Injecting drug use predicts active tuberculosis in a national cohort of people living with HIV

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Full title: Injecting drug use predicts active tuberculosis in a national cohort of people living with HIV from 2000 to 2014

Short title: Injecting drug use predicts TB in people with HIV

Joanne R WINTER, MSc,[1*] Helen R STAGG, PhD,[1] Colette J SMITH, PhD,[1] Alison E BROWN, PhD,[2] Maeve K LALOR, PhD,[2] Marc LIPMAN, MD,[3,4] Anton POZNIAK, MD,[5] Andrew SKINGSLEY, MRCP,[2] Peter KIRWAN, BSc,[2] Zheng YIN, PhD,[2] H Lucy THOMAS, MFPH,[2] Valerie DELPECH, FFPH,[2†] Ibrahim ABUBAKAR, PhD[1†]

1. Institute for Global Health, University College London, 30 Guildford Street, London, WC1N 1EH, UK
2. National Infections Service, Public Health England, 61 Colindale Avenue, London, NW9 5EQ, UK
3. Royal Free London National Health Service Foundation Trust, Royal Free Hospital, Pond Street, London, NW3 2QG, UK
4. UCL Respiratory, Division of Medicine, University College London, Royal Free campus, Pond Street, London, NW3 2PF, UK
5. Chelsea and Westminster Hospital, 369 Fulham Road, London, SW10 9NH, UK

* Corresponding author. Telephone: 02076796619. Email: joanne.winter.14@ucl.ac.uk

† Joint senior authors

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This paper utilised two surveillance datasets collected by the respiratory (Tuberculosis section) and HIV departments in the National Infections Service at Public Health England. In light of the work involved in collecting and linking these two datasets, and designing a study utilising both of them, we have listed 13 authors for this paper.

Abstract and keywords

Objectives

Tuberculosis (TB) is common in people living with HIV (PLHIV), leading to worse clinical outcomes including increased mortality. We investigated risk factors for developing TB following HIV diagnosis.

Design

Adults aged ≥15 years first presenting to health services for HIV care in England, Wales or Northern Ireland from 2000-2014 were identified from national HIV surveillance data and linked to TB surveillance data.

Methods

We calculated incidence rates for TB occurring >91 days after HIV diagnosis and investigated risk factors using multivariable Poisson regression.

Results

95,003 adults diagnosed with HIV were followed for 635,591 person-years (PY); overall incidence of TB was 344/100,000PY (95% confidence interval 330-359). TB incidence was high for people who acquired HIV through injecting drugs (PWID; men 876 [696-1,104], women 605 [528-593]) and black Africans born in high TB incidence countries (644 [612-677]). The adjusted incidence rate ratio (IRR) for TB amongst PWID was 4.79 [3.35-6.85] for men and 6.18 [3.49-10.93] for women, compared to men who have sex with men. The adjusted IRR for TB in black Africans from high-TB countries was 4·27 (3·42-5·33), compared to white UK-born individuals. Lower time-updated CD4 count was associated with increased rates of TB.

Conclusions

PWID had the greatest risk of TB; incidence rates were comparable to those in black Africans from high TB incidence countries. Most TB cases in PWID were UK-born, and likely acquired TB

through transmission within the UK. Earlier HIV diagnosis and quicker initiation of ART should reduce TB incidence in these populations.

Keywords

HIV, tuberculosis, co-infection, observational study, cohort studies, risk factors

Introduction

Tuberculosis (TB) and HIV are leading causes of morbidity and mortality. Globally, in 2014 there were 1.2 million new cases of TB in people living with HIV (PLHIV), accounting for one in eight TB diagnoses.[1] TB was responsible for one in three HIV-related deaths in 2014.

In England, Wales and Northern Ireland, 25% of AIDS-defining illnesses from 2001-2010 were TB.[2] The rate of TB disease in PLHIV in the UK was estimated as 328/100,000 person-years (PY) between 1996 and 2005 (excluding patients diagnosed with TB and HIV simultaneously [within 91 days]),[3] and 669/100,000PY across all groups 2007-2011.[4] Estimated TB incidence in the general population is much lower; 10/100,000 population in 2015.[5]

Previous studies in the UK have found higher rates of TB in PLHIV who acquired HIV abroad, or had black African or Indian/Pakistani/Bangladeshi ethnicity, than in white and UK-born populations.[3, 6] TB incidence decreased with increasing CD4 count at HIV diagnosis, and was lower for individuals on antiretroviral therapy (ART). However, [6] was limited in its implications for UK TB-HIV control as it was restricted to heterosexuals and did not adjust for time on ART, which is known to be linked to TB incidence.[4] It also included patients diagnosed simultaneously with TB and HIV, many of whom are only diagnosed with HIV as a result of their TB diagnosis.[6] Furthermore, the UK-CHIC study [3] did not provide estimates of TB incidence in PWID.

TB incidence in HIV-positive people who inject drugs (PWID) in the 1980s and 1990s was very high;[7] however the link between TB and HIV-positive PWID in the ART era is less clear. Five cohort studies found TB rates were elevated by a factor of 1.7-4.4 when compared to men who have sex with men (MSM) or people who do not inject drugs,[8-12] whilst one cohort[13] and one cross-sectional study[14] found no significantly increased risk. In the UK, PWID are typically diagnosed with HIV late[15] and have high rates of death,[16, 17] despite good levels of ART coverage (90%), similar to other risk groups.[18] No recent studies in the UK have investigated the risk of TB for PWID. This study aimed to investigate risk factors for developing TB following HIV diagnosis, including HIV acquisition by injecting drug use, to address the paucity of evidence in resource-rich countries in the ART era.

