TITLE PAGE

Prevalence, incidence and associated risk factors of tuberculosis in children with HIV living in the UK and Ireland (CHIPS): a cohort study

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Running head: TB in HIV-infected children in UK/Ireland

Tuberculosis in HIV-infected children in the UK and Ireland: incidence, risk factors and outcomes

ABSTRACT

Background: Tuberculosis (TB) remains the most common serious co-infection in people living with HIV worldwide, but little is known about its incidence in HIV-infected children in high-resource settings with low tuberculosis prevalence We aimed to assess the incidence and prevalence of tuberculosis in children with HIV living in the UK and Ireland to understand rates, risk factors and outcomes of the diseases in this group.

Methods: We did an analysis or children enrolled in CHIPS, an observational multicentre cohort of children receiving HIV care in the UK and Ireland. We assessed characteristics and prevalence of tuberculosis at baseline, measured incidence of disease through the follow-up period using the CHIPS database, and calculated associated risk factors in these children with multivariable logistic and Cox regression models.

Findings: Between Jan 1, 1996 to Sept 18, 2014, data for 1848 children with 14761 years of follow-up were reported to CHIPS. 57 (3%) children were diagnosed with tuberculosis: 29 children had tuberculosis at presentation (prevalent tuberculosis) and 29 had the disease diagnosed during follow-up (incident tuberculosis), including one child with recurrent tuberculosis events. Median age at TB diagnosis was 9years (IQR 5, 12). 25 children (43%) had pulmonary tuberculosis, 24 (41%) extrapulmonary with or without pulmonary involvement, and the remainder (n=9, 16%) had unspecified-site tuberculosis. The overall incidence rate was 196 cases per 100000 person-years (95%CI 137-283). In our multivariable model, tuberculosis at presentation was associated with more severe WHO immunological stage at baseline (odds ratio 0.25, 95% CI 0.08-0.74; p=0.0331; for none vs severe) and being born abroad (odds ratio 0.28, 0.10-0.73; p=0.0036; for UK and Ireland vs abroad). Incident tuberculosis was associated with time-updated more severe WHO immunological stage (hazard ratio 0.15, 95% CI 0.06-0.41; p=0.0056; for none vs severe) and older age at baseline (1.11, 0.47-2.63; p=0.0027; for age >10 years vs 5-9 years).

Interpretation: Tuberculosis rates in HIV-infected children in the UK and Ireland were higher than those reported in the general paediatric population. Further study is warranted of tuberculosis screening and preventive treatment for children at high-risk of this disease to avoid morbidity and mortality in this population.

Funding: NHS England, PENTA Foundation

Key words: tuberculosis, HIV, co-infection, children, UK, Ireland, risk factors

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed using the terms “HIV”, “tuberculosis”, and “children” for studies published in English before June 1, 2015. Only four studies reported tuberculosis rates in HIV-infected children in high-resource countries with low TB prevalence. Two studies from 2000 and 2001 reported on tuberculosis in HIV-infected children in the USA; however, data were collected in 1989-1998, before combination antiretroviral treatment (ART) was widely available). The other two studies were subject to selection bias: the 2012 study in Spain analysed tuberculosis rates in HIV-infected children who had been admitted to hospital, and the 2008 study from the UK was restricted to HIV infected children attending a single tertiary clinic in London.

Added value of this study

To our knowledge, this is the first nationwide study to assess the prevalence and incidence of tuberculosis in HIV-infected children in the ART era in a low tuberculosis prevalence setting. We show that tuberculosis rates in HIV-infected children in the UK and Ireland are markedly higher than those in the general paediatric population. In adjusted analysis, risk factors for incident TB in children after entry to HIV care were older age at baseline (older than 5 years), and severity of immunological status at time of follow-up appointment.

Implications of all the available evidence

Our findings highlight the need for evaluation of screening practices and implementation of preventive tuberculosis treatment for HIV-infected children living in high-resource countries. Future research should include record linkage with the national tuberculosis databases, which would permit a direct comparison of incidence between children with HIV and those without.

