

1 **TITLE PAGE**

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

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

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

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56 **SUMMARY**

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

59 **Objective:** To describe incidence, presentation, treatment and treatment outcomes of tuberculosis (TB)
60 in human immunodeficiency virus (HIV) infected children.

61 **Design:** Observational study of TB diagnosed in HIV-infected children in 2011-2013.

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

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

76

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95 **INTRODUCTION**

96 In 2014, there were an estimated 9.6 million new cases of tuberculosis (TB) globally, including 1 million
97 children. TB is the leading cause of mortality and morbidity in people living with the human
98 immunodeficiency virus (HIV), and in 2015 TB caused 55,000 deaths in HIV-infected children, comprising
99 40% of all TB-related childhood deaths.¹ The highest burden of coinfection occurs in sub-Saharan Africa,
100 with 3-47% of HIV-infected children reported to have TB in different cohorts.²⁻⁵

101 Although antiretroviral therapy (ART) substantially reduces TB incidence in HIV-infected children,^{2,4-7} it
102 may not completely restore functional immune response against the disease and other environmental
103 TB risk factors remain in this population. In the ART era TB incidence remains higher in HIV-infected
104 children than in non-infected children or the general paediatric population, regardless of setting.^{3,5,8,9} TB
105 diagnosis is difficult in children with HIV infection due to overlapping clinical presentations and frequent
106 HIV-related respiratory comorbidities. Furthermore, confirmation of TB is challenging because of the
107 paucibacillary nature of disease and difficulties in obtaining specimens in children; diagnosis is therefore
108 often presumptive, complicating effective management.

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

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

117

118 **MATERIALS AND METHODS**

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

126 Anonymised patient data were collected on standardised forms by collaborating physicians. Variables
127 included sociodemographics, history of TB contact, growth measurements, HIV Centers for Disease
128 Control and Prevention (CDC) clinical stage before TB diagnosis, clinical site of TB disease, TB diagnostic
129 tests, including radiology, drug susceptibility testing, laboratory tests (CD4 count and percentage, VL,
130 liver function tests), treatment, and TB outcomes. Data collection started in April 2013, with final follow-
131 up in December 2015. Individual cohorts followed their local ethics approval procedures for
132 collaborative observational studies.

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135 *Definitions*

136 TB was categorised as confirmed or clinically diagnosed.¹⁵ Confirmed cases were verified by isolation of
137 *Mycobacterium tuberculosis* complex using culture and/or molecular tests or identification of acid-fast
138 bacilli by microscopy in the absence of positive cultures for non-tuberculous mycobacteria.

139 Immunological evidence of *M. tuberculosis* infection included positive tuberculin skin test (TST) and/or
140 interferon-gamma release assays (IGRA). Clinical forms of TB were categorised into pulmonary, extra-
141 pulmonary, and both pulmonary and extrapulmonary; TB disease was classified as severe and non-
142 severe.¹⁶ We adapted the consensus adult TB-immune reconstitution inflammatory syndrome (IRIS) case
143 definition for paediatric use.¹⁷ TB-IRIS was defined as a new TB diagnosis or worsening of TB without
144 alternative explanation following initiation, reintroduction or change in ART and evidence of either (1) a
145 more than two-fold rise in CD4 count, (2) a reduction in VL of >0.5 log₁₀, or (3) weight gain or other signs
146 of clinical improvement in response to ART. ATT outcomes were classified as cured, treatment
147 completed, treatment not completed, TB recurrence, TB-related death, TB-unrelated death, and
148 outcome not known. Time of viral suppression was defined at the midpoint of the first VL≤400 copies/ml
149 and the preceding measurement. Height-for-age and body mass index (BMI) Z-scores were used to
150 assess stunting and wasting, respectively.¹⁸

151

152 *Statistical analysis*

153 TB incidence per 100,000 PY was calculated as the reported number of incident TB cases in the
154 participating cohorts in the three year study period divided by the number of children at risk (estimated
155 as 3*number of children under follow-up at the end of 2013). Characteristics of children were compared
156 according to TB outcome using Fisher's exact test for categorical variables and Wilcoxon's rank-sum test
157 for continuous variables. Adjusted analysis was not possible due to the small sample size. Statistical
158 analyses were conducted in Stata v14.0 (Stata Corp, College Station, TX, USA).