Methods

Study population

Adults (aged 15 years or older) notified to Public Health England (PHE)’s HIV and AIDS Reporting System (HARS), first presenting with HIV to health services in England, Wales and Northern Ireland between 2000 and 2014 were included. HARS comprises four linked data sources: reports of all new HIV/AIDS diagnoses and deaths, national laboratory data for CD4 count, annual reporting of demographic and clinical information of PLHIV from all national clinics, and death reports from the Office of National Statistics.[17, 19]

Outcome: TB disease diagnosed from 2000-2014

TB cases included both culture-confirmed and presumptive (clinical and radiological signs, including a response to specific therapy) diagnoses.

UK HIV and TB surveillance are undertaken separately, necessitating data linkage to analyse co-infection. TB cases across England, Wales and Northern Ireland are reported to the PHE’s Enhanced Tuberculosis Surveillance (ETS) system. To identify PLHIV with TB disease, HARS and ETS data were linked using a probabilistic matching algorithm (adapted from [20]), with supplementary deterministic matching to accept/reject borderline matches.[21]

Incident TB was defined as TB disease notified to ETS or reported to HARS as a new AIDS-defining illness, that was diagnosed >91 days after HIV diagnosis. TB cases diagnosed within 91 days of HIV diagnosis were considered simultaneous diagnoses, to differentiate patients who were not aware of their HIV infection prior to their TB diagnosis. TB cases diagnosed >91 days before HIV were considered existing disease. A 91 day threshold for defining simultaneous diagnoses was a pragmatic choice to account for delays in diagnosis and reporting, and to exclude ART-induced unmasking immune reconstitution inflammatory syndrome.

Exposure variables

We included demographic (age at HIV diagnosis, sex, ethnicity, country of birth, TB incidence in country of birth, route of HIV infection, year of HIV diagnosis, index of multiple deprivation [IMD] decile) and clinical (viral load at first presentation, and time-updated CD4 count and ART initiation) exposure variables. IMD score deciles represent relative levels of deprivation of income, employment, health, education, housing and services, crime and living environment for small areas in England and Wales, where 1=most deprived and 10=least deprived.[22, 23]

Composite variables were created combining ethnicity and country of birth or sex and infection route due to mutually exclusive combinations (e.g. being a woman and a MSM is impossible) and known associations. As a proxy TB exposure, countries of birth outside the UK were grouped by TB incidence; 'high incidence' was defined as >40 cases/100,000 adult population in 2013. The most recent IMD data for each country between 2000 and 2014 were used; 2010 for England and 2014 for Wales.

Statistical Analysis

Data were analysed in Stata version 13.1. Descriptive analyses of the cohort were undertaken. To investigate risk factors for developing TB, we calculated incidence rates of TB per 100,000PY follow-up and assessed TB incidence over time using Nelson-Aalen cumulative hazard plots. We estimated incidence rate ratios using univariable and multivariable Poisson regression models, offset by follow-up time, Cox regression was precluded as our data did not satisfy the proportional hazards assumption for key variables such as route of HIV infection. Individuals diagnosed with TB ≤91 days after HIV diagnosis were excluded to investigate subsequent TB. Follow-up began 92 days from date of HIV diagnosis or first presentation to UK health services and ended on the date of TB diagnosis, death, or 31/12/2014, whichever was earliest. CD4 count and ART initiation were included as time-updated covariates. Incidence rates for different CD4 strata were calculated using the number of days from each CD4 count to the date of the next CD4 count for each patient. To compare incidence between ART-naïve patients and patients who had initiated ART, we split each patient's follow-up period at the date they first initiated ART to calculate the duration of ART-naïve person-time, and person-time having initiated ART.

Potential confounders and effect modifiers were prospectively identified.[24] Our causal framework determined that viral load should be excluded from the multivariable model because of the potential for causal loops between viral load and CD4 count, which could not be adequately accounted for in the data available. We excluded patients missing data on one or more variables. Linearity (of age, CD4 count and year of HIV diagnosis) and statistical interactions (between ART status and CD4 count) were assessed using likelihood-ratio tests. As we were not investigating a single "main" exposure variable, there were no confounders in the traditional sense, and therefore the multivariable model was informed by a causal inference framework defined *a priori*. To assess the likely impact of missing data, we compared the distributions of age, sex, route of HIV infection, CD4 count and ethnicity/country of birth for cases with missing vs. complete data on infection route, CD4 count, IMD score and country of birth. Statistical interactions were considered significant at $P<0.05$. All stated confidence intervals are two-sided 95% confidence intervals.

Planned sensitivity analyses investigated the impact of using a 6-month threshold (182 days) for simultaneous diagnosis; excluding weaker matches between HARS and ETS; and excluding people who acquired HIV infection through mother-to-child transmission, as the dataset only contained adults and so individuals infected through this route could be missing 15 years follow-up.

Ethics, consent and permissions

This analysis was approved by the UCL student Research Ethics Committee (5683/001). PHE has authority under the Health and Social Care Act 2012 to hold and analyse national surveillance data for public health and research purposes.

Role of the funding source

The funding source had no involvement in the study design; the collection, analysis and interpretation of the data; the writing of the report or the decision to submit the paper for publication.

Results

Description of co-infected patients

Between 2000 and 2014, 102,202 adults were newly diagnosed with HIV, among whom 5,649 (6%) had TB. 3,103 (55%) were simultaneously diagnosed with TB and HIV, 2,187 (39%) developed TB after >91 days and 359 (6%) were diagnosed with TB first (Table 1).