Introduction

The UK and Ireland are classified as countries with low tuberculosis incidence , with rates between 7.3 and14·4 cases per 100000 population.[1,2] Three-quarters of cases in the UK occur in adults born abroad, with most in settled migrants who are diagnosed more than two years after entering the UK. By contrast, most children diagnosed with tuberculosis are born in the UK, reflecting continuing transmission within the country. In European Union and European Economic Area countries, tuberculosis notification rates in children younger than 15 years has decreased from 5.1 to 3.3 per 100000 population in the past decade.[1] The tuberculosis rate in UK-born children ranged from 2·0 to 3·1 cases per 100000 population, with substantially higher rates in black African (12-30cases per 100000) and Indian (11 -17cases per 100000) ethnic groups.[2,3] The highest rate of 64·8 per 100000, was reported among black African children living in London.[4]

Worldwide, tuberculosis remains the most common serious co-infection in people living with HIV, despite a substantial decrease in incidence of tuberculosis after the scale-up of antiretroviral therapy (ART). Although ART reduces the incidence of tuberculosis, it does not completely restore the functional immune response against the disease,[5,6] and higher rates continue to be recorded in HIV-infected adults on ART as compared with the general population in both high and low tuberculosis incidence countries.[7–11] Tuberculosis still accounts for a quarter of deaths in people with HIV, with the highest burden in sub-Saharan Africa.[12] In Western Europe, tuberculosis is the third most common AIDS-defining illness in HIV-infected adults.[13]

Incidence of tuberculosis in HIV-infected children in low-resource settings has been reported to be between 830 cases and 17500 cases per 100000 person-years,[14-18] with rates varying widely because of different burden of the disease ,uptake of HIV testing, and difficulties in diagnosis of tuberculosis in children. Few equivalent data are available in countries with low prevalence of tuberculosis. In 2000, two studies reported rates of tuberculosis in children in the USA, but these studies were done before ART was widely available and therefore the results are not generalizable to the current situation.[19,20] One study in Spain reported tuberculosis rates in hospitalised HIV-infected children during 1997–2008 to be 15·3 per 1000 hospital admission years, eight-fold higher than that in children without HIV. However this rate may be an overestimate because the study was restricted to children requiring hospitalisation.[21] A second study, based in a large clinic in London, reported that 5.5% of HIV-infected children were diagnosed with tuberculosis over the 15-year period of 1991–2006,[22] although this might reflect the higher overall tuberculosis incidence rate in London and in key groups.

In this study, we calculated the prevalence and incidence of tuberculosis in HIV-infected children living in the UK and Ireland who are registered in the nationwide Collaborative HIV Paediatric Study (CHIPS) and assessed risk factors associated with tuberculosis co-infection.

Methods

CHIPS is an observational multi-centre cohort study of children receiving HIV care in the UK and Ireland. All infants born to HIV-infected women and children aged younger than 16 years diagnosed with HIV in the UK and Ireland, irrespective of their place of birth, are reported to the National Study of HIV in Pregnancy and Childhood (NSHPC). Once HIV infection is confirmed and the child receives care at a centre participating in CHIPS (56 centres as of June, 2015) throughout the IK and Ireland, annual follow-up data are collected while in paediatric HIV care, as described online (www.chipscohort.ac.uk).[23,24] Demographic, clinical, laboratory, and ART-related data have been collected since April 2000, with data from 1996 retrospectively obtained. Both NSHPC and CHIPS have received ethics approval from the National Health Service.

Definitions

We obtained date for prevalent tuberculosis (tuberculosis at presentation), defined as the disease diagnosed 30 days before or after entry to HIV care in the UK/Ireland, and incident tuberculosis (tuberculosis during follow-up) defined as the disease diagnosed more than 30 days after entry to HIV care. Additionally, we obtained data for tuberculosis before entry to HIV care, defined as patient-reported or documented disease more than 30 days before presentation to HIV care.
The date of first presentation to an HIV clinic in the UK and Ireland was defined as earliest of first clinic visit date, first ART initiation, or date of first CD4 cell count or viral load test; those missing an entry date were excluded from analysis. Children with no reported clinic visit for 24 months or more (to allow for reporting delays) were considered lost to follow-up.

All events classified as category B or C by the US Centers for Disease Control (CDC), hospital admissions, and deaths are routinely reported in the HCIPS database. Events documented as tuberculosis -related were reviewed by an independent clinician (AT), whereas those documented as suspected TB were checked with the clinics. Latent tuberculosis entered in error and events which were subsequently ruled out by the attending clinicians as not tuberculosis were excluded from further analysis. Tuberculosis events were reported as either definitive (supported by microscopy, histology, cytology, culture, antigen detection or molecular tests) or presumptive (characteristic clinical presentation, supported by other investigations and after exclusion of other causes in the differential diagnosis). Tuberculosis clinical forms were categorised by site of infection as pulmonary only, extrapulmonary (with and without pulmonary involvement) or unspecified site. Recurrent tuberculosis events reported within 12-months of each other were assumed to be a

relapse and considered as one event. Deaths were classified as tuberculosis -related when tuberculosis was one of the reported underlying causes of death.