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162 **RESULTS**

163 Of 4,265 children aged <16 years under follow-up, 127 (3%) were diagnosed with TB between 2011 and
164 2013. The proportions of children with TB were respectively 1%, 3%, 5% and 8% for participating cohorts
165 in Western Europe, Eastern Europe, Thailand and Brazil; the estimated TB incidence rates were
166 respectively 239, 982, 1633 and 2551/100,000 PY.

167
168 Sociodemographic characteristics and anthropometry at TB diagnosis are presented in Table 1. The
169 median age at diagnosis was 6.8 years, with 51 (40%) aged <5 years. Children in Eastern Europe were
170 significantly younger than those elsewhere ($p=0.0050$, comparing median age). Of 119 children with
171 available data, 115 were residing in their country of origin.

172
173 HIV characteristics and ART at the time of TB diagnosis are presented in Table 2. The majority of the
174 children had been infected perinatally (94%) and were diagnosed with TB after HIV (80%). In Thailand
175 children were more immunocompromised than in other regions ($p<0.0001$, comparing none/mild and
176 advanced/severe immunological stage); and in Brazil, more children had a CDC stage C event before TB
177 diagnosis than elsewhere ($p=0.0003$). Of those children not on ART at TB diagnosis ($n=67$), 93%
178 initiated/restarted ART at a median 1.8 months (interquartile range [IQR] 0.8-3.9). Children who
179 developed TB on ART ($n=60$) had their TB diagnosis at a median 29.7 months (IQR 6.1-55.0) after ART
180 initiation, and 51% (23/45) of those with available results had VL ≤ 400 copies/ml. Five patients had
181 conventional substitutions to avoid or minimise drug interactions with rifampicin (RMP) following TB
182 diagnosis; 12 had a change of ART due to toxicity and 23 for treatment failure during ATT. Of the 51 ART-
183 naïve children who started ART while on ATT and had measurements available, 48 (94%) achieved VL
184 ≤ 400 copies/ml in the first 12 months. Of those on ART at TB diagnosis with measurements available,
185 3/21 were not virologically suppressed at the end of ATT and after 12 months on ART.

186
187 TB characteristics are presented in Table 3. Overall, 59 (46%) children had a history of TB contact. Eight
188 children had a history of previous TB, of whom 2 were cured, 5 completed treatment and 1 had an
189 unknown outcome; 3 children had completed treatment for previous TB within 2 years of the current
190 episode, suggesting possible relapse. The use of preventative ATT was reported in 23% ($n=23$) of the 102
191 children who were diagnosed with HIV before TB: 18 received isoniazid (INH) preventive treatment (IPT),
192 4 received INH and pyrazinamide, and 1 received INH and ethambutol (EMB).

193
194 Overall, 97 (76%) children had mycobacterial culture and/or molecular tests sent; 35 (28%) were
195 confirmed cases based on culture or polymerase chain reaction, increasing to 48 (38%) confirmed based
196 on any test; the proportion with confirmed TB was lowest in Thailand (Table 3). Of the 111 (87%)
197 children with immunological tests for tuberculous infection, 4 underwent IGRA, 101 underwent TST and

198 6 underwent both IGRA and TST. Of those tested 46 (41%) had evidence of tuberculous infection based
199 on positive IGRA or TST >5 mm.

200
201 Of 23 children who underwent drug susceptibility resistance testing, five (4 in Eastern Europe, 1 in
202 Western Europe) had drug-resistant *M. tuberculosis*: 1 had resistance to INH, 1 to INH plus EMB, 3 had
203 multidrug-resistant TB (MDR-TB, defined as resistance to at least INH and RMP) (2 with resistance to INH
204 and RMP, and 1 with resistance to INH, RMP, EMB, streptomycin [SM], kanamycin and capreomycin, i.e.
205 pre-extensively drug-resistant TB). A further four children in Eastern Europe had presumed MDR-TB
206 based on the DST pattern of the source case.

