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The impact, effectiveness and outcomes of targeted screening thresholds for programmatic latent TB infection testing in HIV: cohort study results

Short title: Optimal latent TB testing threshold in HIV

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Abstract

Background Screening and treatment for latent tuberculosis infection (LTBI) are key for TB control. In the UK, the National Institute of Health and Care Excellence (NICE) and the British HIV Association (BHIVA) give conflicting guidance on which groups of people living with HIV (PLWH) should be screened, and previous national analysis demonstrated heterogeneity in how guidance is applied. There is an urgent need for a firmer clinical effectiveness evidence base on which to build screening policy.

Methods We conducted a systematic, programmatic LTBI screening intervention for all PLWH receiving care in Leicester, UK. We compared yields (percentage IGRA positive) and number of tests required when applying the NICE and BHIVA testing strategies, as well as strategies targeting screening by TB incidence in patients' countries of birth.

Results Of 1053 PLWH tested, 118 were IGRA-positive (11.2%). Positivity was associated with higher TB incidence in country-of-birth (adjusted odds ratio, 50-149 cases compared to <50 cases/100,000: 11.6 (95%CI 4.79–28.10)). There was high testing uptake (1053/1069, 98.5%). Appropriate chemoprophylaxis was commenced in 100/117 (85.5%) patients diagnosed with LTBI, of whom 96/100 (96.0%) completed treatment. Delivering targeted testing to PLWH from countries with TB incidence >150/100,000 or any sub-Saharan African country, would have correctly identified 89·8% of all LTBI cases while cutting tests required by 46·1% compared to NICE guidance, performing as well as BHIVA 2018 guidance.

Conclusions Targeting screening to higher-risk PLWH increases yield and reduces the number requiring testing. Our proposed 'PLWH-LTBI streamlined guidance' offers a simplified approach, with the potential to improve national LTBI screening implementation.

Key words: Human Immunodeficiency Virus; latent tuberculosis; tuberculosis; screening; testing; IGRA

Introduction

In 2019, tuberculosis (TB) incidence in England rose for the first time in nine years, from 4,615 in 2018 to 4,725 (2.4%).[1] Incidence remains higher in the UK than most other countries in western and northern Europe[2] and its public health importance remains: until the SARS-CoV-2 pandemic, TB was the leading cause of death from an infectious disease among adults worldwide, with an estimated 10 million people falling ill with TB in 2019, a number that has been declining only very slowly in recent years.[3]

There is now increasing focus on latent TB infection (LTBI) screening to reduce TB incidence in high-risk populations. Once latently infected, an individual is at highest risk of developing

TB disease within the first two years, but can remain at risk for their lifetime.[4] As the global community looks to meet ambitious targets for reduction (90% reduction in TB incidence by 2035) and elimination of TB (<1 incident cases/1,000,000 per year) by 2050,[5] reducing the LTBI reservoir will be essential and is one of the World Health Organization (WHO)'s key performance indicators.[6]

The WHO has published guidelines on groups at high risk to target for LTBI screening and treatment: people living with HIV (PLWH) are prime amongst these. HIV accelerates progression from LTBI to active TB from around a 10% lifetime risk to as high as 15% per year.[7] While antiretroviral therapy (ART) reduces TB risk, it does not return to that of the HIV-negative population.[8, 9] Screening and treatment (chemoprophylaxis) for LTBI reduce the risk of developing active TB, thereby preventing active TB with its attendant morbidity and mortality, transmission as well as additional costs for the health system.[10]

Both 2019 European Centre for Disease Control (ECDC) guidance for use in the European Union and European Economic Area[11] and WHO guidelines for low TB burden countries[12] recommend that all PLWH should be targeted for LTBI screening. In the UK, national guidance is conflicting: the updated 2016 National Institute for Health and Care Excellence (NICE) guidance aligns with international recommendations to test all PLWH.[13] By contrast, the British HIV Association (BHIVA) updated 2018 guidance recommends offering interferon gamma release assay (IGRA) testing to all PLWH from high (≥150/100,000 population) or medium (40-150/100,000 population) TB incidence countries, and only screening those from low TB burden countries (<40/100,000 population) if additional risk factors for TB are present (listed in the guidance[14]).

This contradictory guidance may have contributed to the extreme heterogeneity in how LTBI testing for PLWH is applied in the UK. Our national evaluation of practice highlighted that no widespread LTBI programmatic screening has been implemented in the UK in this population, with approximately half of HIV services offering no LTBI testing[15] despite LTBI screening and treatment being highly acceptable to this population.[16] Reasons for this heterogeneity in screening practice remain unclear but it likely represents a lack of confidence in existing guidelines and uncertainty as to which individuals should be offered LTBI screening. With patchy testing coverage, it is unsurprising that there are few previously published data on prospective, programmatic screening in low TB burden settings. Those which are available from cohort studies in low-incidence settings, including the UK, have included only a proportion of the active cohort being treated in that centre,[17, 18] contained estimated data,[19] or had small sample sizes.[17, 20] This highlights the need for a firmer clinical effectiveness evidence base on which to base national, and potentially international, screening policy.