We categorised tuberculosis events into the following three categories: less than 4 months, 4-12 months and more than 12 months after initiation or restart of ART. The less than 4 month cut-off was chosen based on the upper range of the reported median time from start of ART to tuberculosis associated immune reconstitution inflammatory syndrome (IRIS) diagnosis in children.[25] Children on ART for 1 day or longer at time of tuberculosis diagnosis were classified as receiving ART, those who were off all antiretroviral drugs for longer than 30 days were classified as off-ART (previously treated). HIV-1 RNA virological suppression was defined as less than 400 copies per mL to allow for historical variation in assay lower limit of detection.

Statistical analyses

We describe baseline characteristics of children at time of presentation to HIV care by tuberculosis status Characteristics of children with tuberculosis at presentation or during follow-up were compared with those with no tuberculosis with use of the χ^2test for categorical variables (or Fisher's exact test when numbers were lower than 5), and Wilcoxon's rank-sum test for continuous variables.

For the analysis of TB incidence, children with tuberculosis before entry to HIV care were considered at risk 12 months after their tuberculosis diagnosis date, based on the assumption that they received TB treatment for 6-12 months depending on the clinical form and extent of the disease. Those without tuberculosis at presentation to HIV care were at risk from 31 days after enrolment. Children were censored at their first tuberculosis diagnosis after entry to HIV care, last clinic visit, date of transfer to adult care or death. Incidence of tuberculosis during follow-up was calculated overall as cases per 100000 person-years and by key risk factors.

Potential risk factors for tuberculosis include clinical status (pre-AIDS vs AIDS), viral load (VL) and WHO immunological stage at entry to HIV care, defined as the nearest measurement to the date of entry (up to 90 days after presentation). HIV-associated immunodeficiency for age was classified asnone, mild, advanced or severe as per WHO 2007 classification.[26] This was chosen as it reflects age-adjusted risk of progression to AIDS or death.[27]

To assess factors associated with having tuberculosis at presentation to HIV care, we used multivariable stepwise logistic regression models that included the following baseline variables: sex,

age, place of birth, ethnic origin, region, calendar year, AIDS status, viral load and WHO immunological stage at presentation. To assess factors associated with incident tuberculosis during follow –up we plotted Cox survival models with the above parameters plus time-updated immunological stage, ART status (off ART, on ART for less than 4 months, 4-12 months or more than 12 months), and viral load (per 0.5 $\log_{10}$ increase and viral load <400 copies per mL as proxy of effective ART). Variables with $p<0.15$ in this univariable analyses were included in a multivariable models, and backwards selection (exit probability p=0·1) was used to identify those with the strongest association. Statistical analyses were performed using Stata version 13·1.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 2265 children diagnosed with HIV and reported to NSHPC between Jan 1, 1996 to Sept 18, 2014, 1907 (84%) were listed in CHIPS, of whom 1848 (97%) had a known date of presentation to HIV care and were included in this analysis. The median duration of follow-up after entry to HIV care was 8·1 (IQR 4·1-11·8) years, with a total of 14761 person-years of follow-up. As of Sept 18, 2014, 97 (5%) children had died, 98 (5%) left the country, 102 (6%) had been lost to follow up, 635 (34%) had transferred to adult care, 4 (<1%) had transferred to another centre and 912 (49%) remain in follow up in paediatric care. Among those currently in follow up in paediatric care the median age at last clinic visit was 13.4 years (IQR 10.0-15.7). Among those transferred to adult care, the median age at last visit was 17.5 years (IQR 16.6-18.3).

Fifty-seven (3%) children were diagnosed with 58 tuberculosis events. During follow up, 29 children had tuberculosis at presentation and 29 had incident tuberculosis, including one child with recurrent tuberculosis events (Figure 1). Additionally, 39 (2%) children were reported to have had tuberculosis pre-entry to HIV care, of whom two had recurrent disease at presentation and one developed the disease during follow-up. Of 1831 CDC classified events reported at or after presentation, 52 (2%) were tuberculosis -related, of which 30 (58%) were stage B and 22 (42%) were stage C. Of these 52 TB-related CDC events, 21 were reported as definitive, 16 as presumptive and 15 as unspecified. An additional five tuberculosis events in five children were captured through tuberculosis -related hospital admissions (no CDC classified event reported). Overall, 64% (37 of 58) of tuberculosis events required hospitalisation, representing 1% of the total 3738 hospitalisations reported in the CHIPS cohort during this time period. Of the 97 deaths reported in CHIPS during paediatric care, five (5%) were probably tuberculosis -related: one died with disseminated tuberculosis and four with tuberculosis meningitis (case-fatality rate 5 [9%] of 57). Three of these children were diagnosed with tuberculosis at presentation and two had incident tuberculosis during follow-up. All were severely immunocompromised or had other AIDS-indicator disorders at time of death.