Of people with TB who acquired HIV infection through heterosexual sex, over half were diagnosed simultaneously with TB and HIV; 60% for men and 54% for women. In contrast, more TB cases in MSM and PWID were diagnosed more than 91 days after diagnosis of HIV infection (51% and 54%, respectively). The proportion of TB cases occurring after HIV diagnosis was highest in white, UK-born individuals (179/359, 48%) and those born in low TB incidence countries (116/245, 47%); these two groups comprise 38% of the cohort.

Incidence of TB following HIV diagnosis

95,003 adults were TB-free 92 days after presenting for HIV care, with a total of 635,591PY follow-up. Median age at HIV diagnosis was 34 years (inter-quartile range [IQR] 28-42) and median CD4 count was 340 cells/µl (IQR 170-527). 95% of patients had >1 CD4 count (median 14).

Overall TB incidence was 344/100,000PY (95% CI: 330-359, Table 1). The probability of developing TB was highest in the year following HIV diagnosis and then decreased (Figure 1a). Incidence was high in PWID (men 876/100,000 [696-1,104/100,000]; women 605/100,000 [386-949/100,000]) and heterosexuals (men 598/100,000 [555-645/100,000], women 559 [528-593/100,000]), particularly compared with MSM (111/100,000 [98-126/100,000]). The largest differences in cumulative probability of TB diagnosis between PWID, black Africans from high-TB incidence countries and MSM were in the first two years following HIV diagnosis; the rate of diagnosis remained relatively constant across all groups thereafter (Figure 1b).

TB incidence increased with decreasing time-updated CD4 count, from 139/100,000 (123-157/100,000) for those with CD4 count ≥500 cells/μl to 2,788/100,000 (2,368-3,282/100,000) for those with CD4 count <50 cells/μl. TB incidence was 511/100,000 (484-539/100,000) in people who had never received ART (26% of all PY) compared to 228/100,000 (213-243/100,000) in people who had (74% of PY). TB incidence was higher for PWID who had never initiated ART (1,478/100,000 [95% CI 1,157-1,888/100,000] than for black Africans from high-TB incidence countries who had never initiated ART (991/100,000 [929-1,058/100,000]) although incidence rates following ART initiation were similar in both groups (384/100,000 [264-560/100,000] for PWID versus 421 [389-456/100,000] for black Africans). TB incidence was highest in those living in areas of England and Wales with the lowest decile of IMD score (485/100,000 [437-537/100,000]).

Factors associated with developing TB disease

62,684 individuals with complete case data and a TB-free follow-up period of >91 days following HIV diagnosis were included in the time-to-event analysis. There were a total of 414,714 PY of follow-up (median follow-up 7·1 years, IQR 3·6-10·4), during which there were 1,591 TB diagnoses (Table 2). The median duration of follow-up was 7.3 years (IQR 3.9-10.4) for patients who did not develop TB, whilst patients who did develop TB did so in a median of

0.2 years (IQR 0.1-0.5). Black African patients born in high-TB countries had a slightly higher median follow-up period of 8.2 (4.7-11.0) years, compared to 6.3 (3.1-9.8) for MSM and 6.5 (3.4-9.8) for PWID, as black Africans were more likely to be diagnosed earlier in the study period than PWID or MSM.

All exposures were included in the multivariable Poisson regression model (Table 2), except viral load and IMD decile. IMD decile was excluded as there was a high degree of missing data and no association with the outcome in a multivariable model (supplementary tables 1-3). CD4 count and age at HIV diagnosis were treated as categorical variables (tests for linearity P<0·001, P=0·005, respectively), year of HIV diagnosis was treated as a linear variable (P>0.05).There was a statistically significant interaction between time-updated CD4 count and time-updated ART status (P<0·001).

Compared to MSM, PWID had increased rates of TB (incidence rate ratio [IRR] for men 5·47 [95% confidence interval 4·07-7·35]; women 4·59 [2·75-7·67]). Rates were also higher in those infected through heterosexual sex (men 1·70 [1·38-2·10]; women 1·86 [1·51-2·29]). UK-born black Africans (1·97 [1·10-3·51]) and people of other ethnicities (1·92 [1·29-2·84]) were associated with increased incidence rates versus white UK-born individuals, as were those born in high TB incidence countries (black African 4·27 [3·42-5·33], white 2·19 [1·53-3·15], other ethnicities 3·36 [2·57-4·39]).

Overall, and within each stratum of CD4 count, TB rates were greatly reduced in individuals who had received ART compared to those who had not (Table 3). When stratifying by ART initiation status, lower time-updated CD4 count was strongly associated with increased TB rates (Table 4). For individuals who had never initiated ART, the IRR for TB increased with decreasing CD4 count to 6·42 [4·87-8·46] for 0-49 cells/µl *cf.* ≥500 cells/µl. The increased risk at low CD4 count was higher in individuals who had initiated ART, with an IRR of 44·21 [30·90-63·24] for 0-49 cells/µl, *cf.* ≥500 cells/µl.

In a post-hoc analysis of patients who had initiated ART, we found that those who developed TB were more likely to have discontinued ART at their last clinic visit (27%, versus 6% of those without TB, P<0.001, Supplementary table 4). ART initiation rates and time from the most recent clinic visit to the end of the study were similar for MSM, heterosexuals and PWID.

There was no substantial difference in the age, sex, ethnicity/country of birth, route of HIV infection or CD4 count of patients with missing data on any of the following variables: route of HIV infection, CD4 count, IMD decile and country of birth. Patients with missing route of infection were less likely to be diagnosed with TB; however there were no substantial differences for patients missing data on any other variable.