We aimed to address this evidence gap by implementing a prospective screening programme for LTBI among PLWH to understand levels of LTBI testing uptake, prevalence of LTBI and levels of LTBI chemoprophylaxis uptake and completion for those testing positive, amongst this population. We also explored factors associated with LTBI in PLWH, such as ethnicity and TB incidence in country-of-birth, to evaluate the performance of targeted screening

strategies including the 2018 BHIVA[14] and NICE[13] guidance and formulate an alternative targeted testing strategy identifying groups of PLWH to prioritise for testing which optimises testing yield (IGRA positivity rate amongst those tested) and efficiency (minimal IGRA tests required).

Methods

Study design and setting

We implemented a LTBI screening programme in Leicester, UK, an ethnically diverse city with one of the highest TB incidence rates in the UK (40.5/100,000 general population in 2018[21]). HIV prevalence is 3.96/1000 population aged 15-59 years, making Leicester one of 84 (out of 317) local authorities in England with "high-diagnosed prevalence" (≥2/1000 population).[22] Only inconsistent, patchy LTBI screening amongst PLWH had been occurring in Leicester since the introduction of IGRA tests.

From 22nd February 2014 onwards, we prospectively screened all remaining active HIV patients in Leicester for LTBI followed by treatment, irrespective of ethnicity, country-of-birth, age, sex or co-morbidities, to assess acceptability and uptake of LTBI screening and treatment among PLWH, IGRA positivity rate, LTBI treatment completion rate and correlates with IGRA positivity.

Study population and participants

We included all PLWH who had sought care for HIV at University Hospitals Leicester (UHL) NHS Trust (which is the sole provider for HIV and TB care in Leicester city and Leicestershire) up until 30th June 2017. We excluded those who had had active TB or LTBI treated previously and those who had died, moved away from Leicester, been lost to follow-up or who had been screened for LTBI previously. Results from IGRA screening of the cohort, together with chemoprophylaxis uptake and completion data, were included until 30th June 2021 for the purposes of this analysis.

Ethics

No ethics approval was required as this was considered to be implementation of clinical care in line with national recommendations. Approval was given by the UHL Trust TB Board, the UHL HIV department and the UHL Microbiology department.

Screening and management

In our prospective screening study we used QuantiFERON-TB® Gold In-Tube (QFN-GIT),, with gradual switching to QuantiFERON-TB® Gold Plus (QFT-Plus) between May 2016 and January 2017. Results were positive, negative or indeterminate, dependent on manufacturers' criteria. Indeterminate results were included in the denominator.

The majority of PLWH with CD4 counts ≥200 cells/mm^3 received a single IGRA test. Those with CD4 counts <200 cells/mm^3 generally received two tests (T-SPOT®.*TB* plus a QuantiFERON-TB® test), in most cases performed on the same day (where this was not possible, dual results were included if tests were taken within 14 days). PLWH taking two tests were classed IGRA positive if either test was positive.

The most recent previous CD4 count to an IGRA test was used as the CD4 count classification at the time of the test. Individuals who had CD4 counts performed more than a year prior to the planned time of IGRA testing had testing withheld until a more recent CD4 count became available.

Individuals with positive IGRA tests were recalled for chest radiography and further clinical assessment to exclude active TB.[13] We defined LTBI as PLWH with a positive IGRA and normal chest radiography in the absence of any clinical features that would suggest active disease.[23] PLWH diagnosed with LTBI were offered chemoprophylaxis, in most cases 6 months of isoniazid, in accordance with UK guidelines,[13] although individual clinicians made the final decision dependent on clinician and patient preference. Where active TB was diagnosed,[23] treatment again followed UK guidelines:[13]

Data acquisition

Date of birth and sex at birth were recorded, together with NHS number where available, to verify records. Ethnicity and country-of-birth were ascertained from electronic hospital, HIV records, or paper hospital records, and ethnicity was coded according to the national NHS data dictionary:[24] Countries of birth were further classified into regions according to the World Bank Analytical Grouping.[25] We took TB incidence in country-of-birth (<50, 50-149, 150-249, 250-349 and ≥350 per 100,000 population) from WHO's Global Health Observatory and used figures available in March 2019.[26]