At time of presentation to HIV care, children diagnosed with tuberculosis (at presentation or during follow-up) were older ($p<0·0001$) than those with no tuberculosis (table 1). . Most children with tuberculosis at presentation and diagnosis during follow up were born abroad. Most cases of tuberculosis occurred in black African children (table1): no tuberculosis cases were diagnosed in white children. None of the children with tuberculosis at presentation and only one with tuberculosis during follow-up had ever received ART, whereas more than a tenth of those who had no tuberculosis had initiated ART before entry to HIV care in UK and Ireland (table 1).

Children with tuberculosis at presentation were younger at diagnosis than children who developed the disease during follow-up (p=0·0110; table 2). Immunological stage did not differ between the two groups (p=0·2323), although children with tuberculosis at presentation had higher viral load at the time of diagnosis (p=0.0003). Of the 58 children diagnosed with tuberculosis, 25 (43%) had pulmonary tuberculosis only, 24 (41%) had extrapulmonary disease (with or without pulmonary involvement), and the remainder (nine [16%]) had unspecified disease (table2).

Among children with tuberculosis at presentation (n=29), three were diagnosed with HIV and TB concurrently (within one day), and 20 children presented with tuberculosis before HIV diagnosis. Of those with tuberculosis during follow-up, the median time from presentation to HIV care to first tuberculosis event was 18 months (IQR 7·0-59·7). Recurrent tuberculosis within the study period was reported in one child who had tuberculosis of intra-thoracic lymph nodes at presentation (clinically diagnosed) and pulmonary tuberculosis (microbiologically confirmed) 9 years later.

Overall, 39 (67%) tuberculosis events occurred in children who were ART naïve (n=37) or off-ART (n=2) at time of TB diagnosis; 35 children initiated or re-started ART at a median of 2·9 (IQR 0·7 - 13·7) months after their diagnosis with tuberculosis (Table 2). Of the four children who did not initiate ART, one left the country, one was lost to follow-up, one transferred to adult care and one died a month after diagnosis. The remaining 19 (33%) events recorded during follow-up were noted at a median 14·3 months (IQR 6·2-44·0) after ART initiation. Five patients had changes to their ART regimens within 6 months of their tuberculosis event report. None had conventional substitutions to avoid or minimise drug interactions with anti-tuberculosis treatment; only one had an increase of nevirapine dose and none had extra ritonavir added.

In multivariable analysis of factors associated with tuberculosis prevalence at presentation to HIV care, the only factors independently associated with diagnosis were being born abroad (odds ratio for born in the UK or Ireland vs abroad 0.28, 95% CI 0.10-0.73) and severe WHO immunological stage at presentation (0.25, 0.08-0.74 for stage none vs severe; table 3).

The overall tuberculosis incidence rate during follow-up in HIV care was 196 cases per 100000 person-years (95% CI 137-283In univariable analyses, factors associated with incident tuberculosis during follow-up were having been born abroad, black African ethnicity, older age (both baseline and time-updated), more severe immunosuppression status (time-updated), higher viral load (time

updated copies per mL) and time on ART of less than 4 months (table 4). After adjustment in multivariable analysis, older age at presentation (hazard ratio 1.11, 0.47-2.63, p=0.0027; for >10 years vs 5-9 years) and more severe current WHO stage immunological status (hazard ratio 0.15, 95% CI 0.06-0.41; p=0.0056; for none vs severe) remained independent predictors of tuberculosis diagnosis during follow up.

Discussion

In the UK and Ireland (as in many other European countries), HIV status is not reported at tuberculosis notification to the national surveillance programme, and paediatric HIV-TB record linkage has not been established. Therefore the tuberculosis incidence rates in HIV-infected children can be estimated only with use of data from national HIV cohorts. To our knowledge, this is the first comprehensive analysis of tuberculosis incidence and associated risk factors in HIV-infected children in a high-income country with low tuberculosis prevalence. The CHIPS cohort had 84% coverage for all children receiving HIV care in the UK/Ireland from 1996 onwards; this coverage has approached 100% in recent years,[24] with nearly 15,000 person-years of follow-up, and so it is highly representative of the HIV-infected paediatric population in the UK and Ireland.

