HIV related tuberculosis in the United Kingdom: epidemiology, practice and control

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by

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Abstract

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Background
Latent tuberculosis infection (LTBI) reactivation amongst people living with HIV (PLWH) remains significant, despite HIV virological control.

Methods
Four studies were undertaken. A UK survey of HIV clinicians determined current LTBI screening practice in PLWH. An evaluation of the Leicester HIV cohort defined overall risk of active TB amongst PLWH, and risk factors for incident TB. A patient questionnaire cohort study examined attitudes and planned behaviour towards LTBI screening/treatment amongst PLWH and correlated these with actual screening outcomes. Finally, systematic LTBI screening/treatment of the entire Leicester HIV cohort defined LTBI risk factors and assessed feasibility of programmatic screening.

Results
National LTBI screening practices were heterogeneous and offered by 57.4% HIV centres; this was not congruent with local TB-HIV burden. 325/2158 (15.1%) of the Leicester HIV cohort had had active TB; 100/325 (30.8%) was incident TB occurring more than 3 months after HIV diagnosis, with incidence rate 4.47/1000 person years. Incident TB risk and the time taken to develop incident TB were significantly associated with TB incidence in the country of birth ($p<0.0001$). There was overwhelming support for LTBI screening amongst 444 PLWH answering Likert-scale questions; screening uptake 390/393 (99.2%); acceptance of LTBI chemoprophylaxis 36/37 (97.3%); treatment completion 34/36 (94.4%). Programmatic screening identified 142/1167 (12.2%) IGRA positive results; one had active TB and the remainder LTBI. LTBI diagnosis was significantly associated with TB incidence in the country of birth ($p<0.0001$). The greatest yield in terms of the proportion of LTBI positive cases/total screened occurred when PLWH from countries where TB incidence was >150/100,000, plus other sub-Saharan Africa countries, underwent screening. 120/141 (85.1%) commenced chemoprophylaxis; 114/120 (95%) completed.

Conclusions
PLWH are still burdened by TB and more LTBI screening is required in the UK. It is supported by PLWH and is programmatically feasible. Cost-effectiveness analysis based on this data is planned.

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Declaration

I declare that this thesis has been written by me and its contents are my own work except where acknowledgment has been given.

I designed the survey entitled "National survey of current LTBI screening practices amongst people living with HIV" which was discussed with an ethics committee but did not require ethics approval. I personally contacted all respondents to this survey, collected responses, and collated the data. I analysed the results of this with assistance from Dr Manish Pareek but prepared the manuscript for publication alone. My co-authors edited this.

I designed the study entitled "Attitudes and intended behaviour of HIV positive adults towards accepting screening and treatment for latent tuberculosis infection" and obtained ethics approval for this. I wrote all the study materials but co-produced the questionnaire with Prof John Maltby.

I entered data for all four studies reported in this thesis into appropriate databases and prepared this for statistical analysis. A statistician (Miss Hajra Okhai) analysed the data for the patient questionnaire study, the TB cohort study and the LTBI screening study, with guidance and input from me and Dr Manish Pareek.

No part of this thesis has been submitted previously as part of a higher degree.

Dr Helena Angharad White
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List of abbreviations

AAFB	Acid - alcohol fast bacilli
AFB	Acid -fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
BCG	Bacillus Calmette-Guerin
BHIVA	British HIV Association
CFP-10	Culture filtrate protein 10
ECDC	European Centre for Disease Control
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immune absorbent spot
ESAT-6	Early secretory antigenic target 6-kD protein
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
HSCT	Health and Social Care Trust
IFN-γ	Interferon-gamma
IGRA	Interferon gamma release assay
IPT	Isoniazid preventive therapy
IQR	Interquartile range
IRIS	Immune Reconstitution Inflammatory Syndrome
LA	Local Authority
LTBI	Latent tuberculosis infection
MSM	Men who have sex with men
MTb	*Mycobacterium tuberculosis*
MTBC	*Mycobacterium tuberculosis* complex
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NRES	National Research Ethics Service
OR	Odds ratios
PCR	Polymerase Chain Reaction
PHE	Public Health England