Sensitivity analysis

Sensitivity analyses were conducted as follows: (1) excluding 241 individuals who acquired HIV infection through mother-to-child transmission, (2) excluding 595 individuals with TB whose probabilistic matching scores (linking to their HIV record) were in the lowest quartile, (3) excluding 137 individuals with TB who were matched to their HIV record using the three lowest-ranked deterministic criteria, (4) excluding 424 individuals diagnosed with TB 92-182 days after HIV diagnosis, (5) including IMD score and excluding data on 12,432 individuals missing IMD score. All analyses provided consistent results with the main model (supplementary tables 1-3).

Discussion

People who acquired HIV infection through injecting drug use (largely UK-born patients) had a high risk of TB following their HIV diagnosis, with incidence rates comparable to those in black Africans born in high TB incidence countries; almost five-fold more than MSM after accounting for other factors including starting ART. Consistent with previous research,[3, 6] declining CD4 count was associated with higher TB rates.

This study benefits from the very large national HIV-positive cohort, providing comprehensive results for England, Wales and Northern Ireland. The algorithm linking patients with TB and HIV utilises ethnicity, year and country of birth; all variables with very high completeness: 97·3%, 99·9% and 90·5% respectively.

We found no substantial differences in the demographics or proportion of TB in patients missing data on each of these variables; however patients missing data on one variable were more likely to have other missing data. Additionally, patients missing data for multiple variables were less likely to be linked to a TB notification and therefore we may have underestimated TB incidence rates; it is likely that the low incidence of TB in patients with “unknown” route of HIV infection is a symptom of this and patients with extensive missing data may be more likely to be from populations at high risk for TB. Additionally, the record linkage algorithm is less sensitive to non-English names,[20] therefore we may have underestimated TB incidence in foreign populations.

One limitation was missing CD4 count data for approximately a third of patients, who were therefore excluded from the risk factor analysis. This is partly due to difficulties linking data, and partly because some large hospitals do not supply CD4 count data to HARS. However, we found no evidence that patients with missing CD4 count data were systematically different to our analysis cohort. As our sample size remained very large, and there was no evidence that patients missing data were systematically different, we chose not to use multiple imputation due to the complexity of the dataset as a result of using time-updated CD4 count and ART initiation. Data were available on ART discontinuation, but were of poor quality and could not be included in the model. Consequently we may have underestimated the association between starting ART and lower TB incidence by assuming all individuals remained on treatment for the duration of our study.

Individuals entered the study cohort 92 days after HIV diagnosis or first presentation to UK health services; therefore we may have underestimated TB incidence in people diagnosed abroad who were at risk prior to entering the UK, as we would have missed TB cases diagnosed during the initial period following HIV diagnosis when TB incidence is highest. A recent study of PLHIV had 18% loss to follow-up over 4 years, and 14% of TB cases diagnosed >91 days after HIV diagnosis were in these patients.[4] As TB and HIV are sometimes treated (and usually reported) separately in the UK, dropping out of HIV care does not prevent notification of a TB diagnosis. We therefore used passive censoring, continuing follow-up until 31/12/2014 rather than the date last seen for HIV care. Consequently, migration out of the UK may mean we underestimated TB incidence.

A limitation of the Poisson regression model was censoring due to competing risks, specifically deaths from non-TB causes. However, few patients died (3%) and median time to death was 3.4 years, substantially longer than median time to TB diagnosis (1·8 years); therefore any impact of censoring is likely to be minimal.

While PWID represented <2% of PLHIV, they accounted for 3% of TB cases in this population and >4% of cases diagnosed >91 days after HIV diagnosis. TB incidence in PWID in our study (876/100,000PY in men and 605/100,000 in women) was substantially higher than that in a cohort of German PLHIV,[25] possibly because this cohort utilises active rather than passive follow-up and excluded patients who did not present to care for 6 months or more, who may be more likely to develop TB disease than patients who remain engaged with care. PWID are typically diagnosed with HIV late,[18] have slower rates of linkage to care and lower rates of viral suppression,[26] all of which may contribute to increased risk of TB. We found ART initiation and the time from the last clinic visit to the end of the study were comparable for MSM, heterosexuals and PWID; and that PWID did not have higher rates of ART discontinuation at their last clinic visit prior to study end (Supplementary Table 4).

Consequently, it seems high rates of TB among PWID are caused by difficulties in linking to care and not lack of engagement with health services once linked. Many PWID have other co-morbidities which may cause immunosuppression, make HIV care more challenging, or be associated with increased risk of TB.[27] Additionally there are high rates of alcoholism and homelessness, and living in hostels is common.[28] These, in addition to injecting drugs in shared social settings, may drive close mixing of people with similar risk factors for TB disease, driving transmission. High rates of smoking may also have impacts on both local lung immunity and TB transmission. Further studies are needed to explore the impact of these factors and to design effective interventions. BHIVA guidelines currently recommend testing and treating LTBI among PLHIV using criteria based on CD4 count, time on ART and country of birth.[29] As the incidence of TB among PWID was comparable to that of black African patients born in countries with high TB incidence, we suggest that additionally screening and treating PWID for LTBI should be considered.