Statistical analysis

Continuous data were summarised with median and interquartile range (IQR) and categorical responses as proportions/percentages. Comparisons were made using Pearson's chi-square test (or Fisher's exact test if appropriate). We assessed univariate associations of IGRA positivity with age at IGRA test, CD4 count at IGRA test, year of HIV diagnosis, sex, ethnicity, UK birth status, region of birth, TB incidence level in country-of-birth and type of IGRA performed using logistic regression, reported as crude odds ratios (OR) and 95% confidence intervals (95% CIs). Region of birth and black ethnicity categories were collapsed due to small numbers for some regions/groups. Multivariable models were adjusted for age, sex and year of HIV diagnosis (selected *a priori*). Based on univariate associations, models were further adjusted for CD4 count at IGRA test. However, as ethnicity, UK birth status and region of birth were closely linked to the TB incidence in country-of-birth, only TB incidence in country-of-birth was included in the multivariable logistic regression.

To evaluate the performance of NICE and BHIVA guidelines alongside other targeted testing strategies using different thresholds of TB incidence in country-of-birth, for each screening scenario we calculated number of PLWH needing to be screened, LTBI yield and the proportion of all those IGRA positive correctly identified. TB incidence thresholds evaluated were: 1) >350/100,000, 2) >250/100,000, 3) >150/100,000, 4) >50/100,000 and 6) no threshold i.e. screening all PLWH, the strategy recommended by NICE 2016 guidelines,[13] ECDC guidelines for the EU/EEA[11] and WHO guidelines for low TB incidence countries.[12] We compared these strategies to 2018 BHIVA guidance which recommends targeted IGRA testing for those born in low TB incidence countries (<40/100,000) for those with TB risk factors including recent exposure to a known TB case, injecting drug use and diabetes mellitus.[14] We therefore prospectively collected risk factor data for patients testing IGRA-positive and from a low incidence (<40/100,000) country from 2018 onwards, and retrospectively extracted data from medical notes for those testing IGRA-positive pre-2018. Since BHIVA guidance changed part-way through our study we did not prospectively collect data on risk factors for patients who tested IGRA-negative from low incidence countries.

Finally, we compared these guidelines to our proposed 'PLWH-LTBI streamlined guidance': targeting testing to PLWH with country-of-birth TB incidence >150 cases/100,000 population or any sub-Saharan African country. This alternative guidance was formulated to maximise yield while minimising testing required, while streamlining guidance to be as simple and user-friendly for physicians as possible.

All data were analysed using Stata v15.1 (StataCorp, Texas, USA). All statistical tests were considered significant when $p \leq 0.05$.

Findings

Cohort description

Recruitment into the study is outlined in figure 1. 323 patients had already had active TB and were excluded from screening, as were 30 patients who had had already been diagnosed with and treated for LTBI. Ten of 1069 patients eligible for screening (0.9%) remained untested at the end of follow-up and six (0.6%) patients declined screening, leaving 1053 who underwent LTBI screening.

Table 1 shows the demographic and HIV and LTBI testing-related characteristics of the screened population (n=1053). Median age at IGRA testing was 42 years (IQR 36–49) and median CD4 count was 530 cells/mm^3 (IQR 380–700). Only 48 (4.6%) had a CD4 count <200 cells/mm^3. The dominant ethnic groups were Black African (498, 47.3%) and White (388, 36.8%). Sub-Saharan Africa and Europe & Central Asia were the most common regions of birth (51.1% and 40.0%, respectively).

IGRA testing outcomes

IGRA results were available for all participants. Overall, 118 (11.2%) PLWH had a positive IGRA result (figure 1 and table 1) and two had indeterminate results (0.2%, further information in table S1, http://links.lww.com/QAD/C621, Supplemental Digital Content).

All PLWH with a positive IGRA test were diagnosed with LTBI apart from one individual who was found to have active TB disease during clinical/radiological assessment of a positive T-SPOT®.TB test, performed at a CD4 count of 340 cells/mm^3 but with a detectable HIV viral load of 182 copies/ml.

Of the 117 PLWH diagnosed with LTBI, 100 (85.5%) commenced LTBI chemoprophylaxis (figure 1). 9/117 (7.7%) declined; treatment was not advised by the treating physician in 2/117 (1.7%) cases; and 4/117 (3.4%) moved away before chemoprophylaxis could be given. Treatment is pending in 2/117 (1.7%) cases. Reasons behind declination were not well documented in patient notes. 98/100 (98%) of those initiating chemoprophylaxis had isoniazid monotherapy; the remaining 2 (2%) had combined rifampicin/isoniazid.

Of the 100 patients commencing chemoprophylaxis, 96 (96%) completed treatment to the satisfaction of the treating physician. One individual moved away and it was unclear whether chemoprophylaxis had been completed, and one defaulted from treatment. Only 2/100 (2%) had to stop treatment prematurely due to adverse drug effects.