PLWH	People living with HIV
PPV	Positive predictive value
QFN-GIT	QuantiFERON-TB® Gold In-Tube Test
QFT-Plus	QuantiFERON-TB® Gold Plus
REC	Research Ethics Committee
TB	Tuberculosis
TNF	Tumour necrosis factor
TST	Tuberculin skin test
UHL	University Hospitals of Leicester NHS Trust
UK	United Kingdom
UKCHIC	United Kingdom Collaborative HIV Cohort
UN	United Nations
UTLA	Upper Tier Local Authority
WHO	World Health Organization

Chapter 1. Introduction

1.1 Tuberculosis

1.1.1 Causative organism

Clinical infections with tuberculosis (TB) are caused by mycobacterial pathogens from the *Mycobacterium tuberculosis* complex (MTBC) (1). These include the principal aetiological agent in humans, *Mycobacterium tuberculosis* (MTb), along with *Mycobacterium africanum, Mycobacterium bovis,* and *Mycobacterium canettii,* which also cause clinical TB in humans (2) but are much less epidemiologically important overall. The causative agent of the clinical entity of "phthisis" (wasting), which had long been recognised by physicians and lay people alike, was isolated by Koch in 1882 (3).

Mycobacterium tuberculosis is from the genus *Mycobacterium*, belonging to the family Mycobacteriaceae, of the order Actinomycetales. It is a slow-growing, intracellular bacillus, which resists staining with acid or alcohol (hence "acid-alcohol fast bacilli" or "AAFB", "acid-fast bacilli", or "AFB"). Mycobacteria are non-spore forming, non-motile, aerobic bacilli (4).

1.1.2 Tuberculosis epidemiology

In 2016, TB affected 140 in every 100,000 people globally (down from 172 per 100,000 in 2000) (5), with the highest incidence consistently reported across sub-Saharan Africa, South-East and South Asia, and Eastern Europe (6). Rates in some countries exceed 500 per 100,000 population, contrasting starkly with the lowest rates of fewer than 10 per 100,000 in some Western European countries (6). Out of the 10 million or so incident cases reported globally, nearly half a million cases occurred in those infected with the Human Immunodeficiency Virus (HIV) (7).

Tuberculosis control has long been a priority for global health strategies. Often affecting young, economically productive individuals, in low and middle-income countries, the

burden of disease can be crippling for families, communities and wider society. International desire for TB control has led to the formulation of strategies to improve case-finding of TB, increase cure rates, reduce overall incidence of TB, and reduce TB-related mortality (7) across all global regions but particularly in areas with high TB burden. TB control goals were incorporated into the United Nations (UN) Millennium Development Goals (8), the subsequent UN Sustainable Development Goals (5), and concurrently into the World Health Organization's (WHO) EndTB Strategy (7).

In the United Kingdom (UK), there was a significant reduction in the number of cases seen after the introduction of effective treatment in the mid-twentieth century, associated with a reduction in transmission rates and improved prognosis from the disease (9). Increasing cases between the 1980s and the early years of the twenty first century subsequently occurred, with the predominant contributory factor being increasing migration of individuals from high-burden TB countries to the UK (9, 10). Incidence peaked at around 14.1/100,000 population in 2011 but since then, numbers of cases have declined again, to 8.4/100,000 population in 2017 (11-13). Contributory factors to this success include; the introduction of the UK pre-entry migrant TB screening programme (12, 14); targeted case finding in vulnerable populations (13); the implementation of TB Control Boards (12); and a focus on latent TB infection case-finding and treatment (12, 15).

Regionally, the rate in East Midlands in 2017 was 7.4/100,000 population (11) however, Leicester city, which is an ethnically diverse city, has amongst the highest rates in the UK, with an average annual rate of 37.4/100,000 population over the years 2015-2017. Only some districts in London, and Slough, have similar or higher rates (11).

1.1.3 Tuberculosis pathogenesis

TB is spread via droplet-transmitted airborne transmission (16). During primary pulmonary infection, the bacilli enter the alveoli and are transported to regional lymph nodes following phagocytosis by macrophages and dendritic cells, which subsequently leads to T-cell response and migration of lymphocytes and macrophages to the primary site of infection (17). Ensuing granuloma formation can lead to containment and killing

of MTb (18) or provide a potential harbour for non-replicative or very slowly replicating bacilli to remain contained, although this may also be true of other areas of the lungs (19). Persistence of viable bacilli but in the absence of any clinical symptoms, or radiological abnormalities, is termed "latent tuberculosis" (17, 20).