Our results suggest that tuberculosis in HIV-infected children in the UK and Ireland affects 3% of the entire cohort, with half of all tuberculosis cases diagnosed at presentation to HIV care. This is similar to reports from adult studies in western Europe.[11,28] Nearly half (49%) of specified tuberculosis cases in our cohort were extrapulmonary, with or without pulmonary involvement, with a high proportion of severe extrapulmonary tuberculosis cases, including central nervous system disease in 16%. In comparison, the data collected through the British Paediatric Surveillance Unit (BPSU) in the UK and Ireland showed that overall extrapulmonary tuberculosis comprise 60% of all tuberculosis forms in the general paediatric population, with most forms being hilar lymphadenopathy (i.e. non-severe tuberculosis); disease in the central nervous system was diagnosed only in 6% of these cases.[29] Studies from areas with high tuberculosis and HIV-prevalence suggest that HIV-infected children have more frequent disseminated tuberculosis,[30,31] and severe pulmonary tuberculosis.[32] Clinical spectrum is likely to depend on the degree of immune deficiency, with severe forms more common in children with advanced HIV.[33] A larger study should investigate whether this excess of severe tuberculosis disease still occurs in children with none or mild immunodeficiency. Although only 5 tuberculosis related deaths were noted in CHIPS in the 18-year study period, case-fatality rate was nearly 5 times higher than that reported in the BPSU study (9% vs 2%). Additionally, this was not that dissimilar with results from high-TB settings reporting 3.3-11.7% case-fatality rate in HIV-infected children.[14,31,34,35]

We report an overall incidence of tuberculosis of 196 cases per 100000 person-years during follow-up in HIV care. This is much lower than that in countries with a high tuberculosis burden, for which rates vary from 830 per 100000 to 17500 per 100000,[14-18] reflecting higher exposure and higher proportion of vulnerable (malnourished and severely immunocompromised) children. Almost all

children with incident tuberculosis in CHIPS were of black African ethnicity (89%) and more than half resided in London. Tuberculosis incidence in HIV-infected children in the ART era seems to remain substantially higher than that in the general paediatric population,[2,3] and more than triple the reported rate among black African children in London.[4] Similar results that show increased rates of tuberculosis in HIV-infected adults compared with the general population have been reported across Europe, despite widespread access to ART.[10,11,28,36,37] Furthermore, tuberculosis events in HIV-infected children in the UK and Ireland would have contributed towards the incidence estimate in the general paediatric population; therefore the true incidence in the HIV-uninfected paediatric population is likely to be even lower. Of note, there were no tuberculosis events reported in white children with HIV in the UK and Ireland, reflecting national trends of higher incidence in black and Asian ethnic origin communities, as well as the small proportion (9%) of white children in CHIPS.

The reasons for higher rates of tuberculosis in HIV-infected children than in uninfected children in this low prevalence setting are likely to be multifactorial. First, HIV-infected children are likely to have higher risk of tuberculosis -exposure because of higher prevalence of the disease TB in HIV-infected close family members and, for those whose families came from abroad (mostly from sub-Saharan Africa), due to greater contact with communities from countries with a high tuberculosis burden. Secondly, immune dysfunction which is likely to be present despite ART, predisposes to increased progression to tuberculosis infection and subsequent disease. Indeed, immunosuppression and black African ethnicity were independently associated with incident tuberculosis in our univariable analysis, and immunosuppression in our multivariable analysis, and reported in several adult cohorts on ART in Europe.[10,11,28,36,37] As shown in adults,[10,28] tuberculosis events increase during the first few months of ART initiation in children, which is likely to be caused by ART unmasking subclinical tuberculosis as a manifestation of IRIS.

Furthermore, children who were older at presentation to HIV care (age older than 5 years) were at higher risk of developing tuberculosis during follow-up than younger children, and this might partly reflect the reduced capacity for immune restoration in children who initiate ART at older ages.[38] A substantially lower rate of incidence was shown in children on ART for longer than 12-months and in those with suppressed viral load (<400 copies per mL; a proxy of effective ART) in univariable analysis. These observations are consistent with highly protective effect of ART shown in the studies from settings with a high tuberculosis.[15,16,18,31,34,39]. However, these factors were not associated with infection in multivariate analysis in our study, probably because of insufficient power.