The majority of PWID were white (51%) and born in the UK or low TB incidence countries (72%). It is therefore likely that most TB in this group was acquired in the UK, meaning these cases may be preventable by diagnosing HIV sooner and ensuring prompt ART initiation. We could also do more to diagnose TB cases sooner; the impact of active case finding in PLHIV should be evaluated. In contrast, heterosexuals were typically black African (61%) and born in high TB incidence countries (69%), both populations which also have high rates of TB among HIV-negative people. Consequently, they are likely to have acquired TB abroad, limiting our ability to prevent these TB infections if they present with clinical TB at the time of HIV diagnosis.[30] As >60% of heterosexuals were diagnosed with TB simultaneously or prior to HIV diagnosis, greater efforts to diagnose these HIV infections and initiate ART would reduce TB in this population. A greater focus on screening and treating latent TB infection (LTBI) could also prevent these cases.[31] There is little data available on the prevalence of LTBI and the use of preventive therapy among PLHIV in the UK. Rates of LTBI screening and uptake of preventive therapy vary substantially between HIV clinics,[32, 33] and a survey of UK HIV healthcare providers providing care to 90% of PLHIV in the UK found that only 54% offered LTBI screening and preventive therapy.[34] Health economics evaluations would be useful to determine the most effective screening measures for these populations.

Over half of all TB cases (55%) were diagnosed simultaneously with HIV infection, and of the 39% diagnosed later, the probability of a TB diagnosis was highest in the first year following HIV diagnosis (Figure 1). This suggests that TB disease is largely the result of TB infection acquired prior to HIV diagnosis. This could result from late diagnosis of existing active TB, particularly in migrants who have recently moved to the UK from high-burden countries and whose TB is largely attributable to reactivation of remotely acquired infection.[35] Additionally, the incidence of TB amongst migrants decreases with time since entry to the UK, as new TB infection is less likely in the UK than their country of origin. Other factors which could explain this trend are increased surveillance for opportunistic infections following HIV diagnosis, or “unmasking-type” immune reconstitution inflammatory syndrome as a consequence of ART. Whilst TB incidence was lower after the first year since HIV diagnosis (Table 1), 25% of all TB cases occurred more than one year after HIV diagnosis. These cases can certainly be attributed to reactivation of LTBI and could be preventable with LTBI treatment.

Patients who had initiated ART had greatly reduced rates of TB compared to those who had not (Table 3); however time-updated CD4 count and ART initiation status interacted within our model. Higher rate ratios for TB at low CD4 count in people on ART may be attributable to late ART start (i.e. long periods of low CD4 count prior to initiating ART and then little time on ART prior to TB diagnosis), or due to ART discontinuation. The SMART trial demonstrated an association between stopping ART and increased risk of opportunistic disease and death.[36] Our post-hoc analysis of patients who had started ART demonstrated that patients who went on to develop TB were more likely to have discontinued ART at their last study visit than individuals who remained TB-free (Table 5). This suggests ART discontinuation could leave patients at risk of new TB disease.

In England, Wales and Northern Ireland, PLHIV who acquired HIV by injecting drugs had higher rates of TB after their HIV diagnosis than MSM, comparable to black Africans born in countries with high TB incidence. High rates of TB in PWID are likely to result from transmission within the UK. ART is highly protective against TB, but the majority of TB diagnoses were in people who have never started ART. ART discontinuation rates were much higher in people who subsequently developed TB than those who did not. Quicker initiation of ART, as per the recently updated BHIVA guidelines,[37] and improving retention in care and ART continuation should decrease incident TB in PLHIV.

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Author contributions

JRW designed the study, linked the TB and HIV surveillance datasets, conducted the analysis and drafted the paper. HRS and CS designed the study, analysed and interpreted the data and critically revised the paper. AB, MKL, AS, HLT, ZY and PK gave input on the study design, collected the data, linked the datasets, interpreted the results and critically revised the paper. VD and IA designed the study, collected, linked, analysed and interpreted the data and revised the paper. ML and AP interpreted the results and critically revised the paper. All authors approved the final version of the paper for publication.

Declaration of interests

JRW, AEB, MKL, ML, AS, PK, ZY, HLT, VD and IA have no conflicts of interests to declare. HRS declares funding from the National Institute for Health Research, UK during the conduct of the study; and, outside of the submitted work, grants and personal fees from Otsuka Pharmaceutical, non-financial support from Sanofi, and other support from the WHO. Outside the submitted work, CJS reports personal fees from Gilead Sciences and ViiV Healthcare. AP is chair of the BHIVA TB guidelines committee. JRW had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Figures

Figure 1: Cumulative hazard plot of the probability of developing TB from >91 days following HIV diagnosis

Tables

Table 1: TB diagnoses in people notified with HIV from 2000 to 2014 in England, Wales and Northern Ireland, and the incidence rates of TB in people who were diagnosed with TB >91 days following HIV diagnosis.