Substances such as interferon gamma (IFN-γ), and tumour necrosis factor (TNF) can lead to MTb killing (21) but are also important for containment of MTb, as evidenced by studies that demonstrate that immunosuppressive treatment with anti-TNF leads to an increased risk of reactivation of TB in those who have previously been exposed (22). In the absence of clearance or containment, MTb continues to replicate and leads to primary TB infection, although the traditional dichotomy of active versus latent TB may be more nuanced, with potential additional subgroups of incipient TB and subclinical active TB inbetween these two states (23), reflecting a more fluid and dynamic process than was hitherto described.

1.1.4 Risk factors for developing active tuberculosis

The risk factors for developing active TB can be broadly separated into those which increase an individual's likelihood of acquiring the infection, and those biological, behavioural or health determinants which impair the host response to the organism and render an individual more susceptible to developing clinical disease. On a global level, TB disproportionately affects socioeconomically disadvantaged groups who have poor living and working conditions, and are highly vulnerable to acquiring TB through close proximity to individuals with infectious TB (24). Closely congregated settings such as prisons (25) and healthcare settings (26) also increase the risk of transmission to staff as well as amongst inmates and patients. There is also evidence that some ethnic groups are more susceptible to acquiring TB than others (27) with, for example, a demonstrated increase in inherent macrophage susceptibility to MTb amongst black individuals (28). Additional behaviours that increase susceptibility to TB include smoking (29) and occupations that predispose to the development of silicosis through exposure to silica dust (30).

Biological factors which increase susceptibility to developing active disease include; young children up to the age of five years (2), malnutrition (although the relationship is relatively poorly understood) (31), and underlying health conditions, including diabetes mellitus (32), solid organ cancer and haematological malignancies (33), treatment with immunosuppressive agents (22) and being a dialysis recipient (34). However HIV is probably the most important health condition predisposing to the development of active TB (35, 36).

1.2 Human Immunodeficiency Virus

1.2.1 Causative organism

The Human Immunodeficiency Virus (HIV) is from the genus Lentivirus, belonging to the family Retroviridae, of the order Ortervirales (37). Unusual clusters of cases were reported in the US in 1981, including *Pneumocystis jirovecii* pneumonia (38) and cases of Kaposi's sarcoma (39), amongst young men who have sex with men (MSM). All were profoundly immunocompromised, and the clinical entity known as Acquired Immune Deficiency Syndrome (AIDS) was described. HIV was subsequently identified as the causative virus in 1983 (37).

1.2.2 HIV disease progression

Uncontrolled HIV replication leads to viral infection of, and subsequent depletion of CD4+ (CD4) lymphocytes in an infected individual. Progression of immune deficiency leads to a multitude of clinical syndromes, with escalating risk of infections with opportunistic pathogens, and a risk of developing malignancy, although the rate at which immune deficiency occurs in any one individual is variable, and dependent upon a complex pathogen-host interaction (40).

1.3 Tuberculosis-HIV co-infection epidemiology

The seminal paper describing the risk of TB in injecting drug users with HIV (41) has been followed by other data showing that people living with HIV (PLWH) are at high

risk of acquiring TB and progressing to active TB disease through reactivation of latent tuberculosis infection (LTBI) or developing polyclonal disease as a result of LTBI reactivation in conjunction with newly acquired infection (35, 42-45). In countries with a high burden of TB, individuals with HIV constitute the predominant risk group for active TB, above those with malnutrition, diabetes mellitus, heavy alcohol use, smoking, and indoor pollution (2).

Although TB risk is reduced by highly active antiretroviral therapy (HAART), cohort data from the UK, including around 80,000 PLWH, and from Stockholm with over 2,000 PLWH, show that it does not fall to the same background risk as that of HIV-negative individuals, even in those of white ethnicity, despite HAART (42, 46). TB is also associated with increased mortality in the HIV-positive cohort as evidenced by linked cohort data from the UK of over 44,000 PLWH, and international WHO data (47, 48). Factors associated with increased mortality include disseminated TB disease, inadequate management of multi-drug resistant TB, and the country in which treatment is given (49).

A meta-analysis performed in 2018, examining multiple study data from low TB incidence countries, found that prominent risk factors for active TB and LTBI amongst PLWH are related to ethnicity and origin from high prevalence TB areas, together with clinical factors related to the control of HIV (44). Thus LTBI reactivation is particularly high in those of black African ethnicity (35, 42, 46, 50, 51) even after starting HAART, and in people with a low blood CD4 count (42, 50-53).

