BMJ open
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Comparison of screening strategies to improve the diagnosis of latent tuberculosis infection in the HIV-positive population: a cohort study

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To cite: Pollock KM, Tam H, Grass L, *et al*. Comparison of screening strategies to improve the diagnosis of latent tuberculosis infection in the HIV-positive population: a cohort study. *BMJ Open* 2012;**2**:e000762. doi:10.1136/bmjopen-2011-000762

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2011-000762).

Received 14 December 2011
Accepted 23 January 2012

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ABSTRACT

Background: HIV is the most important risk factor for progression of latent tuberculosis infection (LTBI) to active tuberculosis (TB). Detection and treatment of LTBI is necessary to reduce the increasing burden of TB in the UK, but a unified LTBI screening approach has not been adopted.

Objective: To compare the effectiveness of a TB risk-focused approach to LTBI screening in the HIV-positive population against current UK National Institute for Health and Clinical Excellence (NICE) guidance.

Design: Prospective cohort study.

Setting: Two urban HIV treatment centres in London, UK.

Participants: 114 HIV-infected individuals with defined TB risk factors were enrolled prospectively as part of ongoing studies into HIV and TB co-infection.

Outcome measures: The yield and case detection rate of LTBI cases within the research study were compared with those generated by the NICE criteria.

Results: 17/114 (14.9%, 95% CI 8.3 to 21.5) had evidence of LTBI. Limiting screening to those meeting NICE criteria for the general population (n=43) would have detected just over half of these, 9/43 (20.9%, 95% CI 8.3 to 33.5) and those meeting criteria for HIV co-infection (n=74) would only have captured 8/74 (10.8%, 95% CI 3.6 to 18.1) cases. The case detection rates from the study and NICE approaches were not significantly different. LTBI was associated with the presence of multiple TB risk factors (p=0.002).

Conclusion: Adoption of a TB risk-focused screening algorithm that does not use CD4 count stratification could prevent more cases of TB reactivation, without changing the case detection rate. These findings should be used to inform a large-scale study to create unified guidelines.

ARTICLE SUMMARY

Article focus

- HIV is the single most important risk factor for the progression of LTBI to active TB.
- Despite this, the UK approach to screening for LTBI in HIV co-infected individuals is not unified as the evidence base is insufficient.
- We hypothesised that LTBI screening in HIV co-infected individuals required an approach focused on TB risk factors that was broader than recommended by NICE.

Key messages

- Screening strategies for LTBI in HIV co-infected patients that focus on limited TB risk factors (recent entrance from a TB endemic area or history of TB contact) or limit screening to those with a CD4 count of ≤500 cells/μl would detect approximately half the total cases in this cohort.
- A TB risk-focused approach could aid in the prevention of more cases of active TB and HIV co-infection.

Strengths and limitations of this study

- This study addresses the utility of NICE guidance for LTBI screening in the HIV co-infected population.
- Numbers were relatively small, therefore a large study is needed to better inform UK guidance on LTBI screening in the HIV co-infected population.

INTRODUCTION

The incidence of disease caused by *Mycobacterium tuberculosis* (MTB) infection in the UK has increased over the past 20 years and there were 8483 notifications of tuberculosis (TB) in 2010.[1] Co-infection with HIV was found in 4.9% of UK active TB cases in 2010,[1] and the total number of co-infection cases has increased year on year in the European region, from 9200 in 2007 to 13 821 in 2009.[2] The prevention of co-infection cases rests in part on treating latent tuberculosis infection (LTBI); however, there is little empiric evidence guiding LTBI screening in the HIV-positive population.