	HIV cases	**TB cases**						
		Total	**Prior to HIV diagnosis**	**Simultaneous with HIV diagnosis**	**Following HIV diagnosis**			
	n (column %)	**n (row %)**	**n (row %)**	**n (row %)**	**n (row %)**	**PY follow-up**	**Incidence rate* (95% CI)**	**Incidence rate after 1 year from HIV diagnosis* (95% CI)**
Total	102,202	5,649 (5.5)	359 (6)	3,103 (55)	2,187 (39)	635,591	344 (330 - 359)	247 (234 - 260)
Route of HIV infection								
MSM	35,879 (35.1)	462 (1.3)	31 (7)	195 (42)	236 (51)	212,844	111 (98 - 126)	86 (74 - 100)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
Heterosexual men	18,738 (18.3)	2,013 (10.7)	127 (6)	1,205 (60)	681 (34)	113,802	598 (555 - 645)	402 (365 - 443)
Heterosexual women	30,489 (29.8)	2,815 (9.2)	167 (6)	1,520 (54)	1,128 (40)	201,644	559 (528 - 593)	404 (376 - 434)
Men who inject drugs	1,453 (1.4)	132 (9.1)	5 (4)	55 (42)	72 (55)	8,216	876 (696 - 1,104)	660 (499 - 873)
Women who inject drugs	532 (0.5)	35 (6.6)	1 (3)	15 (43)	19 (54)	3,138	605 (365 - 945)	526 (295 - 868)
Blood/Tissue transfer	505 (0.5)	58 (11.5)	6 (10)	31 (53)	21 (36)	2,928	717 (468 - 1,100)	527 (288 - 883)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
Mother-to-child	253 (0.2)	15 (5.9)	1 (7)	4 (27)	10 (67)	863	1,159 (556 - 2,131)	836 (307 - 1,819)
Unknown≠	14,353 (14.0)	119 (0.8)	21 (18)	78 (66)	20 (17)	92,155	22 (14 - 34)	13 (7 - 24)
Ethnicity/Country of birth								
White, UK-born	27,320 (26.7)	359 (1.3)	24 (7)	161 (45)	174 (48)	160,488	108 (93 - 126)	84 (70 - 100)
Black African, UK-born	947 (0.9)	51 (5.4)	6 (12)	25 (49)	20 (39)	5,556	360 (232 - 558)	260 (151 - 448)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
Other ethnicity, UK-born	2,687 (2.6)	72 (2.7)	6 (8)	26 (36)	40 (56)	14,948	268 (196 - 365)	217 (151 - 313)
Ethnicity unknown, UK-born	403 (0.4)	3 (0.7)	0 (0)	3 (100)	0 (0)	544	0 (0 - 678)‡	0 (0 - 876)‡
Born in low-TB incidence country	11,551 (11.3)	245 (2.1)	11 (4)	118 (48)	116 (47)	65,376	177 (148 - 213)	125 (99 - 157)
White, born in high-TB	7,461 (7.3)	126 (1.7)	4 (3)	71 (56)	51 (40)	47,593	107 (81 - 141)	84 (61 - 116)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
incidence country								
Black African, born in high-TB incidence country	35,035 (34.3)	3,877 (11.1)	223 (6)	2,142 (55)	1,512 (39)	234,853	644 (612 - 677)	454 (426 - 483)
Other ethnicity, born in high-TB incidence country	6,756 (6.6)	518 (7.7)	52 (10)	311 (60)	155 (30)	35,614	435 (372 - 509)	290 (236 - 356)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
Ethnicity unknown, born in high-TB incidence country	1,140 (1.1)	13 (1.1)	2 (15)	10 (77)	1 (8)	7,556	13 (0 - 74)‡	15 (0 - 81)
White, country of birth unknown	3,065 (3.0)	52 (1.7)	4 (8)	31 (60)	17 (33)	23,968	71 (41 - 114)	54 (28 - 95)
Other ethnicity, country of birth unknown	4,226 (4.1)	300 (7.1)	23 (8)	181 (60)	96 (32)	33,093	290 (237 - 354)	210 (164 - 268)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
Both Unknown≠	1,611 (1.6)	33 (2.0)	4 (12)	24 (73)	5 (15)	6,002	83 (27 - 194)	39 (5 - 141)
Age at HIV diagnosis (years)								
15-24	11,513 (11.3)	437 (3.8)	25 (6)	173 (40)	239 (55)	73,647	325 (286 - 368)	260 (224 - 302)
25-34	38,910 (38.1)	2,227 (5.7)	129 (6)	1,121 (50)	977 (44)	261,955	373 (350 - 397)	280 (260 - 302)
35-44	31,894 (31.2)	1,944 (6.1)	133 (7)	1,147 (59)	664 (34)	199,946	332 (308 - 358)	232 (211 - 255)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
45-64	18,357 (18.0)	973 (5.3)	64 (7)	619 (64)	290 (30)	93,708	309 (276 - 347)	183 (156 - 214)
65+	1,479 (1.4)	68 (4.6)	8 (12)	43 (63)	17 (25)	5,764	295 (172 - 472)	99 (172 - 472)
CD4 count at HIV diagnosis† (incidence rates are calculated for time-updated CD4)								
≥500	20,153 (19.7)	381 (1.9)	30 (8)	88 (23)	263 (69)	187,994	139 (123 - 157)	122 (106 - 139)
350-499	14,801 (14.5)	455 (3.1)	34 (7)	133 (29)	288 (63)	114,505	259 (231 - 290)	270 (241 - 304)
200-349	16,282 (15.9)	861 (5.3)	61 (7)	388 (45)	412 (48)	81,579	527 (480 - 579)	454 (407 - 506)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
100-199	9,514 (9.3)	1,039 (10.9)	79 (8)	613 (59)	347 (33)	24,933	1,356 (1,219 - 1,508)	785 (673 - 916)
50-99	5,039 (4.9)	718 (14.2)	35 (5)	525 (73)	158 (22)	6,247	2,209 (1,870 - 2,610)	1,072 (817 - 1,407)
0-49	8,731 (8.5)	1,241 (14.2)	63 (5)	956 (77)	222 (18)	5,166	2,788 (2,368 - 3,282)	891 (648 - 1,224)
Unknown≠	27,682 (27.1)	954 (3.4)	57 (6)	400 (42)	497 (52)	-	-	-
Viral load at diagnosis (copies/ml)								