In England in 2015 (the latest year for which data is available), 3.8% of all TB cases were co-infected with HIV, representing a small increase in the proportion of co-infected TB cases, following a sustained decline in the proportion of cases over the preceding decade (54). 82% of these individuals were non-UK born, of whom 69% were born in sub-Saharan Africa (54).

1.4 Tuberculosis control

Reduction in incidence of active TB can be achieved by two methods. Firstly, by treating those with infectious TB, such as those with active pulmonary or laryngeal TB, in order

to reduce the spread to others, and prevent new infections occurring (55). This strategy includes active case-finding of other individuals connected to the index case who may also have active TB, through contact tracing, which is usually undertaken by the clinical teams managing caseloads of patients in a specific locality. Contact tracing may involve strategies pertinent to local communities, such as involvement of social networks, location-specific investigations (e.g. homeless shelters, prisons) and the use of community workers (56). Since the rate of TB in non-UK born individuals is 15 times higher than in UK-born individuals (49.4/100,000 versus 3.2/100,000 population) (54), individuals from these communities receive particular attention during contact tracing, although recent clustering work indicates that there may be more transmission between different ethnic, age and migrant groups than was previously thought (57). Contacts of those with extra-pulmonary TB may also have high rates of active TB (58), although are not included in the national UK policy for contact screening currently (55).

Policies directed at this approach of case-finding should, if delivered at a high enough coverage rate, reduce TB incidence, although they would have little impact on the pool of latently infected individuals. Therefore the second approach is to identify and treat those with latent infection, in order to reduce the risk of reactivation in these individuals and thus prevent morbidity, mortality, and the subsequent spread of TB to others. Latent TB control is a particular focus for national and international intervention strategies (55, 59, 60), with recommendations for programmatic LTBI screening and treatment of individuals who fall into groups with high risk of progression to active TB, as detailed below.

1.5 Latent tuberculosis

1.5.1 Description of latent tuberculosis

The term latent tuberculosis infection (LTBI) describes a situation where there are persistent, *Mycobacterium tuberculosis* (MTb)-specific T-cell responses, but where there is no clinical evidence of active disease (17). Bacilli may be lying in a non-replicative, or 'dormant' phase, although adjustment of the immunological environment (for example, through immune-modulating drugs such as cancer chemotherapy or anti-TNF treatment, or the development of immunosuppression from HIV) may result in replication

of the bacilli to the extent where there are sufficient numbers to cause clinical disease. The rate at which this occurs depends on the host phenotype, but is in the region of 10% over a lifetime for HIV uninfected individuals (61) and 2-10 times this for HIV positive individuals, depending upon whether the HIV is virologically suppressed or not (41, 62).

1.5.2 Diagnosis of latent tuberculosis

1.5.2.1 Available methods

LTBI is diagnosed by methods which confirm that exposure to MTb has occurred, but where there is no clinical evidence of active infection; such approaches include demonstrating evidence of radiological abnormalities such as calcified granulomas or fibronodular changes (63), *in vivo* tuberculin skin tests (TST), and the *ex vivo* Interferon Gamma Release Assay (IGRA) tests.

In vivo TST utilise proteins derived from MTb cultures, but many of these proteins are shared by other mycobacteria, including *M. bovis*, Bacillus Calmette-Guerin (BCG), and some other environmental mycobacteria, leading to low specificity in populations where BCG vaccination is common, or where there is high exposure to environmental mycobacteria (17, 64, 65). In addition, the sensitivity of TST is low in situations of advanced immunosuppression due to HIV, where CD4 counts are low (66). It also requires two visits several days apart in order to administer and read the test, which can be logistically challenging and patients have often failed to return during this two-step process (67, 68). TST have largely been superseded by the *ex vivo* IGRA tests which have much higher specificities in the order of 98-100% (64) and are more sensitive than TST for the diagnosis of LTBI in HIV positive individuals (69).

IGRA tests are blood tests that measure an immunological, cell-mediated response to stimulation by MTb antigens. T-lymphocytes which have been previously primed through an individual's exposure to MTb, subsequently produce interferon-gamma (IFN-γ) when re-exposed to MTb antigens *ex vivo* (17). The detection of IFN-γ is therefore indicative of prior MTb exposure.