Treatment of LTBI reduces the risk of progression to active TB,[3] which in the

setting of HIV co-infection is more severe and associated with extrapulmonary disease[4–6] and reduces the risk of onward transmission and infection.[7] The complex pharmacological interactions, risk of immune reconstitution inflammatory syndrome and considerable pill burden consequent upon treating both infections contemporaneously are thus avoided. Preventing active TB has potential cost savings; active TB treatment costs £7095.08 more than 6 months of isoniazid therapy.[8]

It is unknown whether the criteria for LTBI screening should be the same as in the general population or whether they should be tailored to the needs of the HIV-infected. Recently published National Institute for Health and Clinical Excellence (NICE) guidance[9] recommends that testing should be carried out in all contacts of active TB and new entrants from high incidence countries for the general population and the use of single- or dual-step screening based on CD4 count for the immunosuppressed. We postulated that the target HIV-infected population for LTBI screening should be broader because of the wealth of data demonstrating the resurgence of TB due to the HIV epidemic.[10 11] HIV is the single most important risk factor for progression of LTBI to active disease and the risk of active TB increases with immunosuppression[12 13] and is associated with MTB infection and re-infection.[14] Therefore, an effective screening strategy to detect and treat LTBI in those most likely to become infected and to progress to active disease is of public health interest.

Concerns regarding the sensitivity of both the tuberculin skin test (TST) and interferon-γ (IFN-γ) release assays (IGRAs) in the HIV-infected population have hindered their widespread use in HIV co-infection. The TST has poor sensitivity in HIV-infected patients[15] and poor specificity in those who have been BCG vaccinated[16] or those with a non-tuberculous mycobacterial infection. It is a well-characterised assay, however, which can improve targeting of chemoprophylaxis to those most likely to benefit.[17] New HIV guidelines suggest using IGRAs rather than TST for LTBI screening,[18] and NICE recommends IGRAs, with or without TST, dependent on CD4 count.[9] IGRAs use the antigenic targets, ESAT-6 and CFP-10, which are absent from BCG, improving sensitivity and specificity for the diagnosis of MTB infection.[16 19] There is some evidence that the ELISpot platform is more sensitive in the setting of HIV than the TST,[19 20] but more data are needed.

Current clinical practice for LTBI screening in the HIV population is not uniform. Some units, as exemplified by the two large HIV clinics studied, screen a broader target population for LTBI than the NICE criteria because of the increased risk of active TB. Since this approach is not based on empiric evidence, we examined the yield and case detection rate of LTBI cases using both the criteria recommended by NICE and by our broader research study criteria. To our knowledge, this is the first work to specifically address the effectiveness of the NICE criteria in the HIV-positive population.

METHODS

Subjects with HIV infection were prescreened by notes review for LTBI risk factors and recruited from two London HIV clinics (Imperial College Healthcare NHS Trust and Northwest London Hospitals NHS Trust) during January 2008–December 2010 as part of ongoing studies into HIV and MTB co-infection. Radiological findings, TST results and demographic data were collected. A cut-off of ≥5 mm was used for TST positivity.[17 21] Patients with clinical (cough, fever, night sweats, haemoptysis, weight loss), radiological or microbiological evidence of active TB and those with a history of TB treatment or chemoprophylaxis were excluded. Data on risk factors for TB were systematically recorded as part of the parent study. A history of TB contact at any time (recent or remote) was recorded.

Box 1 summarises current UK guidance for LTBI screening in HIV.

Box 1 UK guidance for latent tuberculosis infection (LTBI) screening with reference to HIV co-infection

National Institute for Health and Clinical Excellence guidance on LTBI diagnosis[9]

1. Tuberculosis (TB) contacts

Offer Mantoux testing in line with the Green Book to diagnose latent TB in people who are:

- household contacts (aged 5 years and older) of all people with active TB.
- non-household contacts (other close contacts, eg, in workplaces and schools).

Consider interferon-γ testing for people whose Mantoux testing shows positive results or in people for whom Mantoux testing may be less reliable, eg, BCG-vaccinated people.

If Mantoux testing is inconclusive, refer the person to a TB specialist.

2. New entrants from high-incidence countries

Offer either an interferon-γ test alone or a dual strategy in people aged 16–35 years. For people aged 35 years or older, consider the individual risks and benefits of likely subsequent treatment, before offering testing.

3. Immunocompromised

For people with HIV and CD4 counts less than 200 cells/μl, offer an interferon-γ test and a concurrent Mantoux test. If either test is positive: perform a clinical assessment to exclude active TB and consider treating latent TB infection.