Factors associated with IGRA-positivity and LTBI

Non-UK born individuals were significantly more likely than UK-born individuals to be IGRA positive (15.6% versus 2.8%, $p<0.0001$). The majority of those testing positive were from sub-Saharan Africa (96/118, 81.4%), with the IGRA positivity rate for this group being 17.8%. Black African and South Asian patients had the highest IGRA positivity rates (both 18.1%). Patients from a country where TB incidence was more than 50/100,000 population had higher positivity rates: 17.3% (106/614) compared to 2.7% (12/439) for patients from low TB incidence countries (<50/100,000). Of the 12 from low TB incidence countries, only four (33.3%) had risk factors (table S2, http://links.lww.com/QAD/C621, Supplemental Digital Content).

In univariable analysis, being born abroad, specifically in sub-Saharan Africa and the South Asia and East Asia & Pacific regions, and being of black African or South Asian ethnicities, were associated with positive IGRA (table 2). TB incidence in country-of-birth was significant in both univariable and multivariable analysis with increasing likelihood of having a positive IGRA amongst individuals born in countries with TB incidence >50/100,000 population.

Yields by testing threshold

Table 3 outlines the outcome of PLWH IGRA test screening in Leicester stratified by TB incidence in country-of-birth, as well as outcomes for other screening strategies including

BHIVA 2018[14] and NICE[13] guidance and our proposed alternative 'PLWH-LTBI streamlined guidance' for targeted testing. As the incidence at which screening is instigated increases, fewer PLWH are eligible to be screened and, consequently, the number of identified LTBI cases also decreases. The yield (IGRA positivity rate amongst those tested) does not correspondingly increase once above the 40/100,000 BHIVA 2018 incidence threshold because we did not observe a linear increase in IGRA positivity for PLWH from countries with TB incidence in country-of-birth more than 40/100,000 population (table 1).

The strategy we identified as optimising yield and efficiency of testing (the 'PLWH-LTBI streamlined guidance') involves testing all PLWH with country-of-birth TB incidence >150/100,000 plus all sub-Saharan African countries. Application of NICE[13] and international[11, 12] guidance i.e. screening all PLWH in our cohort, identifies 100% of IGRA positive cases with yield 11.2%. Applying BHIVA 2018[14] guidance or our proposed 'PLWH-LTBI streamlined guidance' both reduce the number of patients eligible for screening (to 622, 59.1% and 568, 53.9%, respectively). These screening strategies produce yields of 17.7% and 18.7%. Both yields are significantly higher than NICE[13] guidelines, (proposed guidance v NICE, p<0.0001; BHIVA guidance v NICE, p=0.0002). BHIVA 2018[14] guidance misses marginally fewer infections than in our proposed strategy (percentage IGRA positives correctly identified 93.2% versus 89.8%). There was no statistically significant difference in any of the outcomes shown in table 3 between BHIVA 2018[14] and the 'PLWH-LTBI streamlined guidance' (p=0.66).

Discussion

Our study describes a large prospective, systematic LTBI screening programme implemented among PLWH in a low TB incidence country and is the first to report chemoprophylaxis treatment uptake and completion rates. Overall, 11.1% (117/1053) of screened patients had LTBI, confirming that there is significant potential to reduce incident TB rates amongst PLWH in the UK. TB incidence in this Leicester cohort is extremely high: of the 2158 patients ever treated for HIV in Leicester, 325 (15%) have had active TB, with 100 of these (31%) having incident TB occurring more than 3 months after HIV diagnosis.[15, 27] Therefore it is imperative that the burden of LTBI amongst PLWH is addressed to prevent incidence of active infection. Our study showed high acceptance of LTBI testing among PLWH, with high chemoprophylaxis uptake and completion for IGRA-positive patients. It is therefore feasible to achieve high levels of retention at each stage of the cascade of care.

Our assessment of the outcomes of IGRA screening at difference incidence thresholds and using different testing guidelines showed that an alternative to current NICE[13] and BHIVA[14] guidelines, the 'PLWH-LTBI streamlined guidance', performed statistically significantly as well as BHIVA guidelines in reducing number of IGRA tests performed and increasing yield of LTBI identified. Additionally, it offered a simpler, more streamlined approach to testing than BHIVA guidance, without the need to consult a complex set of TB risk factors to determine test eligibility that may constitute a barrier to effective implementation. 89.8% of IGRA positive cases could have been identified by restricting screening to those from countries

with TB >150/100,000 or any sub-Saharan African country. This strategy led to a significantly higher yield (LTBI positivity rate) in those tested than if all patients were screened, as is currently proposed in the ECDC, WHO and 2016 NICE guidelines.[11-13]