There are two commercially available IGRA tests, the first of which consists of the QuantiFERON-TB® Gold test series, in which plasma incubation with MTb antigen peptides leads to stimulation of CD4 T-lymphocytes and production of IFN-γ, the concentration of which is measured by Enzyme-Linked Immunosorbent Assay (ELISA) technique. Negative (nil) and positive (phytohaemagglutinin) controls are included (17). The previously used QuantiFERON-TB® Gold In-Tube Test (QFN-GIT) was a three-tube test which utilised early secretory antigenic target 6-kD protein (ESAT-6), culture filtrate protein 10 (CFP-10), and tuberculosis-7.7, in addition to the negative and positive controls. The newer QuantiFERON-TB® Gold Plus (QFT-Plus, Qiagen, Hilden, Germany) is a four-tube test which has two antigen-containing tubes. The first contains CFP-10 and EAST-6, and the second also contains these peptides, but in addition has shorter chain versions of each, designed to stimulate CD8 T-lymphocytes. The tuberculosis-7.7 antigen is not present in QFT-Plus. The enhanced stimulation of CD8 T-cells may theoretically enable the test to be more sensitive in recently infected individuals (70), who have been found to have higher CD8 T-cell stimulation, and immunosuppressed HIV positive individuals (71), as it does not rely so heavily on CD4 stimulation, which is reduced in advanced HIV. Specificity is similar to QFN-GIT (71, 72) and concordance between the two tests has been demonstrated, including in immunocompromised patients and those with active TB (73, 74) although there do not appear to be any head to head studies involving PLWH.

The second IGRA test is the T-SPOT®.*TB* (Oxford Immunotec*,* Abingdon, UK*)* in which peripheral blood mononuclear cells are separated out before exposure to CFP-10 and ESAT-6. The proportion of CD4 lymphocytes producing IFN- γ are then confirmed through ELISPOT and the test is considered positive if the spot counts in the TB antigen well exceeds that in the control wells (17, 65).

1.5.2.2 Comparison between interferon gamma release assays in HIV

Concordance between IGRA tests in individuals with HIV infection has been studied in a limited number of high-income settings, and all have used the older QuantiFERON-TB® Gold assays, rather than the newer QFT-Plus. Results of studies show low to moderate concordance (67, 69, 75-78).

It is still not entirely clear whether reversion to IGRA negativity occurs after treatment of active TB infection. IGRA positive results have been seen in 28-43% of HIV positive individuals previously treated for TB (75, 76, 79).

There has been previous concern that the older QuantiFERON-TB® Gold assays may not have performed as well as T-SPOT®.*TB* tests in HIV positive cohorts with low CD4 counts (<200 cells/mm^3). In 2012, a meta-analysis reported pooled rates of indeterminate QuantiFERON-TB® Gold results of 8.2% and indeterminate T-SPOT®.*TB* results of 5.9%, but was unable to reach a conclusion as to whether there was a statistical relationship between indeterminate IGRA tests and immunosuppression in the form of low CD4 counts (80). Subsequent studies have reported rates of indeterminate QuantiFERON-TB® Gold tests ranging from 2 – 27.1%, and rates of indeterminate T-SPOT®.*TB* tests ranging from 7-7.4%, again with variable association with low CD4 counts (67, 69, 81, 82). Specifically in relation to T-SPOT®.*TB* tests, an indeterminate result due to a lack of cells seen in some studies (67, 82) may actually constitute test failure, rather than being an indication that the test is less sensitive in a highly immunosuppressed individual (80). As mentioned previously, the newer QFT-Plus may prove to perform better in immunocompromised patients than its older versions, but data is currently lacking.

1.5.2.3 Positive predictive value of interferon gamma release assays

The positive predictive value (PPV) for progression determines the proportion of IGRA-positive individuals who will progress to developing reactivated clinical TB disease (in the absence of treatment). Previous meta-analysis of four studies (not in recently exposed individuals) found a range of 2.8-14.3% for positive QuantiFERON-TB® Gold tests and 3.3-10% for positive T-SPOT®.*TB* tests (64) although only two studies were in individuals with HIV infection. However, the recently reported PREDICT study, which is the largest study to examine progression rates, and which included recently exposed individuals and recent migrants to the UK, demonstrated positive predictive values towards the lower end of these ranges (4.2% for positive T-SPOT®.*TB* tests and 3.3% for QuantiFERON-TB® Gold In-Tube tests). The T-SPOT®.*TB* tests were significantly

better at predicting progression to active TB than QuantiFERON-TB® Gold In-Tube tests or TST, with higher prediction overall in those with recent exposure to active TB. Previous evidence also supports this finding (83). However, the numbers of participants with self-reported HIV infection in the PREDICT study were too low to allow any subgroup analysis.