Limitations

There are several limitations to this study. First, we relied on the diagnosis of tuberculosis made by clinicians. This is notoriously challenging in HIV-infected children, because of overlapping clinical presentations of HIV, tuberculosis and other comorbidities; difficulties with obtaining specimens; and difficulties with microbiological confirmation secondary to the paucibacillary nature of childhood tuberculosis. Tuberculosis diagnosis therefore might have been underestimated or overestimated. However, all cases were reviewed by an independent clinician, and a third of tuberculosis -related CDC classified events were reported as definitive, which is comparable to proportions confirmed in the general paediatric population. Secondly, we were unable to identify or rule out tuberculosis-associated-IRIS. Third, because of the small number of tuberculosis events, we could not assess whether children on suppressive ART with immune reconstitution were still at higher risk of incident tuberculosis compared with the general paediatric population. Fourth, data for tuberculosis screening practice and preventive treatment over time and across clinics were not collected and could not be assessed.

Conclusion

Tuberculosis infection rates and case-fatality rates in HIV-infected children in the UK and Ireland are markedly higher than those reported in the general paediatric population, raising the important question of whether tuberculosis screening and prevention practices could be improved to avert morbidity and mortality in this population. Children at high risk of incident tuberculosis as identified by this study (older children, children of black African ethnic origin and those with severe immunosuppression) might benefit from repeat exposure-history and symptom-based screening during follow-up, and targeted preventive treatment. Further studies to evaluate current screening and prevention practices and potential gaps in care are warranted.

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Anna Turkova, Ali Judd, Ruth Goodall, Di Gibb and Intira Collins were responsible for the study concept and design. Elizabeth Chappell carried out the statistical analyses. Anna Turkova, Elizabeth Chappell, Ali Judd, Ruth Goodall, Di Gibb and Intira Collins drafted the manuscript. Steve Welch, Caroline Foster, Andrew Riordan, Delane Shingadia, Fiona Shackley, Katja Doerholt and Di Gibb collected the data. All co-authors participated in discussions about the design of the study, interpretation of the findings, and critically reviewed the manuscript.

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Table 1: Patient characteristics at presentation to HIV care in the UK/ Ireland

Characteristic (n=number with data available if not complete)	TB at presentation (n=29)	TB during follow-up* (n=28)	No TB (n=1791)	Overall (n=1848)	p-value†
	n (%) or median [interquartile range, IQR]				
Male	17 (59%)	15 (54%)	852 (48%)	901 (48%)	0·2023
Age (years)†	7·0 [4·3, 10·5]	8·2 [5·8, 10·9]	4·8 [1·4, 9·0]	4·9 [1·5, 9·1]	<0·0001
<5 years	11 (38%)	5 (18%)	920 (51%)	936 (51%)	0·0005
Place of birth† (n=29, 28, 1781)					0·0005
UK/Ireland	5 (17%)	6 (21%)	798 (45%)	809 (44%)	
Abroad	24 (83%)	22 (79%)	983 (55%)	1029 (56%)	
In high TB burden country	15 (63%)	16 (73%)	609 (62%)	640 (62%)	0·4572
Region					0·0848
London	20 (69%)	19 (68%)	1020 (57%)	1059 (57%)	
Rest of UK/Ireland	9 (31%)	9 (32%)	771 (43%)	789 (43%)	
Ethnicity† (n=29, 28, 1778)					0·0176
White	0	0	163 (9%)	164 (9%)	
Black African	25 (86%)	26 (93%)	1396 (78%)	1447 (78%)	
Asian/Middle East/Mixed/Other	4 (14%)	2 (7%)	219 (12%)	238 (13%)	
Mode of presentation†					0·0001
Pre-AIDS	15 (52%)	25 (89%)	1568 (88%)	1608 (87%)	
AIDS	14 (48%)	3 (11%)	223 (12%)	240 (13%)	
Source of HIV infection (n=29, 28, 1752)					0·4617
Perinatal	28 (97%)	28 (100%)	1699 (95%)	1755 (95%)	
Blood transfusion	0	0	35 (2%)	35 (2%)	
Other	1 (3%)	0	18 (1%)	19 (1%)	
CD4%, age <5 years (n=10, 4, 746)	21 [16, 27]	25 [9, 30]	24 [16, 33]	24 [16, 33]	0·2820
CD4 count (cells per µL), age ≥5 years (n=16, 20, 684)	148 [35, 410]	273 [124, 542]	408 [200, 684]	400 [195, 673]	0·0055
WHO immunological stage (n=28, 27, 1599)					0·0761
None	4 (14%)	9 (32%)	568 (32%)	581 (31%)	
Mild	5 (17%)	3 (11%)	237 (13%)	245 (13%)	
Advanced	2 (7%)	3 (11%)	200 (11%)	205 (11%)	
Severe	17 (59%)	12 (43%)	594 (33%)	623 (34%)	
Viral load ($\log_{10}$) (n=29, 25, 1436)	5·1 [4·6, 5·6]	4·6 [4·0, 5·0]	4·7 [3·8, 5·3]	4·7 [3·8, 5·3]	0·4059
Viral load <400 (copies per mL)	2 (7%)**	1 (4%)	133 (7%)	136 (7%)	0·4749
ART prior to UK/Ireland HIV care†	0	1 (4%)	197 (11%)	198 (11%)	0·0262