Extremely few patients declined IGRA testing (0.6%), although a higher proportion of those IGRA-positive declined chemoprophylaxis (7.7%). Over 85% of IGRA-positive individuals started chemoprophylaxis, comparing favourably with rates of 17–87% from elsewhere in the UK and other low TB incidence countries.[18, 20, 28] 96% successfully completed treatment and adverse drug effects from chemoprophylaxis led to cessation of therapy in only 2/100 (2%) cases, supporting previous evidence showing that chemoprophylaxis regimens, and particularly isoniazid monotherapy regimens, are safe in PLWH.[10, 29] Although there was high retention at each stage of the cascade of care, small drop-outs at each stage still led to 14.5% of IGRA positive cases not being treated. Further research to identify barriers and facilitators to improve uptake are required in order to avert reactivation to active TB cases as far as possible.

We were fortunate to have all data available on the country of birth for patients in our cohort, which made analysis straightforward. Encouraging the recording of country-of-birth without stigma or discrimination is helpful in health systems, so that any targeted testing based on country-of-birth can be implemented effectively UK-wide.

Our work has several limitations. Most notable of these is generating testing eligibility estimates according to the 2018 BHIVA guidance testing criteria, which recommends offering IGRA testing to PLWH from low TB burden countries (<40/100,000 population) only if additional risk factors for TB are present (see details in table 3 footnotes).[14] TB risk factor data were not collected prospectively for IGRA tests performed pre-2018 (date of BHIVA guidance[14] publication). Information on risk factors was retrieved from medical records only for IGRA positive cases from low TB burden countries. Therefore our estimate of IGRA eligibility under BHIVA guidance[14] is likely to be an underestimate. This would make our proposed 'PLWH-LTBI streamlined guidance' even more efficient than BHIVA 2018 guidance[14] in reducing IGRA tests required.

Secondly, we included indeterminate results in the denominator which will lead to an under-estimation of the overall IGRA positivity rate. Since there were only two cases of indeterminate results, however, this effect will be marginal. A further limitation was that we used country-specific TB incidence data available at a single time-point in our analysis, rather than using incidence estimates corresponding to year of entry to the UK for non-UK-born PLWH. TB incidence may have changed in individual countries over time; however, date of UK entry was incomplete in our dataset and may not be routinely available, and an accessible, risk-based testing approach requires a simplified approach.

LTBI prevalence was moderately high at 11.1% for the whole cohort compared to 7–10% in other settings.[18-20] IGRA positivity for PLWH from low TB incidence countries was comparable: 3.1% among PLWH born in countries with TB incidence <30/100,000 in London[20] compared to 2.7% for those from <50/100,000 in our study. Key to the performance

of screening criteria dependent on TB incidence in country-of-birth is LTBI prevalence amongst those from countries below the determined threshold. It is reassuring to observe a similar prevalence from a contrasting UK region, but more evidence on IGRA positivity rates by TB incidence in country-of-birth for other PLWH populations in the UK would be useful to validate our proposed testing strategy and determine the generalisability of the results.

Our proposed 'PLWH-LTBI streamlined guidance' performed statistically significantly as well as BHIVA 2018 guidance in terms of yield, number screened and proportion of latent infections identified. The next step is to undertake a full cost-effectiveness analysis of this and other LTBI testing strategies for PLWH, both for the Leicester cohort and more generally across the UK. This would bring together the costs of the intervention, not only in terms of IGRA tests and chemoprophylaxis but also costs saved by averting cases of active TB and associated health benefits of reducing active TB morbidity and mortality, under a single framework, to inform formation of the next round of UK guidance. A previous cost-effectiveness analysis of LTBI screening among PLWH based in London found that a targeted approach to screening was more cost-effective than universal testing, but at the expense of missing some cases.[31] We now have the empirical data to inform new health economic analyses with realistic assumptions regarding IGRA positivity rates by risk group, chemoprophylaxis uptake and treatment.

This large, prospective screening cohort showed that PLWH from high TB burden countries are at highest risk of having LTBI but also that programmatic LTBI screening is achievable and can lead to impressive outcomes in terms of chemoprophylaxis completion. We now recommend that a full cost-effectiveness analysis is undertaken in order to produce the most user-friendly, evidence-based guidelines for screening in the UK and other low TB incidence settings, to enable consistent implementation.

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Author contributions: HAW and MP conceived the study and wrote the study protocol. HAW, HP and CB undertook data collection and prepared the dataset, with data verification undertaken by HAW and MP. Analysis was conducted by HAW and HO. HAW and RFB drafted the manuscript, with MP and RFB providing ongoing advice and consultation on the analysis plan and manuscript preparation. All authors contributed to manuscript writing and approved the final, submitted version.

