Tuberculosis incidence in country of origin is key determinant of active tuberculosis risk in HIV: thirty-year observational cohort study data

Supplementary Information

Helena A White[1,2]
Hajra Okhai[3]
Peter Kirwan[3]
Sonia H Rafeeq[3]
Helen Dillon[2]
Phillip Hefford[2]
Martin J Wiselka[2]
Manish Pareek[1,2]

[1]Department of Respiratory Sciences, University of Leicester, Leicester, UK
[2]Department of Infection and HIV Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK
[3]Institute for Global Health, University College London, London, UK
[4]Blood Safety, Hepatitis, Sexually Transmitted Infections and HIV Service, Public Health England, London, UK

Corresponding author:
Dr Manish Pareek
Department of Respiratory Sciences, University of Leicester, University Rd. Leicester LE1 7RH, UK.
Tel. +44 116 258 6952. Fax. +44 116 2585005
Email: manish.pareek@nhs.net

Ascertainment of TB status

Every single patient record was scrutinised in order to identify information pertaining to a diagnosis of active TB. This included paper records of clinic visits, transfer of care letters, and electronic records. Confirmation of active TB was undertaken wherever possible by cross-checking our local TB database, electronic laboratory results programme, and examining paper hospital records for patients who had received care pre-1998. Only the first episode of active TB was included for each individual. Data was included until the end of the study on 1st March 2019.

The definition of active TB included the following; isolation of *Mycobacterium tuberculosis* (Mtb) from microbiological culture; acid-alcohol fast bacilli (AAFB) positivity on sputum smears, even if culture negative, with other clinical or radiological evidence suggestive of TB; clinical or radiological evidence suggestive of TB and treated as such, even if Mtb was not isolated.

The anatomical site of TB was recorded, together with culture positivity status, CD4 cell count and HIV viral load (HIV-RNA) at the time of TB diagnosis. TB site was defined as "pulmonary" if there was pulmonary involvement, with or without involvement elsewhere in the body, and "extrapulmonary" if there was no pulmonary involvement evident. If an individual was smear positive but no culture was available then they were pragmatically classified as culture positive for the purposes of analysis.

To identify cases of active TB which had not been recorded in local TB surveillance systems but which had occurred when patients were under care elsewhere in the UK, cross-referencing with the national HIV and AIDS Reporting System (HARS) and Enhanced TB surveillance system (ETS) held at Public Health England (PHE) was undertaken in March 2019. HARS comprises pseudo-anonymised reports of HIV diagnoses from all clinics in England, Wales and Northern Ireland (E,W & NI) since 1979, and ETS has collected all notifications of TB in E, W & NI since 2000. The study population were verified in the HARS system, then referenced against a routinely linked HIV-TB dataset, generated using a matching algorithm described elsewhere [1]. Details of active TB episodes were extracted from ETS for linked cases.

Dates of TB and HIV diagnosis

The date of HIV diagnosis was recorded as the first date upon which a positive HIV antibody or HIV-RNA level was taken at our centre, or a date recorded in the medical notes if diagnosis was made elsewhere. If only the month was known then the date was recorded as the first day of the month, whereas if only the year was known then 15th July of that year was used as the diagnosis date.

The date of TB diagnosis was recorded as the date upon which a culture positive microbiological sample for TB was taken, or supportive histological sample if cultures were negative. In the absence of microbiological or histological evidence of TB, the date of diagnosis was recorded as that upon which the patient initiated anti-tuberculous treatment. If only the month and year was known then the same procedure was followed as for HIV diagnosis dates. If only the decade was known then the 15th July in the midpoint year of that decade was used.

HIV-RNA thresholds

Our virology laboratory has used different PCR assays to measure HIV-RNA over recent years. The most recent assay in use in this study used a threshold of <40 viral copies/ml to classify HIV-RNA as being undetectable, or virologically suppressed. Prior to some time between mid-2005 and mid-2006, the threshold used was <400 viral copies/ml. Prior to late 1998, there was no threshold specified in the laboratory results; a comment of "undetectable by PCR" was used only.

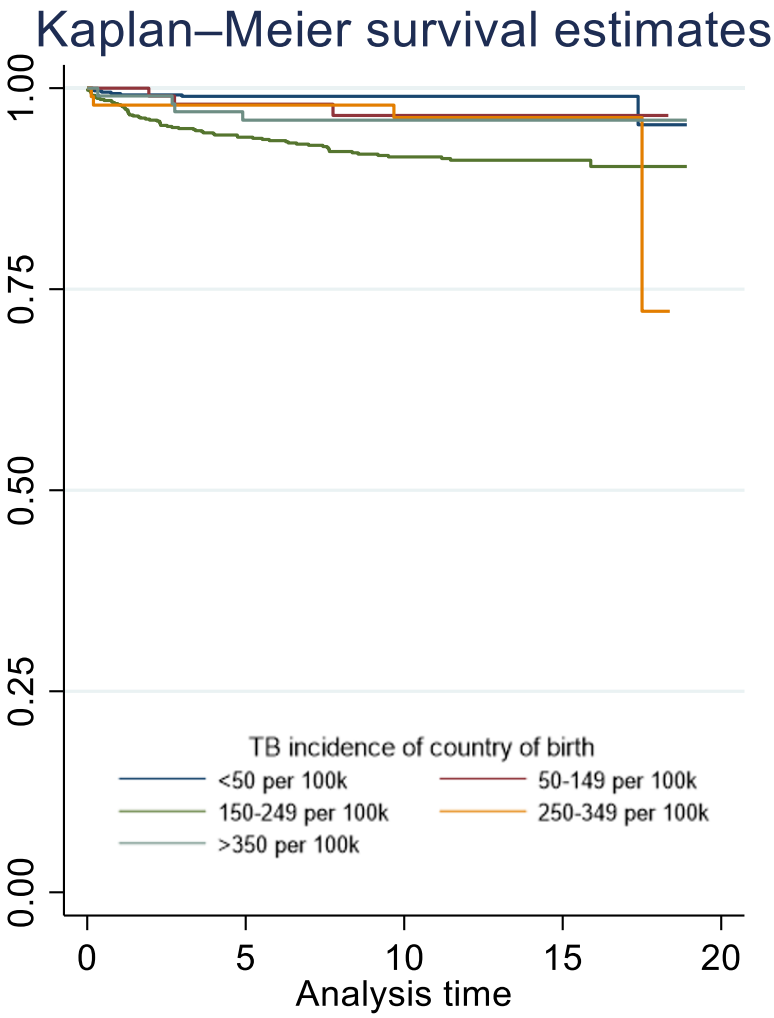
For the purposes of this study, we classified any PCR result reported as "<…." as an undetectable HIV-RNA, and any absolute value as a detectable HIV-RNA.

Results

Kaplan-Meier survival estimates

Figure S1 shows the Kaplan-Meier survival estimates for the development of incident TB, in relation to the categorical TB incidence rate in the country of birth.

Figure S1. Kaplan-Meier survival estimate curve for the development of incident tuberculosis more than 3 months after HIV diagnosis; Leicester HIV/TB cohort study 1983-2017



Number at risk					
<50 per 100k	599	462	258	79	0
50-149 per 100k	102	88	62	18	0
150-249 per 100k	782	677	504	184	0
251-349 per 100k	95	86	61	21	0
>=350 per 100k	103	92	66	23	0

References

1. 1 Winter JR, Delpech V, Kirwan P*, et al*. Linkage of UK HIV and tuberculosis data using probabilistic and deterministic methods. Conference on Retroviruses and Opportunistic Infections. Boston 2016