For people with HIV and CD4 counts of 200–500 cells/μl, offer an interferon-γ test alone or an interferon-γ test with a concurrent Mantoux test. If either test is positive: perform a clinical assessment to exclude active TB and consider treating latent TB infection.

BHIVA 2011 guidelines[18]

Consider country of origin, CD4 count and length of time on highly active antiretroviral therapy. Close contacts of infectious TB should be offered chemoprophylaxis. Interferon-γ release assays rather than tuberculin skin test are recommended, although there is a call for more data.

UK guidance (NICE guidelines)

NICE recommends screening TB contacts and new entrants (≤5 years) from high TB incidence countries (estimated incidence rate of 40/100 000)[9] in those aged 16–35 years and to consider the risks and benefits of treatment before offering testing to those aged 35 years or older. People with HIV who are in close contact with people with sputum smear-positive respiratory TB should have active disease excluded and then be given treatment for latent TB infection. Treatment of LTBI should be for people of any age who have HIV; therefore, an upper age limit for LTBI screening was not imposed in this study. Screening for immunosuppressed is recommended as a dual step (IGRA and TST) for those with a CD4 count <200 cells/μl and as single or dual step for those with a CD4 count 200–500 cells/μl.

Research study screening approach

HIV-positive participants were classified as at risk of LTBI according to a set of TB risk criteria. Those included had a history of TB contact and/or were migrants from a TB endemic country, regardless of date of entry into the UK or had two or more additional risk factors (see table 1 for empirical evidence on TB risk factors): travel to a TB endemic area, smoking, more than occasional alcohol intake, homelessness, injecting drug use, prison stay or healthcare work.

Diagnosis of LTBI

All participants were screened with the research study IGRA, an in-house IFN-γ MTB ELISpot. Evidence of an immunological response (positive IFN-γ secretion) to TB was made using the MTB region of difference−1 (RD−1) antigens, ESAT-6 and CFP-10, which are present in the commercial T-Spot®.*TB* assay, and thus, the results generated were considered to be equivalent to those generated by the commercial assay. The test was performed using pools of overlapping 15-mer peptides, as described previously.[36] A positive response was defined as at least five spot-forming cells more than the negative control well and at least twice the negative control well. Where participants had been screened as part of routine clinical work, this result was also used to define cases of LTBI. The commercial IGRAs, T-Spot®.*TB* or QuantiFERON®-TB Gold—In Tube (QFT), were performed by the clinical diagnostic laboratory. TST data were available for 20 cases but TST was not routinely performed in accordance with BHIVA guidance. We defined LTBI as a positive response in any of the screening assays (IGRA or TST).

Statistical analysis was performed using SPSS® Statistics (IBM®) V.20 and Prism 5 GraphPad Software, Inc, (La Jolla, California, USA). A Fisher's exact test was used to compare proportions. Significance was assessed at the 5% and 1% level.

RESULTS

Research study screening approach

A total of 114 HIV-positive individuals were identified as at risk of LTBI according to the study protocol. Median age was 39 years (IQR 31.0–44.0), 77 (67.5%) were from

