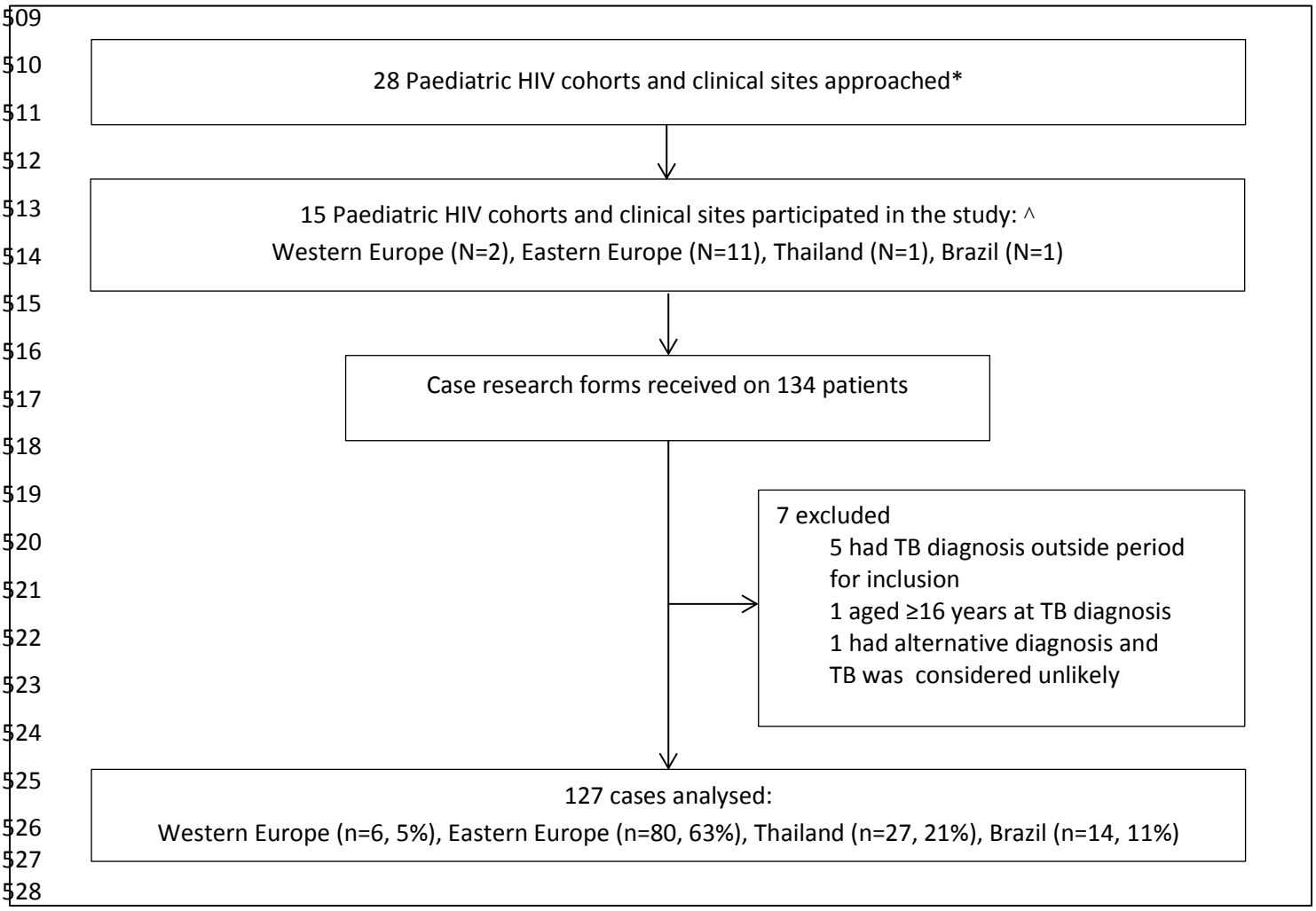

Figure 1 Flowchart of TB cases identified within PENTA cohort collaboration and included in the study

*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; cohort in Argentina did not participate for other reasons.

^Cohorts and clinical sites participated in the study: CoRISPE (Spain); 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); PHPT (Thailand), Instituto de Infectologia Emilio Ribas cohort, São Paolo (Brazil)

N=number of cohorts and clinical sites. n=number of patients.

APPENDIX

We thank all colleagues who have made contribution to the study.

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