1.5.3 Target groups for latent tuberculosis screening

Targeted latent TB screening in the UK aims to identify individuals from two main groups who would benefit from chemoprophylaxis. The first consists of the individuals who are at high risk of having acquired TB. These include migrants from high-burden TB countries (55, 84), especially as they continue to have high rates of active TB disease within the first few years after entry to the UK (54), and those who have had close contact with persons with highly infectious TB, such as pulmonary or laryngeal disease (55). The second group of individuals to target are those in whom reactivation is considered likely by virtue of medical or treatment factors that influence their immunity. Such individuals include those receiving immunosuppressive therapy such as anti-TNF therapy (22, 55), post-organ transplant recipients (55, 85), those with diabetes mellitus (55, 86) and other immunosuppressing conditions such as high corticosteroid use, chronic kidney disease, haematological and solid malignancies (55). Other groups to consider for screening are healthcare workers (55) and in high-incidence areas of the UK, those who misuse substances and those in prison (55). Individuals with HIV infection are listed as a priority group for LTBI screening in European guidelines (60).

1.6 Latent tuberculosis screening in HIV

1.6.1 Screening guidelines in the UK

In the UK, there are recommendations for the screening of PLWH for LTBI in guidelines from two organisations: the British HIV Association (BHIVA), and the National Institute for Health and Care Excellence (NICE).

In 2014, when this research was commenced, the existing 2011 BHIVA guidance on screening for LTBI necessitated categorisation of patients into groups determined by combined parameters of region of origin, duration of HAART and CD4 count (87). LTBI screening was recommended for individuals if they fell into one of three well-defined groups (Table 1.1). The 2011 NICE guidance in force at the time, recommended screening individuals only if they had a CD4 count of <500 cells/mm^3 (88) (Table 1.1). There was no specific recommendation in either guideline as to which IGRA should be used.

Table 1.1. BHIVA and NICE guidance in place in 2014 for LTBI screening of HIV positive individuals

Guideline	Region of origin	Duration of HAART	CD4 count (cells/mm^3)	Screening method	Diagnosis of LTBI
British HIV Association 2011 guidelines (87)	Sub-Saharan Africa	<2 years	Any	IGRA	If IGRA positive
	Medium TB incidence	<2 years	<500	IGRA	If IGRA positive
	Low TB incidence	<6 months	<350	IGRA	If IGRA positive
National Institute For Health and Care Excellence 2011 guidelines (88)	Not assessed	Not assessed	>500	None advised – Treated as immunocompetent	Not applicable
	Not assessed	Not assessed	200-500	IGRA alone or Mantoux and IGRA	If either test positive
	Not assessed	Not assessed	<200	IGRA and Mantoux	If either test positive

1.6.2 Uptake of latent tuberculosis screening in HIV in the UK

In 2014 it was not known, whether, and how, different UK centres interpreted and implemented the national guidelines on screening for LTBI, given their divergent nature, or which of these guidelines was most cost-effective. There was therefore a need to examine the guidelines objectively.

1.6.3 Treatment of latent tuberculosis in HIV

A Cochrane collaboration meta-analysis demonstrated that treating LTBI in PLWH reduced the risk of development of clinical TB by 32% (89), and a reduction in incidence

is also demonstrated in low-incidence TB countries (44). LTBI treatment, or chemoprophylaxis, takes the form of a variety of treatment regimens, the choice of which is principally dependent upon the burden of TB within the country of interest. In high and medium TB burden settings, continuous isoniazid treatment ("isoniazid preventive therapy", IPT) has been trialled for varying lengths of time in PLWH, including in areas where TB incidence is so high, that IPT is given to all PLWH, and not just those who are TST-positive (90, 91). Logistically, operational guidelines and policy implementation oversight need to be robust in order for the approach to be successful (92, 93) but it appears that the strong protective effect for individuals who are TST-positive wanes after cessation, even after prolonged use of up to three years, and despite the use of HAART (94, 95). This most likely reflects the high chance of reacquisition of TB. However the effect lasts longer in medium endemic settings, with TB incidence being reduced for some years after the end of a few months of IPT (96).