Table 1 Evidence for risk factors used in the study

Risk factor	Evidence
Born in a TB endemic area	HR for TB recurrence for foreign born 3.2 (95% CI 1.2 to 9.0)[22]
	Adjusted OR for TST positivity for LTBI in students 43.5 (95% CI 25.2 to 72.3)[23]
Residence in a TB endemic area	OR for QFT positivity in HIV patients 5.7 (95% CI 2.6 to 12.5)[24]
TB contact	OR for QFT positivity in HIV patients 4.9 (95% CI 2.0 to 11.8)[24]
	OR for QFT positivity in HIV patients 7.8 (p=0.023)[25]
Alcohol	HR for incident TB in men drinking 50–99 g alcohol per day 1.2 (95% CI 1.1 to 1.3) and ≥100 g alcohol per day 1.5 (95% CI 1.3 to 1.7)[26]
Smoking	HR for TB mortality in current male smokers 1.6 (95% CI 1.3 to 2.0) and incident TB current male smokers 1.4 (95% CI 1.3 to 1.5)[26]
	Smoking associated with TB (weighted OR 2.4, 95% CI 1.71 to 3.39, p<0.001) and a worse clinical picture, e.g., cavitation (OR 1.76, 95% CI 1.18 to 2.63)[27]
	Smoking associated with pulmonary TB (adjusted HR 2.87, 95% CI 2.00 to 4.11)[28]
	Pulmonary TB associated with smoking aOR (1.5)[29]
Healthcare work	TST conversion associated with nursing and ethnicity[30]
	TST conversion associated with place of healthcare work, e.g., infectious diseases HR 1.94 (95% CI 1.50 to 2.49) in multivariate analysis[31]
	Risk of TB higher for healthcare workers than the general population[32]
Illicit drug use	Higher rates of TST positivity in crack smokers[33]
	HR for TB recurrence 2.9 (95% CI 1.3 to 6.4)[22]
	OR for QFT positivity in HIV patients 9.8 (p=0.031)[25]
Period of homelessness	OR for QFT positivity in HIV patients 5.2 (p=0.018)[25]
Prison	High prevalence of active TB in prisons in sub-Saharan Africa[34]
	Incidence rate ratio for LTBI 26.4 (IQR 13.0–61.8) and TB 23.0 (IQR 11.7–36.1)[35]
Multiple risk factors	OR in HIV patients for one or more risk factors 7.2 (2.9–18.2)[24]

LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test; QFT, QuantiFERON TB test.

sub-Saharan Africa and 11 (9.6%) were from central and southern America (table 2). The median (IQR) CD4 count was 412 (310–628) cells/μl and 72 (63.2%) were prescribed highly active antiretroviral therapy (HAART) at time of recruitment, 64 (56.1%) were women and 50 (43.9%) were men. Seventeen of 114 (14.9%, 95% CI 8.3 to 21.5) participants were diagnosed with LTBI in total. Results of IGRA and TST are presented in table 3. The local LTBI screening protocol detected nine (52.9%, 95% CI 26.5 to 79.3) cases and one had a negative screen (TST and IGRA) in the clinic but a positive study IGRA. Seven individuals (41.2%, 95% CI 15.1 to 67.3) who had not been referred for clinical screening had a positive research study IGRA. Therefore, the research study approach increased the number of individuals diagnosed with LTBI compared with current clinical services, with an overall case detection rate of 14.9% (table 4).

Table 2 Demographic characteristics of participants eligible for LTBI screening

Demographic	N=114	%
Age (years)		
≤25	12	10.5
26–35	32	28.1
36+	70	61.4
Sex		
Female	64	56.1
Male	50	43.9
Origin		
Europe, North America, Caribbean, Australia	13	11.4
Middle East, North Africa	2	1.8
Other Asia	8	7.0
Indian Subcontinent	3	2.6
Sub-Saharan Africa	77	67.5
Central and Southern America	11	9.6
BCG vaccinated		
Yes	87	76.3
No	9	7.9
Unknown	18	15.8
TST (mm)		
≥5	6	5.3
<5	14	12.2
Not done	94	82.5
CD4 count		
0–199	14	12.3
200–500	60	52.6
>500	40	35.1
Viral load		
<50	49	43.0
50–1000	24	21.1
>1000	41	36.0
HAART therapy		
Yes	72	63.2
No	42	36.8

HAART, highly active antiretroviral therapy; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

Table 3 IGRA (commercial or research assay) and TST results

	Positive IGRA	Positive TST	Total positive in either or both tests
IGRA only	10/94	NA	10/94 (10.6%)
TST and IGRA	6/20	6/20	7/20* (35.0%)

*All participants underwent research IGRA screening, of the 20 participants who also underwent TST, discordance occurred in two cases (one was positive who had a negative IGRA result and one was negative who had positive IGRA result).
IGRA, interferon-γ release assay; NA, not applicable; TST, tuberculin skin test.

NICE guidance approach

A smaller proportion would have fulfilled NICE guidance criteria for the general population (recent migrant from a TB endemic area or TB contact). Screening according to NICE guidance would have meant that 43/114 (37.7%, 95% CI 28.6 to 46.8) would have been eligible for screening of whom, 9/43 (20.9%, 95% CI 8.3 to 33.5) would have been diagnosed with LTBI (table 4). The remaining 71 (62.3%, 95% CI 53.2 to 71.3) would not be screened according to NICE guidance and 8/17 (47.1%, 95% CI 20.6 to 73.5) with LTBI would remain undiagnosed. The detection rate was not significantly higher than with the research study approach (p=0.470), and the diagnostic yield was only 52.9% of all LTBI cases detected.