Data sharing: The patient cohort was extracted under Caldicott Guardian approval for a specific purpose and as part of our undertaking with them we are not to further routinely share the data presented here. The data are held in an institutional repository and interested parties, with appropriate approvals, can apply for data access through the Corresponding author. Reasonable requests will be assessed on a case-by-case basis in discussion with the Caldicott Guardian.

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Figure 1. LTBI screening and treatment cascade of care. IGRA, interferon gamma release assay; LTBI, latent TB infection.

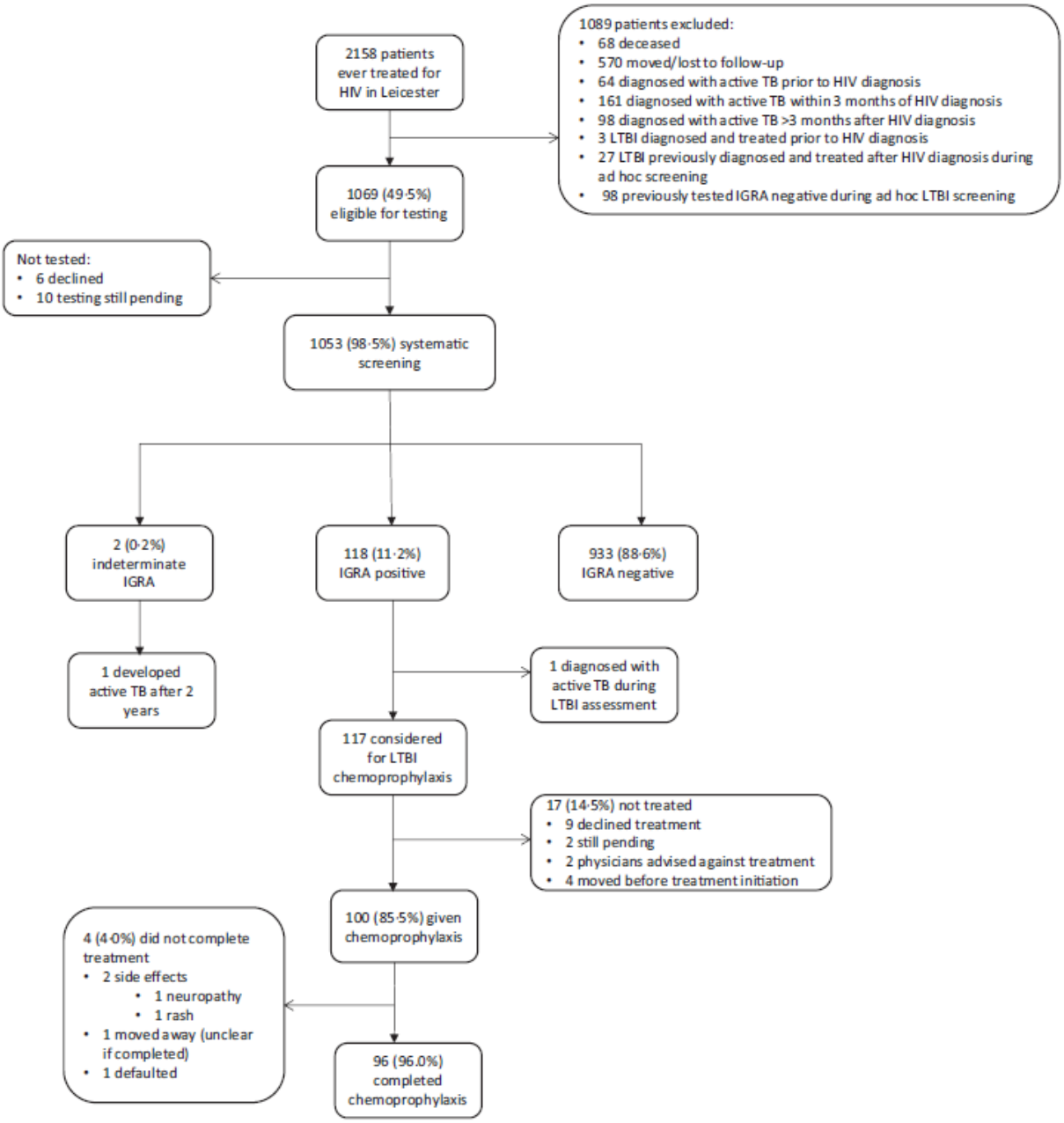

Table 1. Description of total cohort and those testing IGRA positive

Variable	Total screened cohort, n (%)		Proportion IGRA positive, x/n (%)	
Total	1053	(100)	118/1053	(11·2)
Median age at IGRA test, years (IQR)	42	(36–49)	42	(38–48)
Year of HIV diagnosis				
1985 – 1989	8	(0·8)	2/8	(25·0)
1990 – 1999	68	(6·5)	3/68	(4·4)
2000 – 2009	604	(57·4)	74/604	(12·3)
2010 – 2017*	373	(35·4)	39/373	(10.5)
Year of IGRA test				
2014	393	(37.3)	43/393	(10.9)
2015	358	(34.0)	47/358	(13·1)
2016	147	(14.0)	18/147	(12·2)
2017	125	(11.9)	8/125	(6.4)
2018	24	(2.3)	2/24	(8.3)
2019	3	(0.3)	0/3	(0.0)
220	1	(0.1)	0/1	(0.0)
2021†	2	(0.2)	0/2	(0.0)
Sex				
Male	597	(56·7)	53/597	(8.9)
Female	456	(43·3)	65/456	(14·3)
CD4 count at IGRA testing (cells/mm^3)				
Median (IQR)	530	(380–700)	545	(440–720)

Variable	Total screened cohort, n (%)		Proportion IGRA positive, x/n (%)	
Range	10–2260		90–1350	
≤200	48	(4.6)		(4·2)
201-350	181	(17.2)	2/48	(6.6)
351-500	250	(23·7)	12/181	(14·4)
>500	574	(54.5)	36/250	(11·8)
			68/574	
Ethnicity				
Black African	498	(47.3)	90/498	(18·1)
South Asian	94	(8.9)	17/94	(18·1)
White	388	(36.8)	9/388	(2·3)
Mixed	16	(1·5)	0/16	(0·0)
Black Caribbean	14	(1·3)	0/14	(0.0)
Black Other	10	(0·9)	0/10	(0·0)
Other	32	(3·0)	2/32	(6.3)
Unknown	1	(0·1)	0/1	(0·0)
UK birth status				
UK born	361	(34·3)	10/361	(2·8)
Non-UK born	692	(65.7)	108/692	(15.6)

Variable	Total screened cohort, n (%)		Proportion IGRA positive, x/n (%)	