207
208 Most (89%) children were symptomatic at presentation, with cough, fever and weight loss in
209 respectively 61%, 54% and 30%; 17% (n=18) of the 104 children had symptoms for >3 months. The most
210 common clinical presentation was pulmonary TB alone, and overall one-third of children had severe
211 forms of TB. There were no geographic differences in the proportion with severe TB ($p=0.4091$) and no
212 age differences in children with severe and non-severe TB (median age for severe and non-severe TB 7.4
213 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
214 a median of 2.3 months after ART initiation (IQR 1.1-8.8); all had newly diagnosed TB.

215
216 Details of ATT are presented in Table 4. In 118 children treated for suspected drug-susceptible TB, 90%
217 started rifamycin-based treatment, with 9% receiving rifabutin and 2% rifapentin (RPT). Overall, SM was
218 used in 25 (20%) children; almost all (n=24) were from Eastern Europe, including 21 children who had TB
219 for the first time. The use of less than three second-line ATT drugs in the initial regimen without
220 documented or suspected TB resistance was reported in one fifth of treated children, most frequently in
221 Eastern Europe ($p=0.0093$). The overall median duration of ATT among those with drug-susceptible TB
222 was 9.5 months (IQR 7.8-12.4); children in Brazil received the shortest treatment ($p=0.0013$). ATT was
223 generally well tolerated, with only one child experiencing a grade 3 alanine transaminase/aspartate
224 transaminase elevation.

225
226 Eleven (9%) children had unfavourable ATT outcomes. Two children died during initial ATT; both were
227 severely immunocompromised; one died 2 weeks and the other 4 months after TB diagnosis, the latter
228 had TB-IRIS. Five children interrupted ATT and did not complete it, and one was transferred out with no
229 data on TB outcome. Of the children remaining in follow-up, two had TB recurrence, of whom one
230 subsequently died from a systemic infection. One additional child from Eastern Europe died of non-TB
231 related cause (severe HIV encephalopathy) 18 months after completing ATT. None of children with
232 unfavourable outcomes had suspected or confirmed TB resistance.

233

234 In unadjusted analysis (Table 5), children from Brazil, those not virologically suppressed on ART and
235 those with a previous CDC stage C event had a significantly increased probability of an unfavourable TB
236 outcome. Although a greater proportion of children with an unfavourable outcome had
237 advanced/severe World Health Organization (WHO) stage at TB diagnosis, this was not statistically
238 significant.

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244 **DISCUSSION**

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

251 For most TB cases in our study, the HIV diagnosis came first. IPT in known HIV-infected children was
252 underutilised (reported in only 23% children), and represents a missed opportunity for TB prevention.
253 IPT was effective in preventing TB in HIV-infected children in sub-Saharan Africa,^{3,21,22} and is also an
254 effective adjunct to early ART for TB prevention in adults²³, however, its role in unexposed children has
255 been debated.^{3,24} The WHO recommends 6 months of post-exposure IPT for all HIV-infected children
256 and pre-exposure IPT for children aged >1 year²⁶, although IPT implementation has been unacceptably
257 slow in most countries.¹ Increased pill burden, perceived negative effect on ART adherence, exaggerated
258 fear of developing resistance, poor integration between vertical HIV and TB systems, and insufficient
259 training among health professionals may be barriers for implementation that need to be addressed. A
260 recently developed fixed-dose formulation of INH, co-trimoxazole and B6²⁶ may improve coverage
261 among older children. Other simplified approaches, such as preventive treatment with once weekly RPT
262 and INH are promising²⁷ and need further study in HIV-infected children on ART. In the settings with
263 high INH resistance, such as Eastern Europe,²⁸ the efficacy of IPT and other preventive treatment
264 regimens needs further evaluation.

265
266 Two-thirds of study cases had clinically diagnosed TB, similar to other paediatric TB studies.²⁹ This
267 underscores the importance of initiating ATT without laboratory confirmation in the presence of
268 symptoms suggestive of TB and the need for better diagnostics. Unlike natural history studies which
269 showed young children have higher risk of severe TB disease,³⁰ we found no age difference in severe and
270 non-severe disease, possibly because HIV-related immunodeficiency progresses with age in untreated
271 children and ART does not fully restore immune function. In line with other studies from high TB and
272 HIV burden countries,^{2,3,31} we showed a high proportion of severe forms of TB (39%) including severe
273 extrapulmonary TB (27%). In contrast, studies in general paediatric populations reported severe
274 extrapulmonary forms only in 10-15% of all cases.^{32,33}