When examining the criteria specifically for immunosuppressed patients suggested by NICE, 14/114 (12.3%, 95% CI 6.2 to 18.3) had a CD4 count of <200 cells/μl and would have been eligible for dual-step screening and 60/114 (52.6%, 95% CI 43.3 to 61.9) had a CD4 count of 200–500 cells/μl and would have been eligible for single- or dual-step screening. A remaining 40/114 (35.1%, 95% CI 26.1 to 43.4) had a CD4 count of greater than 500 cells/μl and would not have been recommended either approach. Of those with LTBI, none had a CD4 count of <200 cells/μl, 8/17 (47.1%, 95% CI 21.6 to 73.5) had a CD4 count of 200–500 cells/μl and 9/17 (52.9%, 95% CI 26.5 to 79.3) had a CD4 count of >500 cells/μl. Therefore, using this approach, fewer than half the LTBI cases would have been detected, and the detection rate would have fallen to 8/74 (10.8%, 95% CI 3.6 to 18.1), although this was not different from the study approach (p=0.512).

Risk factors for LTBI

A full TB risk history was taken at the time of recruitment to the study. The TB risk factors used for selection of subjects were chosen based on the available evidence (table 1). On univariate analysis, more than occasional alcohol intake (p=0.008), injecting drug use (p=0.023) and two or more (p=0.011) or three or more TB risk factors (p=0.002) were associated with LTBI (table 5). A history of recent or remote TB contact or a history of

Table 4 Case detection rates for latent tuberculosis infection (defined as positive TST and/or IGRA) for different screening strategies

Screening approach	Number tested	Number positive	Case detection rate (%)	Proportion of latent TB infection identified (%)
Study	114	17	14.9	100.0
NICE general population	43	9	20.9	52.9
NICE immunosuppressed	74	8	10.8	47.1

IGRA, interferon-γ release assay; NICE, National Institute for Health and Clinical Excellence; TST, tuberculin skin test.

immigration from a TB endemic area within 5 years was not associated with LTBI. Multivariate analysis was not performed as numbers were small. The presence of multiple, rather than specific, TB risk factors was therefore most strongly associated with LTBI in this cohort.

DISCUSSION

The study has demonstrated that using currently available tools, a structured approach to screening in the HIV-positive population detects LTBI in one in seven of those with TB risk factors. Screening according to NICE guidance using either general population guidance or that specifically suggested for immunosuppressed individuals would only have detected half or fewer of these LTBI cases. This is an important finding given that recently published BHIVA guidance also recommends screening stratified by CD4 count.

The case detection rate from the study approach was not significantly different from the rates generated by the NICE approach. The number needed-to-be screened increased, however, from 43 with NICE-specified risk factors for the general population to 114. Although this represents a 2.7-fold increase, which carries a cost implication, this would place a minimal additional strain on resources. However, if NICE screening stratified by CD4 count were adopted, a total of 74 cases would have been eligible for single- or dual-step screening. The estimated costs of each test are: TST (£16.14); T-Spot®.*TB* (£55) and QFT (£45)[8]. In this study, the estimated additional cost of screening those who did not fulfil NICE criteria for immunosuppressed individuals (n=40) would have been £2200 for T-Spot®.*TB* alone and £2845.60 for a dual TST and T-Spot®.*TB* screening strategy. These costs, in addition to the cost of chemoprophylaxis (estimated at £524.59, range £262.30–£1049.18 for 6 months Isoniazid[8]), are small compared with the cost of treating one case of active TB/HIV co-infection, where treatment of TB alone has been estimated at £7619.67 (range £3809.84–£15239.34).[8]

Recent work has suggested that a single-step IGRA approach is cost effective,[9] as is screening in the immigrant population.[37] In our study, TST was positive in one individual with a negative IGRA. The increased risk of both progression and expensive-to-treat extrapulmonary or invasive disease in the HIV population would therefore be expected to improve the incremental cost-effectiveness ratios and thus increase the cost-effectiveness of screening for LTBI. In other clinical HIV cohorts, where there is a higher proportion of sub-Saharan Africans (in whom the prevalence of LTBI is highest), screening would also be more cost effective. A full cost-effectiveness analysis is required to determine whether single- or dual-step testing would be most appropriate in this population.