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
≤200	13,951 (13.7)	580 (4.2)	51 (9)	311 (54)	218 (38)	63,098	345 (303 - 395)	227 (190 - 270)
>200	58,824 (57.6)	3,735 (6.3)	229 (6)	2,050 (55)	1,456 (39)	339,621	428 (407 - 451)	305 (286 - 325)
Unknown≠	29,427 (28.8)	1,334 (4.5)	79 (6)	742 (56)	513 (38)	232,872	221 (202 - 241)	170 (153 - 188)
Ever started ART (time-updated)								
No	32,207 (31.5)	809 (2.5)	-	-	1336§	261,662	511 (484 - 539)	337 (314 - 362)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
Yes	69,995 (68.5)	4,840 (6.9)	-	-	851§	373,929	228 (213 - 243)	188 (174 - 203)
IMD decile								
1	13,498 (13.2)	900 (6.7)	64 (7)	470 (52)	366 (41)	75,516	485 (437 - 537)	343 (301 - 390)
2	15,075 (14.8)	920 (6.1)	66 (7)	510 (55)	344 (37)	86,339	398 (358 - 443)	286 (251 - 327)
3	12,746 (12.5)	688 (5.4)	53 (8)	385 (56)	250 (36)	72,760	344 (304 - 389)	247 (212 - 288)
4	9,150 (9.0)	474 (5.2)	29 (6)	273 (58)	172 (36)	52,758	326 (281 - 379)	222 (183 - 268)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
5	6,732 (6.6)	336 (5.0)	22 (7)	191 (57)	123 (37)	37,961	324 (272 - 387)	235 (189 - 293)
6	5,233 (5.1)	253 (4.8)	18 (7)	134 (53)	101 (40)	29,630	341 (280 - 414)	238 (186 - 304)
7	3,870 (3.8)	164 (4.2)	10 (6)	89 (54)	65 (40)	21,596	301 (236 - 384)	233 (174 - 312)
8	3,304 (3.2)	140 (4.2)	6 (4)	83 (59)	51 (36)	17,934	290 (221 - 381)	207 (147 - 291)
9	2,809 (2.7)	110 (3.9)	7 (6)	64 (58)	39 (35)	15,846	246 (180 - 337)	163 (108 - 245)
10	2,217 (2.2)	97 (4.4)	3 (3)	52 (54)	42 (43)	11,925	352 (260 - 477)	274 (190 - 394)

	HIV cases	TB cases						
		Total	Prior to HIV diagnosis	Simultaneous with HIV diagnosis	Following HIV diagnosis			
	n (column %)	n (row %)	n (row %)	n (row %)	n (row %)	PY follow-up	Incidence rate* (95% CI)	Incidence rate after 1 year from HIV diagnosis* (95% CI)
Unknown[≠]	27,568 (27.0)	1,567 (5.7)	81 (5)	852 (54)	634 (40)	213,326	297 (274 - 321)	217 (197 - 238)

*** Incidence is given per 100,000 population aged ≥15 years, per year. † Incidence rates are calculated for time-updated CD4 count. [≠] Unknown strata includes both unknown and missing data. [‡]One-sided, 97.5% CI. §Of the 5,649 PLHIV who got TB, 809 never initiated ART. However, of the 2,187 who got TB >91 days after their HIV infection, 1,336 had not initiated TB at the time of their HIV diagnosis. ART: anti-retroviral therapy, CI: confidence interval, IMD: index of multiple deprivation, MSM: men who have sex with men, PWID: people who inject drugs, PY: person-years, TB: tuberculosis.**

Table 2: Univariable and multivariable incidence rate ratios from Poisson regression of factors associated with incident TB disease (>91 days after HIV diagnosis) among PLHIV in England, Wales and Northern Ireland from 2000 to 2014

			Univariable	**Multivariable**
	TB cases	**PY**	**IRR (95% CI)**	**IRR (95% CI)**
Route of HIV infection				
MSM	184	172,708	1.00 (P<0.001)	1.00 (P<0.001)
Male heterosexual	474	82,460	5.40 (4.55 - 6.40)	1.70 (1.38 - 2.10)
Female heterosexual	837	148,391	5.29 (4.51 - 6.21)	1.86 (1.51 - 2.29)
Male PWID	61	5,895	9.71 (7.27 - 12.97)	5.47 (4.07 - 7.35)
Female PWID	16	2,514	5.97 (3.58 - 9.95)	4.59 (2.75 - 7.67)
Blood/Tissue transfer	14	2,251	5.84 (3.39 - 10.05)	2.70 (1.55 - 4.71)

Mother-to-child	5	494	9.51 (3.91 - 23.11)	2.80 (1.13 - 6.97)
Ethnicity/Country of birth				
White, UK-born	134	127,453	1.00 (P<0.001)	1.00 (P<0.001)
Black African, UK-born	13	4,317	2.86 (1.62 - 5.06)	1.97 (1.10 - 3.51)
Other ethnicity, UK-born	31	12,040	2.45 (1.66 - 3.62)	1.92 (1.29 - 2.84)
Ethnicity unknown, UK-born	0	252	†	†
Born in low-TB incidence country	98	53,647	1.74 (1.34 - 2.25)	1.33 (1.02 - 1.73)
White, born in high-TB incidence country	38	12,606	2.87 (2.00 - 4.11)	2.19 (1.53 - 3.15)
Black African, born in high-TB incidence country	1,093	148,017	7.02 (5.87 - 8.40)	4.27 (3.42 - 5.33)
Other ethnicity, born in high-TB	105	22,219	4.50 (3.48 - 5.80)	3.36 (2.57 - 4.39)

incidence country				
Ethnicity unknown, born in high-TB incidence country	1	323	2.95 (0.41 - 21.07)	1.35 (0.19 - 9.71)
White, country of birth unknown	12	15,491	0.74 (0.41 - 1.33)	0.52 (0.29 - 0.94)
Other ethnicity, country of birth unknown	66	18,348	3.42 (2.55 - 4.59)	1.60 (1.17 - 2.20)
CD4 count				
≥500	259	185,719	1.00 (P<0.001)	*
350-499	293	113,185	1.86 (1.57 - 2.19)	
200-349	427	80,443	3.81 (3.26 - 4.44)	
100-199	332	24,367	9.77 (8.30 - 11.49)	
50-99	137	6,093	16.12 (13.11 -	