275
276 Our study highlights different management practices in paediatric TB across the regions, including more
277 SM use and suboptimal use of second-line drugs in Eastern Europe. SM is injected intramuscularly due
278 to poor oral absorption, has high toxicity and limited additional efficacy when added to first-line TB
279 treatment and is therefore not recommended.³⁴ Use of less than three second-line drugs in high MDR-TB

280 burden settings also raises concern as it provides suboptimal activity of the empiric ATT regimen³⁵ and
281 may propagate further resistance. Such practices should be discouraged and addressed through training
282 of paediatric TB and HIV clinicians in the region, expanding international collaboration, audits and
283 studies on implementation of the WHO guidelines, and stewardship of anti-tuberculous drugs.
284 Government commitment to allocate sufficient budget and dedicated personnel for the monitoring and
285 evaluation of collaborative TB-HIV activities is necessary for the successful implementation of WHO
286 guidance.

287
288 RMP has significant drug interactions with protease inhibitors (PIs) and nevirapine. RMP-based ATT was
289 associated with virological failure and resistance in children on PI-based ART.^{12,14} Good HIV outcomes
290 were previously reported for efavirenz (EFV) based ART.^{13,35} Although only a quarter of our cases
291 received EFV-based ART, the overall rate of virologically non-suppressed children was less than 10%.
292 Favourable outcomes were achieved in 92% of children, slightly higher than the 69-88% reported
293 elsewhere.^{2,10,11} Previous acquired immune-deficiency syndrome (AIDS) diagnosis, not being virologically
294 suppressed at TB diagnosis, and region (Brazil) were associated with unfavourable TB outcomes.
295 However as small numbers precluded adjusted analyses, these results should be interpreted with
296 caution as they are subject to confounding (e.g. children from Brazil were older and were more likely to
297 have a previous AIDS diagnosis than other children). The proportion of TB-related deaths (1.6%) is
298 relatively low compared to 3.3-11.7% in the literature.^{2,4,7,10,11} This may reflect the health status of our
299 cases with nearly half had no/mild immunodeficiency and less than a third had AIDS.

300
301 This study has a number of limitations, including an observational design, with inherent limitations such
302 as incomplete data and possible underreporting of cases. However, we distributed reminders to report
303 all children with suspected TB regardless of follow-up status. Over-diagnosis of TB was possible as most
304 of our cases were presumptive. Our incidence rates were estimated based on cohort/clinic size, and
305 should be interpreted with caution. Finally, as we did not have national coverage in each country, except
306 for the United Kingdom, the results may not be generalizable to the whole country as differences in HIV
307 and TB epidemiology and healthcare provision likely exist.

308 309 **CONCLUSION**

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

315

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322 **Authors' contributions:**