Table 5 Comparison of risk factors for latent TB infection from those used in the study screening approach

TB risk factor	Diagnosed with latent TB infection n=17 (%)		No latent TB infection n=97 (%)		p[a]
Born in a TB endemic country	15	88.2	83	85.6	NS
New entrant	4	23.5	13	13.4	NS
TB contact	5	29.4	23	23.7	NS
Travel to a TB endemic area	11	64.7	45	46.4	NS
Alcohol	7	41.2	12	12.4	0.008*
Smoking	6	35.3	22	22.7	NS
Healthcare work	3	17.6	8	8.2	NS
Injecting drug use	3	17.6	2	2.1	0.023†
Period of homelessness	1	5.9	4	4.1	NS
Prison	2	11.8	3	3.1	NS
≥2 risk factors	17	100.0	69	71.1	0.011†
≥3 risk factors	13	76.5	34	35.1	0.002*

[a]p Values are for Fisher's exact test for each risk factor to compare those with and without LTBI.
*Significance at 1% level.
†Significance at 5% level.
NS, not significant; TB, tuberculosis.

Extrapolating the study results to the wider UK setting, in 2010, there were 23 714 black Africans older than 14 years accessing care for HIV in the UK.[38] If we assume 14.9% (95% CI 8.3 to 21.5) would have LTBI (3533.4 cases), then approximately half would be diagnosed according to the NICE criteria for either the general or immunosuppressed population and 1766.7 cases would remain undiagnosed. Estimates of those at risk of developing active TB vary and include data from the pre-HAART era; estimates of 5%–8% in 1 year have been suggested,[3 39] which would mean 88.3–141.3 at risk of developing active TB in the subsequent 12 months. Clinical observation in the HAART era suggests that this estimate may be too high. Long-term observational data are required to quantify this and to add to the limited available evidence for the prognostic power of IGRAs.[40]

The presence of multiple risk factors, rather than particular risk factors, was most highly associated with LTBI in our cohort. Since all patients with LTBI had two or more risk factors, there is potential to reduce the numbers screened by 25%. Studies in HIV-infected populations have been carried out in Europe; in Spain,[41] Germany[42] and Denmark,[24] rates of IGRA positivity of 6.7%–9.3%, 18.9%–24% and 4.6%, respectively, were found. Brock *et al*[24] showed that previous TB diagnosis, history of exposure, long-term residence in a TB endemic country and the presence of one risk factor or more were associated with a positive QFN. Active TB was associated with black African ethnicity, low CD4 count and a shorter time on HAART in a UK study.[43]

The diagnostic ability of the different assay platforms has been previously studied.[19 44–46] There is evidence to suggest that the ELISpot platform retains sensitivity in HIV-infected individuals,[44 47–49] but there is no gold standard test for LTBI and all methods may be affected by HIV-induced immunosuppression. Despite this, the use of the ELISpot platform in our study detected a significant rate of undiagnosed LTBI.

A pragmatic approach to screening for LTBI in HIV co-infection is both necessary and possible. Screening recent immigrants from endemic countries and TB contacts would identify just over half of all cases and can be recommended only as a minimum. Screening by stratification of CD4 count would also only detect less than half the cases. Expanding the screening criteria to include multiple risk factors, which would, using currently available assays double the yield without altering the case detection rate, should be considered as an alternative strategy.

Acknowledgements Dr Lee Potiphar, Mr Samuel Bremang, the staff at the Jefferiss Wing Clinic, St Mary's Hospital, London and Northwick Park Hospital Genitourinary and HIV Medicine clinic, Harrow, UK.