* One patient who had TB at presentation to HIV care and during follow-up is summarised in the TB at presentation group

** Started on ART shortly after presentation to HIV care, first available viral load after ART initiation and within window of 90 days after presentation

† Comparison between those with TB at presentation/during follow-up vs those with no TB

Table 2: Patient characteristics, sites of TB disease and ART status at time of TB diagnosis

Characteristic (n=number with data available if not complete)	TB events at presentation (n=29)	TB events during follow-up (n=29)	Overall (n=58)	p-value†
	n (%) or median [IQR] (range)			
Age (years)†	6·9 [4·2, 10·4]	10·1 [8·6, 13·7]	9·3 [5·3, 12·3]	0·0110
CD4%, age <5 years (n=11, 3)	19 [11, 27]	25 [15, 37]	21 [15, 27]	0·3918
CD4 count (cells per µL), age≥5 years (n=18, 24)	148 [60, 398]	243 [160, 462]	228 [138, 442]	0·2857
WHO immunological stage (n=29, 27)				0·2323
None	5 (17%)	5 (17%)	10 (17%)	
Mild	5 (17%)	5 (17%)	10 (17%)	
Advanced	2 (7%)	7 (24%)	9 (16%)	
Severe	17 (59%)	10 (34%)	27 (47%)	
Viral load (log_{10})† (n=29, 26)	5·1 [4·6, 5·6]	3·7 [2·2, 4·5]	4·6 [2·7, 5·2]	0·0003
Viral load <400 (copies per mL)†	2 (7%)	8 (28%)	10 (17%)	0·0346
TB site				
Pulmonary only	**11 (38%)**	**14 (48%)**	**25 (43%)**	0·5543
Extrapulmonary with and without pulmonary involvement	**14 (48%)**	**10 (35%)**	**24 (41%)**	
TB meningitis	3	5	8	
Miliary	5	0	5	
Disseminated, site not specified	1	1	3	
Osteoarticular	0	2	2	
Abdomen	0	1	1	
Lymph nodes*	2	0	2	
Site not specified	1	1	1	
Pulmonary and peripheral lymph nodes	1	0	1	
Pulmonary and TB meningitis	1	0	1	
Unspecified	**4 (14%)**	**5 (17%)**	**9 (16%)**	
ART†				
ART naïve at TB diagnosis	29 (100%)	8 (28%)	37 (64%)	<0·0001
ART experienced but not on ART at time of TB diagnosis	0	2 (7%)	2 (3%)	
Time from TB diagnosis to ART initiation/restart**	1·4 [0·5, 7·7] (0·1, 45·8)	7.6 [4·4, 25.2] (0·2, 74·0)	2·9 [0·7, 13·7] (0·1, 74·0)	
On ART at time of TB diagnosis	0	19 (66%)	19 (33%)	
Time from initiation of ART to TB diagnosis	-	14.3 [6·2, 44·0] (1·1, 110·0)	14·3 [6·2, 44·0] (1·1, 110·0)	

*Intra- or extrathoracic

**3 of those with TB at presentation and 1 with TB during follow-up who were not on ART at the time of diagnosis never received ART

† Comparison between TB events at presentation and TB events during follow-up.