There are reports of patients developing drug resistant active TB following the use of IPT (94, 95), and prolonged IPT also increases the risk of adverse drug effects (95). The most commonly recommended regimes in low-incidence TB countries are monotherapy with isoniazid for six to nine months, or combination therapy with isoniazid and rifampicin for three months. Efficacy is similar for all regimes in HIV infection (44, 89, 97). The latter regime was previously employed most often when individuals with HIV were not yet on HAART, and therefore concerns about drug-drug interactions were less of an issue, but all individuals with HIV are now recognised to benefit from early HAART (98) and therefore isoniazid monotherapy is most likely to be the commonest regime used.

1.6.4 Acceptability of latent tuberculosis screening/treatment to patients

Previous studies investigating the acceptability of LTBI chemoprophylaxis in PLWH have been predominantly undertaken in high TB burden settings and focused primarily on quantitative analysis of isoniazid preventive treatment uptake (90, 99-101). There are relatively few data available from low burden TB countries, but those that are, indicate that whilst LTBI screening appears to be acceptable, chemoprophylaxis acceptance rates have been quite variable amongst PLWH. Rates of between 17-87% have been reported from London and Auckland (75, 82, 102), for example. Issues such as understanding the

diagnosis, fear of stigma, or perception of being at low risk of TB (82, 99, 100) have been cited in some studies as being factors which potentially impact upon patient acceptability. There is therefore a need to investigate such concerns more fully, and to have a clearer understanding of whether LTBI screening and treatment in low burden countries is acceptable to PLWH, and what the potential limiting factors are, before implementing widespread national screening and treatment programmes.

1.7 Background to this research

The development of active tuberculosis in HIV positive individuals, even in highly resourced countries, constitutes a clinical threat to personal and wider public health, and impacts upon healthcare resources in terms of costs of diagnosis, treatment and monitoring. The risk of reactivation of latent TB infection remains significant, especially amongst PLWH in the UK who were born in high-burden TB countries, and despite virological control of HIV through the use of HAART.

National and international TB control programmes highlight this cohort as a group to focus on during LTBI screening and treatment, and chemoprophylaxis has been shown to be effective in reducing the incidence of active TB in this group. However the two UK guidelines in place for PLWH in 2014 differed in their recommendations and it was unknown how these were being interpreted and implemented. The published literature did not suggest that there was any programmatic screening in place.

Moreover, there was little understanding about whether PLWH themselves are supportive of, or accepting of, LTBI screening and treatment in the UK and this constituted a gap in the knowledge base.

The HIV service for Leicester and the broader Leicestershire county, based at the Leicester Royal Infirmary, University Hospitals of Leicester (UHL) NHS Trust, currently provides HIV care for around 1400 PLWH. This large cohort of individuals, living in a city with high incident rates of TB, and high HIV prevalence, was therefore an ideal group in which to examine the topic of LTBI screening and treatment in more detail.

Chapter 2. Aims and objectives

2.1 Undertake a national survey of latent tuberculosis infection screening practices in HIV positive individuals

The aim was to evaluate, by means of a national survey whether, and how, centres in the UK were screening PLWH for LTBI, given the divergent national guidelines that were in place in 2014. The objective was to fully document the screening practices that were being implemented across the UK, incorporating regional data on HIV prevalence and TB incidence, and to understand the potential barriers to undertaking programmatic screening in this cohort.

2.2 Define the risk of active tuberculosis in a cohort of HIV positive individuals in Leicester, UK

The aim was to evaluate the occurrence of active TB over time in a large, ethnically diverse HIV cohort, many of whom have remained stable patients in Leicester over several years. The objective was to understand more fully when TB occurs in PLWH, in relation to their HIV diagnosis, with a particular focus on incident TB, occurring after the diagnosis of HIV. The identification of risk factors through multivariable regression analysis was planned as a precursor to undertaking systematic LTBI screening in this cohort.

2.3 Undertake a patient questionnaire cohort study to better understand the attitudes and planned behaviour of patients towards accepting latent tuberculosis infection screening and treatment

The aim was to undertake a patient questionnaire cohort study, followed by subsequent IGRA screening and the provision of LTBI treatment where appropriate, in order to examine attitudes and planned behavior towards accepting LTBI screening and treatment amongst PLWH. The objective was to better understand any potential barriers towards

the acceptance of IGRA screening or chemoprophylaxis, and to correlate outcomes of actual offered screening and treatment with demographics and questionnaire responses.