Contributors KMP designed the study, recruited participants, designed and performed the experiments, analysed the data and wrote the manuscript. LG recruited participants and analysed the data. HT analysed the data and wrote the manuscript. SB performed the experiments. MP analysed the data and wrote the manuscript. GSC recruited participants and wrote the manuscript. MK recruited participants. DM-S designed the experiments and provided comments on the manuscript. GPT designed the study and wrote the manuscript. AL designed the study, designed experiments and wrote the manuscript. AL is the guarantor of the study.

Funding This study was funded with a TB Funds Grant TB08/02 from the British Lung Foundation. The funding body was not involved in experimental design, recruitment of participants, experimental work, data analysis, writing the manuscript or manuscript submission.

Competing interests The ESAT-6/CFP-10 ELISpot was commercialised by an Oxford University spin-out company (Oxford Immunotec Ltd, Abingdon, UK) in which Oxford University and Professor Lalvani have a minority share of equity and entitlement to royalties.

Patient consent All patients provided written informed consent using ethically approved Tuberculosis Research Unit research tissue back consent forms.

Ethics approval Ethical approval for this study was obtained from St Mary's REC, 2nd Floor A Block, 50 Eastbourne Terrace, London W2 6LG (07/H0712/85). Signed informed consent was obtained from all participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All participants were assigned a unique anonymised study number and all data are stored under this study number. Data sharing: no additional data available.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	√
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	√
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√
Objectives	3	State specific objectives, including any prespecified hypotheses	√
Methods			
Study design	4	Present key elements of study design early in the paper	√
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	√
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	√
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√
Bias	9	Describe any efforts to address potential sources of bias	See discussion
Study size	10	Explain how the study size was arrived at	See methods and discussion
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	√
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	√
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	√
		(b) Give reasons for non-participation at each stage	√
		(c) Consider use of a flow diagram	Available if required
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	√

		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	√
Outcome data	15*	Report numbers of outcome events or summary measures over time	√
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	√
		(*b*) Report category boundaries when continuous variables were categorized	√
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	√
Discussion			
Key results	18	Summarise key results with reference to study objectives	√
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	√
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	√
Generalisability	21	Discuss the generalisability (external validity) of the study results	√
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	√

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

05-Dec-2011

Dear Dr. Pollock:

I write you in regards to manuscript # thoraxjnl-2011-201204 entitled "Comparison of screening strategies to improve the diagnosis of latent tuberculosis infection in the HIV positive population" which you submitted to Thorax.

We receive many more manuscripts than we can publish. In view of the comments of the reviewer(s) found at the bottom of this letter, your manuscript has not reached a high enough priority for publication in Thorax. I am sorry to disappoint you, and I hope that nonetheless the comments are of value to you as you move forward with the work.

Thank you for considering Thorax for the publication of your research. I hope the outcome of this specific submission will not discourage you from the submission of future manuscripts.

Sincerely,

Professor Andrew Bush
Editor-in-Chief, Thorax

Professor Ian Pavord
Editor-in-Chief, Thorax

Reviewer(s)' Comments to Author:

Reviewer: 1
Comments to the Author
This is straight-forward study retrospectively assessing the increase in detection of LTBI that would be garnered if risk factors were addressed prior to LTBI screening. It clearly shows that asking about risk factors increases yield, while decreasing number screened. I am a bit surprised that this is considered a novel approach, as I had always thought that risk factors for TB often drive the decision to place a TST.

We entirely agree with reviewer one that 'risk factors for TB often drive the decision to place a TST'. In our study we have shown that by standardising this approach, recording multiple TB risk factors and by using both IGRAs and TST, we significantly increased the frequency of LTBI cases detected.

Minor issues:
1. This is a retrospective analysis of pre-recorded data. Is it safe to assume that the quality of the data was adequate for determining the risk factor profile of all patients? Were these data collected systematically in the parent study?

The data was collected prospectively and systematically using a standardised, ethically approved clinical research form as part of the parent study.

2. I think it is important to present the diagnostic criteria for the 16 patients diagnosed with LTBI. How many were TST+/IGRA-, TST-/IGRA+, TST+/IGRA+? As presented, I cannot easily tell how many of each.