Table 3: Factors associated with TB diagnosis at presentation to HIV care

		Univariable			Multivariable		
		Odds ratio	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Gender	Male	1	-	0·2409	-		
	Female	0·64	0·31, 1·35				
Age (years)	<5	0.77	0·31, 1·94	0·1934	-		
	5–<10	1	-				
	≥10	1·75	0·68, 4·47				
Place of birth	Abroad	1	-	0·0020	1	-	0·0036
	UK/Ireland	0·26	0·10, 0·69		0·28	0·10, 0·73	
Ethnicity	Black African	1	-	0·2730	-		
	Other	0·57	0·20, 1·66				
Region	London	1	-	0·1932	-		
	Rest of UK/Ireland	0·60	0·27, 1·32				
Calendar year	<2003	0·94	0·41, 2·20	0·8842	-		
	2003–2006	1	-				
	>2007	0·78	0·27, 2·20				
WHO immunological stage	None	0·25	0·08, 0·74	0·0315	0·25	0·08, 0·74	0·0331
	Mild	0·74	0·27, 2·04		0·73	0·26, 1·99	
	Advanced	0·35	0·08, 1·53		0·36	0·08, 1·60	
	Severe	1	-		1	-	
Viral load, per 0.5 $\log_{10}$ increase		1·10	0·93, 1·29	0·2522	-		

Table 4: Factors associated with TB diagnosis during follow-up

		Number of cases	Crude rate per 100000 PY (95% CI)	Univariable			Multivariable		
				Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Overall		29	196 (137, 283)	-					
Baseline (presentation to HIV care)									
Gender	Male	15	210 (128, 349)	1	-	0·6765	-		
	Female	14	184 (109, 310)	0·86	0·41, 1·77				
Age (years)	<5	6	63 (29, 140)	0·20	0·08, 0·53	0·0004	0·20	0·08, 0·53	0·0027
	5–<10	15	392 (238, 654)	1	-		1	-	
	≥10	8	557 (279, 1114)	1·12	0·46, 2·71		1·11	0·47, 2·63	
Place of birth	Abroad	22	330 (217, 502)	1	-	0·0070	-		
	UK/Ireland	7	87 (41, 182)	0·34	0·13, 0·79				
Ethnicity	Black African	27	247 (169, 360)	1	-	0·0169	1	-	0·0895
	Other	2	52 (13, 209)	0·24	0·06, 1·01		0·34	0·08, 1·44	
Region	London	19	210 (134, 330)	1	-	0·4359	-		
	Rest of UK/Ireland	10	175 (94, 324)	0·74	0·34, 1·60				
Mode of presentation	Pre-AIDS	26	202 (137, 296)	1	-	0·7571	-		
	AIDS	3	160 (51, 495)	0·83	0·25, 2·75				
Calendar year	<2003	12	126 (72, 222)	0·50	0·23, 1·10	0·2006	-		
	2003–2006	13	356 (207, 613)	1	-				
	>2007	4	249 (94, 665)	0·53	0·17, 1·65				
WHO immunological stage	None	9	198 (103, 380)	0·78	0·33, 1·86	0·8301	-		
	Mild	3	146 (47, 452)	0·59	0·17, 2·10				
	Advanced	4	244 (92, 651)	0·98	0·32, 3·04				
	Severe	12	248 (141, 437)	1	-				
ART status	Naïve	28	204 (141, 295)	1	-	0·2653	-		
	Experienced	1	97 (14, 689)	0·38	0·05, 2·79				
Viral load, per 0.5 log_{10} increase		-		0·98	0·83, 1·15	0·7721	-		
Time-updated variables									
Age (years)	<5	3	118 (38, 365)	0·32	0·08, 1·18	0·0087	-		
	5–<10	10	203 (109, 378)	1	-				
	≥10	16	219 (134, 358)	1·82	0·82, 4·03				
Calendar year	<2003	6	166 (75, 371)	0·44	0·16, 1·20	0·2479	-		
	2003–2006	11	296 (164, 535)	1	-				
	>2007	12	161 (92, 284)	0·78	0·34, 1·80				
WHO immunological stage	None	7	76 (36, 159)	0·13	0·05, 0·35	0·0001	0·15	0·06, 0·41	0·0056
	Mild	6	250 (113, 557)	0·45	0·16, 1·25		0·44	0·16, 1·20	
	Advanced	6	498 (224, 1109)	0·90	0·33, 2·48		0·85	0·31, 2·34	
	Severe	10	552 (297, 1026)	1	-		1	-	
ART status	Off ART	10	225 (121, 417)	1	-	0·0656	-		
	On ART <4 months	6	990 (445, 2204)	3·24	1·08, 9·67				
	On ART 4–12 months	5	414 (172, 995)	1·61	0·52, 4·95				
	On ART >12 months	8	94 (47, 188)	0·57	0·22, 1·52				
Viral load (copies per mL)	≥400	20	304 (196, 471)	1	-	0·0161	-		
	<400	9	122 (63, 234)	0·40	0·18, 0·87				
Viral load, per 0.5 log_{10} increase		-		1·51	1·16, 1·98	0·0020	-		