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

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352 **REFERENCES**

- 353 1 World Health Organisation. Global tuberculosis report 2015. WHO/HTM/TB/2015.22 Geneva, World
354 Health Organization, 2015. Available from:
355 http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1 Accessed: Dec
356 21, 2015.
- 357 2 Walters E, Cotton MF, Rabie H, Schaaf HS, Walters LO, Marais BJ. Clinical presentation and outcome
358 of tuberculosis in human immunodeficiency virus infected children on antiretroviral therapy. *BMC*
359 *Pediatr* 2008; 8: 1.
- 360 3 Madhi SA, Nachman S, Violari A, et al. Primary isoniazid prophylaxis against tuberculosis in HIV-
361 exposed children. *N Engl J Med* 2011; 365: 21-31.
- 362 4 Abuogi LL, Mwachari C, Leslie HH, et al. Impact of expanded antiretroviral use on incidence and
363 prevalence of tuberculosis in children with HIV in Kenya. *Int J Tuberc Lung Dis* 2013; 17: 1291-7.
- 364 5 Auld AF, Tuho MZ, Ekra KA, et al. Tuberculosis in human immunodeficiency virus-infected children
365 starting antiretroviral therapy in Cote d'Ivoire. *Int J Tuberc Lung Dis* 2014; 18: 381-7.
- 366 6 Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected
367 infants. *N Engl J Med* 2008; 359: 2233-44.
- 368 7 Mu W, Zhao Y, Sun X, et al. Incidence and associated factors of pulmonary tuberculosis in HIV-
369 infected children after highly active antiretroviral therapy (HAART) in China: a retrospective study.
370 *AIDS care* 2014; 26: 1127-35.
- 371 8 Dangor Z, Izu A, Hillier K, et al. Impact of the antiretroviral treatment program on the burden of
372 hospitalization for culture-confirmed tuberculosis in South African children: a time-series analysis.
373 *Pediatr Infect Dis J* 2013;32(9):972-7.
- 374 9 Turkova A, Chappell E, Judd A, et al; Collaborative HIV Paediatric Study (CHIPS) Steering Committee.
375 Prevalence, incidence, and associated risk factors of tuberculosis in children with HIV living in the UK
376 and Ireland (CHIPS): a cohort study. *Lancet HIV* 2015; 2: e530-9.
- 377 10 Sudjaritruk T, Maleesatharn A, Prasitsuebsai W, et al. Prevalence, characteristics, management, and
378 outcome of pulmonary tuberculosis in HIV-infected children in the TREAT Asia pediatric HIV
379 Observational Database (TApHOD). *AIDS Patient Care STDS* 2013; 27: 649-56.
- 380 11 Dos Santos Dias E, do Prado TN, da Silva Guimarães AL, et al. Childhood tuberculosis and human
381 immunodeficiency virus status in Brazil: a hierarchical analysis. *Int J Tuberc Lung Dis* 2015; 19: 1305-
382 11.
- 383 12 Zanoni BC, Phungula T, Zanoni HM, France H, Feeney ME. Impact of tuberculosis cotreatment on
384 viral suppression rates among HIV-positive children initiating HAART. *AIDS* 2011; 25: 49-55.
- 385 13 van Dijk JH, Sutcliffe CG, Hamangaba F, Bositis C, Watson DC, Moss WJ. Effectiveness of efavirenz-
386 based regimens in young HIV-infected children treated for tuberculosis: a treatment option for
387 resource-limited settings. *PLoS One* 2013; 8: e55111.

- 388 14 Meyers T, Sawry S, Wong JY, et al. Virologic failure among children taking lopinavir/ritonavir-
389 containing first-line antiretroviral therapy in South Africa. *Pediatr Infect Dis J* 2015; 34: 175-9.
- 390 15 World Health Organisation. Definitions and reporting framework for tuberculosis – 2013 revision
391 (updated December 2014). WHO/HTM/TB/2013.2. Geneva, Switzerland: WHO, 2014.
392 http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf Accessed January
393 2016.
- 394 16 Wiseman CA, Gie RP, Starke JR, et al. A proposed comprehensive classification of tuberculosis
395 disease severity in children. *Pediatr Infect Dis J* 2012; 31: 347-52.
- 396 17 Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory
397 syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008; 8: 516-23.
- 398 18 World Health Organization. WHO child growth standards: Length/height-for-age, weight-for-age,
399 weight-for-length, weight-for-height and body mass index-for-age: methods and development.
400 Geneva: WHO, 2006. http://www.who.int/childgrowth/standards/Technical_report.pdf?ua=1
401 Accessed January 2016.
- 402 19 European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis
403 surveillance and monitoring in Europe 2015. Stockholm: European Centre for Disease Prevention
404 and Control, 2015. [http://ecdc.europa.eu/en/publications/Publications/tuberculosis-surveillance-
405 monitoring-Europe-2015.pdf](http://ecdc.europa.eu/en/publications/Publications/tuberculosis-surveillance-monitoring-Europe-2015.pdf) Accessed January 2016.
- 406 20 Lolekha R, Anuwatnonthakate A, Nateniyom S, et al. Childhood TB epidemiology and treatment
407 outcomes in Thailand: a TB active surveillance network, 2004 to 2006. *BMC Infect Dis* 2008; 8: 94.
- 408 21 Zar HJ, Cotton MF, Strauss S, et al. Effect of isoniazid prophylaxis on mortality and incidence of
409 tuberculosis in children with HIV: randomised controlled trial. *BMJ* 2007; 334: 136.
- 410 22 Frigati LJ, Kranzer K, Cotton MF, Schaaf HS, Lombard CJ, Zar HJ. The impact of isoniazid preventive
411 therapy and antiretroviral therapy on tuberculosis in children infected with HIV in a high
412 tuberculosis incidence setting. *Thorax* 2011; 66: 496-501.
- 413 23 TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and
414 Isoniazid Preventive Therapy in Africa. *N Engl J Med* 2015; 373: 808-22.
- 415 24 Schaaf HS, Cotton MF, Boon GP, Jeena PM. Isoniazid preventive therapy in HIV-infected and -
416 uninfected children (0 - 14 years). *S Afr Med J* 2013; 103(10): 714-5.
- 417 25 World Health Organisation. WHO policy on collaborative TB/HIV activities: guidelines for national
418 programmes and other stakeholders. WHO/HTM/TB/2012.1. Geneva, Switzerland: WHO, 2012.
419 http://apps.who.int/iris/bitstream/10665/44789/1/9789241503006_eng.pdf?ua=1&ua=1 Accessed
420 January 2016.
- 421 26 Harries AD, Lawn SD, Suthar AB, Granich R. Benefits of combined preventive therapy with co-
422 trimoxazole and isoniazid in adults living with HIV: time to consider a fixed-dose, single tablet
423 coformulation. *Lancet Infect Dis* 2015; 15: 1492-6.