			19.83)	
0-49	143	4,905	20.90 (17.04 - 25.64)	
Ever on ART				
No	928	107,477	1.00 (P<0.001)	*
Yes	663	307,237	0.25 (0.23 - 0.28)	
Viral load at diagnosis				
≤200	154	43,347	1.00 (P=0.006)	-
>200	1,063	261,249	1.15 (0.97 - 1.36)	
Age at HIV diagnosis				
15-24	169	48,805	0.95 (0.79 - 1.13)	0.92 (0.77 - 1.10)

25-34	714	170,957	1.14 (1.02 - 1.28)	1.06 (0.94 - 1.19)
35-44	477	130,441	1.00 (P<0.001)	1.00 (P=0.332)
45-64	220	61,028	0.99 (0.84 - 1.16)	1.11 (0.95 - 1.31)
≥65	11	3,484	0.86 (0.47 - 1.57)	0.92 (0.51 - 1.68)
Year of HIV diagnosis				
(for each year increase from 2000)	1,591	414,714	0.98 (0.97 - 1.00)	1.02 (1.00 - 1.04)
			P=0.036	P=0.014
IMD decile (England and Wales only)				
1	264	51,685	1.00 (P<0.001)	-
2	269	63,391	0.83 (0.70 - 0.98)	

3	193	54,955	0.69 (0.57 - 0.83)
4	127	38,159	0.65 (0.53 - 0.81)
5	83	26,725	0.61 (0.48 - 0.78)
6	78	20,986	0.73 (0.57 - 0.94)
7	47	15,254	0.60 (0.44 - 0.82)
8	38	12,644	0.59 (0.42 - 0.83)
9	24	10,743	0.44 (0.29 - 0.66)
10	32	8,326	0.75 (0.52 - 1.09)

62,684 PLHIV were included in this analysis; 32,319 were excluded from the model due to missing data on ethnicity and country of birth, route of HIV infection, CD4 count or age at HIV diagnosis. Viral load was not included in the multivariable model due to collinearity with CD4 count and ART status. *Interaction present between time-updated CD4 count and time-updated ART status, see Table 4 and Table 3. †Not calculated as numerator was zero. ART: anti-retroviral therapy, CI: confidence interval, IMD: index of multiple deprivation, MSM: men who have sex with men, PWID: people who inject drugs, PY: person years, IRR: incidence rate ratio, TB: tuberculosis.

Table 3: Multivariable Poisson regression of the association between time-updated ART status and TB disease, stratified by CD4 count, among PLHIV in England, Wales and Northern Ireland from 2000 to 2014

	CD4 count (cells/µl)					
	≥500	**350-499**	**200-349**	**100-199**	**50-99**	**0-49**
Ever on ART	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**
No	1·00	1·00	1·00	1·00	1·00	1·00
Yes	0·07 (0·05 - 0·10)	0·14 (0·11 - 0·18)	0·21 (0·17 - 0·25)	0·32 (0·26 - 0·40)	0·35 (0·25 - 0·49)	0·49 (0·35 - 0·69)

Incidence rate ratios derived from multivariable Poisson regression of the association between time-updated ART status and TB disease, stratified by CD4 count. Model adjusted for the variables in the multivariable model in Table 2. 62,684 PLHIV were included in this analysis; 32,319 were excluded from the model due to missing data on ethnicity and country of birth, route of HIV infection, CD4 count or age at HIV diagnosis. ART: anti-retroviral therapy, CI: confidence interval, IRR: incidence rate ratio, TB: tuberculosis.

Table 4: Multivariable Poisson regression of the association between time-updated CD4 count and TB disease, stratified by ART status, among PLHIV in England, Wales and Northern Ireland from 2000 to 2014

	Ever on ART	
	No	Yes
CD4 count (cells/µl)	IRR (95% CI)	IRR (95% CI)
≥500	1·00	1·00
350-499	1·28 (1·06 - 1·55)	2·51 (1·77 - 3·56)
200-349	2·22 (1·84 - 2·66)	6·37 (4·66 - 8·72)
100-199	4·74 (3·79 - 5·93)	21·21 (15·59 - 28·85)
50-99	7·07 (5·26 - 9·51)	34·29 (24·10 - 48·77)
0-49	6·42 (4·87 - 8·46)	44·21 (30·90 - 63·24)

Incidence rate ratios derived from multivariable Poisson regression of the association between time-updated CD4 count and TB disease, stratified by ART status. 62,684 PLHIV were included in this analysis; 32,319 were excluded from the model due to missing data on ethnicity and country of birth, route of HIV infection, CD4 count or age at HIV diagnosis. Model adjusted for the variables in the multivariable model in Table 2. ART: anti-retroviral therapy, CI: confidence interval, IRR: incidence rate ratio, TB: tuberculosis.