Region of birth				
Sub-Saharan Africa	538	(51·1)	96/538	(17·8)
South Asia	50	(4·7)	8/50	(16)
Europe & Central Asia	421	(40·0)	12/421	(2.9)
East Asia & Pacific	22	(2·1)	2/22	(9.1)
Latin America & Caribbean	13	(1·2)	0/13	(0.0)
Middle East & North Africa	5	(0·5)	0/5	(0·0)
North America	4	(0·4)	0/4	(0·0)
TB incidence in country-of-birth				
<50/100,000 population	439	(41·7)	12/439	(2.7)
50 - 149/100,000 population	58	(5·5)	12/58	(20.7)
150 – 249/100,000 population	427	(40.6)	74/427	(17.3)
250-349/100,000 population	63	(6·0)	11/63	(17.5
≥350/100,000 population	66	(6·3)	9/66	(13·6)
Type of IGRA performed				
QuantiFERON-TB® test‡ only	1013	(96·2)	115/1013	(11·4)
QuantiFERON-TB® tests‡ & T-SPOT®.*TB*	25	(2·4)	2/25	(8)
T-SPOT®.*TB* only	15	(1.4)	1/15	(6.7)

IGRA = interferon gamma release assay; IQR = interquartile range.

* Individuals were included up and including to 30th June 2017.

† 30th June 2021 was used as the cut-off for following up patients for IGRA testing.

‡ QuantiFERON-TB® GIT or QuantiFERON-TB® Plus.

Table 2. Univariate and multivariable logistic regression for having a positive IGRA test at LTBI screening

IGRA = interferon gamma release assay; OR = odds ratio.

Variable		Observation (%)	Unadjusted OR (univariate analysis)	p value	Adjusted OR (multivariable analysis)	p value
Age at IGRA test (years)			1·01 (0·992 – 1·028)	0·26	1·022 (1.0 – 1·05)	0·05
Year of HIV diagnosis			0·99 (0·96 – 1·02)	0·53	1·03 (0·99 – 1·07)	0·23
Sex	Male	53/118 (44·9)	1		1	
	Female	65/118 (55·1)	1·71 (1·16 – 2·51)	0·01	0·95 (0·62-1·45)	0·79
CD4 count at IGRA test (cells/mm^3)	<200	2/118 (1.7)	1		1	
	200-349	12/118 (10·2)	1.63 (0·36 – 7.56)	0·53	1.67 (0·35 – 7.97)	0·52
	350-499	36/118 (30.5)	3.87 (0.90 – 16.65)	0·008	4·39 (0.99 – 19.53)	0·05
	≥500	68/118 (57·6)	3·09 (0.73 – 13.02)	0·12	3.92 (0.89 – 17.12)	0·07
Ethnicity	Black†	90/118 (76·3)	1		- #	-
	South Asian	17/118 (14·4)	1·06 (0·60 – 1.88)	0·84	-	-
	White	9/118 (7·6)	0·11 (0·06 – 0·23)	<0·0001	-	-
	Mixed/Other	2/118 (1.7)	0·20 (0·05 – 0·86)	0·03	-	-
	Non-UK born	108/118 (91·5)	1		- #	-