Additional data on the diagnostic criteria is provided in table form (Table 2).

3. Though not statistically significant, new entrants tended to be LTBI (only 2 less than alcohol which was statistically significant - small numbers!) Same with prison/IDU - very similar. I think the raw data in a study like this is much more telling than the adjusted values, particularly if they are ALL placed in one model as presented.

We agree that reporting the raw data and unadjusted values is more useful in this dataset and have therefore not included adjusted values in the revised manuscript.

Reviewer: 2
Comments to the Author
The paper presents results of screening for latent Tb Infection (LTBI) in the domains of contact and new immigrant screening by including foreign born HIV positive individuals even if arrival was more than 5 years ago, provided additional recognized risk factors were present. In addition they include test results obtained as part of routine clinical work.

This study design deserves a number of comments:

1. The authors refer to current NICE guidance (reference 9) on diagnosing latent Tb infection (LTBI) and aim to compare what they perceive as current guidance on who should be tested with testing in a wider cohort of 115 HIV infected individuals. They are probably correct in stating that current screening for LTBI in the UK is generally performed in contact and new immigrant clinics predominantly. However, the NICE guidance document CG117 does not refer exclusively to these screening scenarios but includes statements on "people who are immunocompromised" (sections 1.1.1.10 - 1.1.1.14), where screening, used here as a very generic term, may be appropriate. Box 1 correctly states this fact.

2. As they are seeking to address and examine current guidance on the management of HIV positive individuals more explicit reference needs to be made to current guidance documents designed for this patient group (BHIVA including draft guidance out for consultation).

Reply to 1 and 2: We agree that 'current screening for LTBI in the UK is generally performed in contact and new immigrant clinics predominantly'. We considered that the NICE statement on people who are immunocompromised ;

'For people with HIV and CD4 counts less than 200 cells/mm3, offer an interferon-gamma test and a concurrent Mantoux test. If either test is positive perform a clinical assessment to exclude active TB and consider treating latent TB infection'

referred to how to test at different thresholds of CD4 count and who to test. We have therefore now compared this recommendation with our data, in addition to the first comparison and found that stratifying screening based on CD4 count would detect less than half the LTBI cases. This has significance for the BHIVA guidance, which also recommends stratifying screening by CD4

count.

3. In their testing methods they do not refer to dual testing as recommended for individuals with HIV and CD4 counts less than 200 cells/mm3 (NICE CG117 1.1.1.11) although 15 individuals (13%) tested fell into this bracket. It is therefore not known if following more recent NICE guidance rather than BHIVA in this respect would have affected the overall case detection rate. Suggesting this approach is cost effective in other screening scenarios does not necessarily mean it will achieve this goal in a HIV positive cohort. A small number of missed cases of LTBI in this at risk population may well put the cost effectiveness of the whole screening effort in jeopardy.

Tuberculin skin testing was only sporadically used in our cohort due to BHIVA guidance available at the time on TST testing. We consider that dual testing could be a cost effective option for HIV patients but that there is insufficient data in our study to test this. We therefore used a positive result in any assay (IGRA or TST) to denote LTBI. We agree that a large study is needed to test which screening approach should be used and that our data will aid the call for such a study.

4. Table 1 contains no reference to Tb contact. Table 4 does contain a reference to Tb contact but it is not clear if contact was close or recent.

Table 1 does not refer to TB contact as this was data that we specifically collected in addition to the clinically available data presented here.

The reported case detection rates clearly deserve further examination as disease prevention in this group of individuals may not only reduce HIV disease associated morbidity but also mortality. However, the data are difficult to interpret in the context of existing studies on contacts and/or immigrants as these two risk factors were not examined in any kind of detail (details of contact / region of origin) or with sufficient power.

Whilst we are aware that the study numbers are small, we agree with the reviewer that our case detection rates required examination. We are also aware that current guidance is informed by insufficient evidence and that even a small data set may be useful in informing the shape of future research and guidance. Given the increasing number of HIV-infected patients accessing all NHS services and the increasing burden of TB in the UK, we felt that these data would provide empirical data to aid the call for a large study in this area. We therefore hope that you will find it suitable for publication in BMJ Open.