- 424 27 Villarino ME, Scott NA, Weis SE, et al. Treatment for preventing tuberculosis in children and
425 adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of
426 rifapentine and isoniazid. *JAMA Pediatr* 2015; 169: 247-55.
- 427 28 Jenkins HE, Zignol M, Cohen T. Quantifying the burden and trends of isoniazid resistant tuberculosis,
428 1994-2009. *PLoS One* 2011; 6: e22927.
- 429 29 Nicol MP, Zar HJ. New specimens and laboratory diagnostics for childhood pulmonary TB: progress
430 and prospects. *Paediatr Respir Rev* 2011; 12: 16-21.
- 431 30 Marais BJ. Tuberculosis in children. *J Paediatr Child Health* 2014; 50: 759-67.
- 432 31 Palme IB, Gudetta B, Bruchfeld J, Muhe L, Giesecke J. Impact of human immunodeficiency virus 1
433 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children
434 with tuberculosis. *Pediatr Infect Dis J* 2002; 21: 1053-1061.
- 435 32 Teo SS, Alfaham M, Evans MR, et al. Epidemiology of childhood tuberculosis in the United Kingdom
436 and Republic of Ireland. *Arch Dis Child* 2009; 94: 263-7.
- 437 33 Hatleberg CI, Prah J, Rasmussen JN, et al. A review of paediatric tuberculosis in Denmark: 10-year
438 trend, 2000-2009. *Eur Respir J* 2014; 43: 863-71.
- 439 34 World Health Organisation. Guidance for national tuberculosis programmes on the management of
440 tuberculosis in children – 2nd ed. WHO/HTM/TB/2014.03. Geneva, Switzerland: WHO, 2014.
441 <http://apps.who.int/medicinedocs/documents/s21535en/s21535en.pdf> Accessed January 2016.
- 442 35 Efsen AM, Schultze A, Post FA, et al. Major Challenges in Clinical Management of TB/HIV Coinfected
443 Patients in Eastern Europe Compared with Western Europe and Latin America. *PLoS One*
444 2015;10:e0145380.

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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)

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462 **Table 2** HIV characteristics at TB diagnosis
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	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)
Nevirapine-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)

464 *Including 15 children diagnosed with HIV after TB, and 3 children who had previously initiated ART but were off
465 ART at TB diagnosis.

466 § Including five children who initiated ART after completing ATT.

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

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

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

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478 **Table 3** Characteristics of current TB
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	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)

480 *Based on culture, molecular tests, microscopy or histology.

481 §Children may have >1 site of TB summarised.

482

483 **Table 4** TB treatment, toxicity and treatment outcomes

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	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)

485 * Including only participants with completed treatment.

486 § One child from Brazil had TB recurrence and died later of non-specified systemic infection– assigned to not TB-related deaths.

487
488 ^ One child from Thailand interrupted treatment for 5 months after 4 months of treatment, before restarting and
489 completing treatment – assigned to treatment completed.