UK birth status	UK born	10/118 (8.5)	0·15 (0·08 – 0·30)	<0·0001	-	-
World Bank region of birth	Europe & Central Asia, North America and Latin America & Caribbean and Middle East & North Africa‡	12/118 (10.2)	1		- #	-
	South Asia and East Asia & Pacific§	10/118 (8.5)	5.79 (2·40 – 13·97)	<0·0001	-	-
	Sub-Saharan Africa	96/118 (81·4)	7.80 (4.22– 14·42)	<0·0001	-	-
TB incidence in country-of-birth[26],	<50/100,000 population	12/118 (10.2)¶	1		1	
	50 – 149/100,000 population	12/118 (10.2)	9.28 (3·94 – 21·85)	<0·0001	11.6 (4·79 – 28·10)	<0·0001
	150 – 249/100,000 population	74/118 (62·7)	7.46 (3·99 – 13·95)	<0·0001	8·26 (4·27 – 15·98)	<0·0001
	250 – 349/100,000 population	11/118 (9.3)	7·53 (3.16 – 17.92)	<0·0001	8·13 (3.33 – 19·86)	<0·0001
	≥350/100,000 population	9/118 (7·6)	5.62 (2·27 – 13·92)	<0·0001	6.16 (2.42 – 15·67)	<0.0001

† All were Black African; none were Black Caribbean or Black Other.

‡ All were from Europe & Central Asia; none were from Latin America & Caribbean, North America or the Middle East & North Africa.

§ 8/10 were from South Asia; 2/11 were from East Asia & Pacific region.

Table 3. Yield and percentage of IGRA positive results obtained by implementing LTBI screening at different TB incidence thresholds

Threshold: TB incidence in country-of-birth	Number screened (%)		Number IGRA positive	Yield (% IGRA positive of those tested)	% of all IGRA positives correctly identified
>350/100,000	66	(6·3)	9	13·6%	7·6%
>250/100,000	129	(12·3)	20	15.5%	16.9%
>150/100,000	556	(52·8)	94	16·9%	79·7%
>150/100,000 plus all sub-Saharan African countries: the proposed 'PLWH-LTBI streamlined guidance'	568	(53·9)	106	18·7%	89·8%
>50/100,000	614	(58·3)	106	17·3%	89·8%
≥40/100,000 plus risk factors: BHIVA 2018 guidelines†[14]	622‡	(59·1)	110	17·7%	93·2%
Screen all PLWH:* 2016 NICE guidelines,[13] ECDC guidelines for the EU/EEA,[11] WHO guidelines for low tuberculosis burden countries[12]	1053	(100)	118	11·2%	100%

BHIVA = British HIV Association; ECDC = European Centre for Disease Prevention and Control; EEA = European Economic Area; EU = European Union; IGRA = interferon gamma release assay; NICE = National Institute for Health and Care Excellence; WHO = World Health Organization. All included guidelines mention dual use of IGRA/Mantoux testing in some, or all PLWH. We have assumed in this table that IGRA is as effective at diagnosing LTBI as Mantoux.

† Recommends screening all those from high (≥150/100,000 population) or medium (40-150/100,000 population) TB incidence countries; only screening those from low TB burden countries (<40/100,000 population) if additional risk factors for TB are present: CD4 cell count <200 cells/mm^3; recent exposure to a known TB case; diabetes mellitus; stage 4/5 chronic kidney disease; receipt of chemotherapy for malignancy; immunosuppression following transplantation; biological disease modifiers for inflammatory conditions; prolonged duration of high-dose corticosteroids (prednisolone 20 mg od, or equivalent, for ≥2 months); travel to or periods of time spent in medium- or high-incidence countries; history of

working in medical settings in countries with medium or high TB incidence; injecting drug use (detailed in Table 6.1 of guidance[14]).

‡ This figure is an underestimate (includes all patients from countries where TB ≥40/100,000 population; plus 4 IGRA positive patients from countries where TB incidence <40/100,000 for whom BHIVA cited additional risk factors were evident, but does not include patients with negative IGRA results from countries where TB incidence <40/100,000 because BHIVA-cited risk factors were not collected prospectively