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

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494 **Table 5** Outcomes of TB

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	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	0.0429^
ART experienced	52 (83)	11 (17)	
VL≤400	22 (96)	1 (4)	
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)	

496 *Favourable clinical outcomes are cure and treatment completed.

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

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

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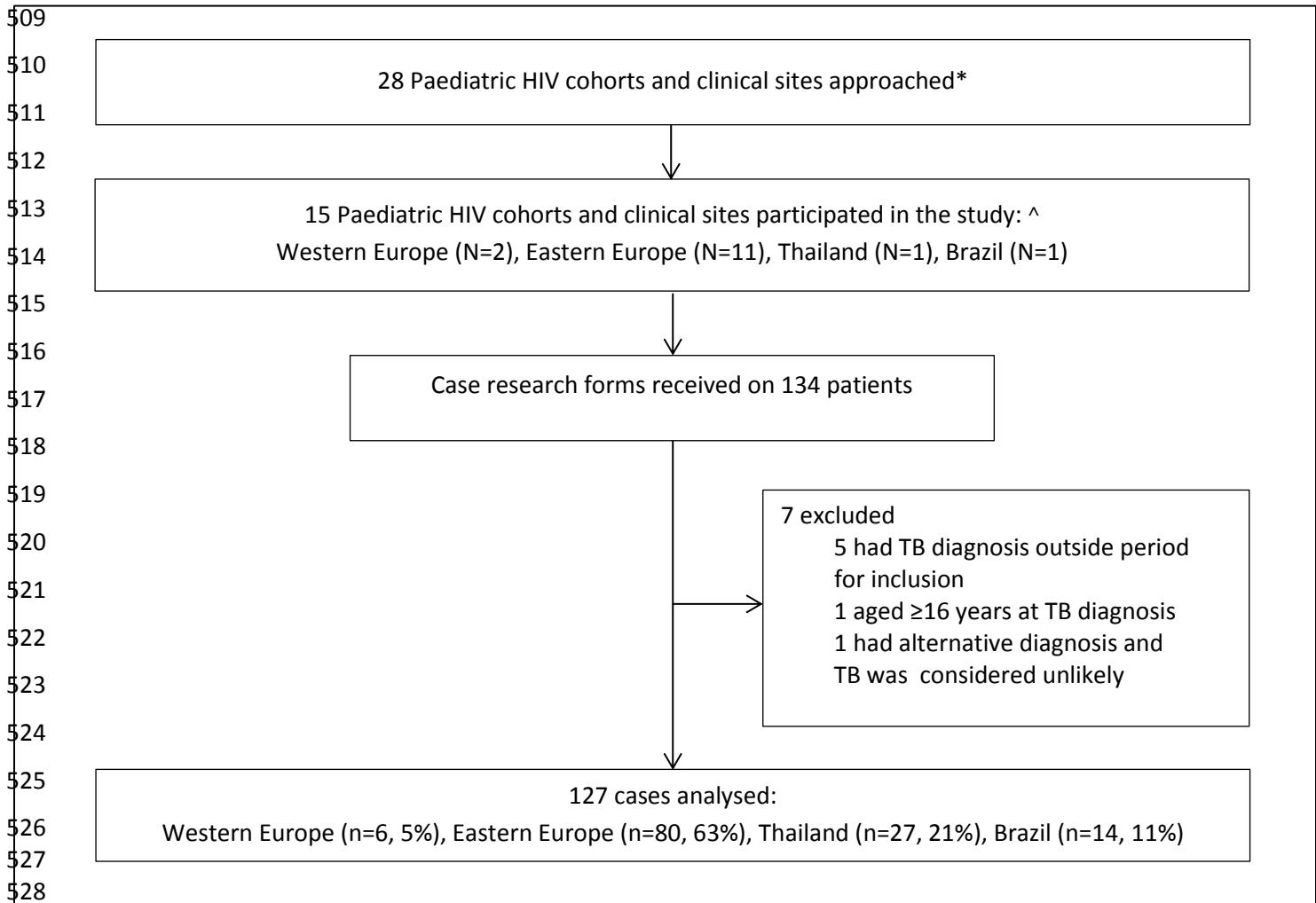
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530 **Figure 1 Flowchart of TB cases identified within PENTA cohort collaboration and included in the study**

531

532 *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.

533

534

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

553 **APPENDIX**

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

555

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