2.4 Implement programmatic screening for latent tuberculosis infection in a cohort of HIV positive individuals in Leicester, UK

The aim was to implement a systematic programme of screening for, and treatment of, LTBI in the HIV positive Leicester cohort. The objective was to better understand the groups of individuals in whom LTBI was diagnosed, including identification of risk factors through multivariable regression analysis, and also to establish the completion rates of chemoprophylaxis. In addition there was an objective to better understand the cascade of care in the management of this group for LTBI. Future research objectives in the area of LTBI identification and management in PLWH could then be established. This was likely to include the construction of a decision-based health-economic model to evaluate the cost effectiveness of screening HIV positive individuals for LTBI from a National Health Service (NHS) viewpoint and to establish which, if any, model should be recommended as national guidance.

Chapter 3. National survey of current latent tuberculosis infection screening practices amongst people living with HIV

3.1 Introduction

In 2014, the screening of HIV positive individuals for LTBI was, in theory at least, advocated by two guidelines in the UK (87, 88) as previously mentioned. Exclusion of active infection followed by chemoprophylaxis to reduce the risk of progression to active TB disease was recommended by both BHIVA and NICE if LTBI was diagnosed.

Although the UK had had national LTBI screening guidance in place for HIV positive individuals for several years there was little known about whether, and how, different HIV healthcare providers implemented these guidelines. A national evaluation of UK practice was therefore highly topical and policy relevant with respect to understanding how screening is provided, the level of adherence to current guidance and whether the TB/HIV burden in different centres has any impact on practice. I therefore undertook a comprehensive survey of UK HIV professionals, and compared the results with known HIV prevalence and TB incidence data across the UK.

3.2 Methods

3.2.1 Questionnaire design

I devised an online questionnaire (Appendix 1) using SurveyGold software (© 2014 Golden Hills Software, Inc, Colorado Springs, USA), incorporating skip logic ("conditional branching") functions to allow respondents to skip to relevant subsequent questions conditional on answers submitted to specific initial questions. Free text space was also provided at certain points of the questionnaire, to enable respondents to clarify or augment their answers. The predominant themes of the questionnaire were to identify, in the respondent's centre, whether testing for LTBI was offered to HIV positive adults, and if so, whether either published UK national guidelines or other criteria were used to

guide testing, which screening tests were used, whether chemoprophylaxis was given if LTBI was diagnosed, and if so, which drug regimen was offered. Finally, if respondents reported that no current screening for LTBI was undertaken, future intentions to provide screening for, and treatment of, LTBI were explored.

3.2.2 Administration of questionnaire

One HIV professional working for each HIV healthcare provider organisation in the UK was identified through personal contacts, and by contacting healthcare organisations directly. Most organisations nominated the Head of HIV service, or another HIV physician, with a minority nominating a specialist HIV nurse. A request for participation in the survey was also advertised in the BHIVA newsletter, *Members Matters*, on 21st January 2014. If an organisation such as an NHS Trust did not provide direct HIV care to its local population, then providers supplying HIV care on behalf of these organisations were identified, and contact details obtained. Each identified professional was approached by email, explaining that the purpose of the questionnaire was to investigate current national practice as part of a research degree. Participation was invited either by following a web link and completing the questionnaire online, or by arranging a telephone interview with me, during which I electronically inputted the responses directly into the SurveyGold questionnaire.

The questionnaire was piloted amongst five HIV providers known personally to me. Minor adjustments to the wording of questions were made following feedback, and the final participation invitation emails were sent in April 2014.

3.2.3 Statistical methods

All data were extracted on to a standardised database. Continuous data were summarised with median and interquartile range (IQR), and compared using the non-parametric Mann-Whitney U-test. Categorical responses were expressed as a simple descriptive percentage and comparisons made using Pearson's chi-square test (or Fisher's exact test if appropriate). All analyses used v9.2 (StataCorp, Texas, USA). P-values ≤ 0.05 were considered significant.

3.2.4 HIV prevalence and tuberculosis incidence data

Public Health England (PHE) documented 81,512 patients as having received care for HIV in the UK up to the end of December 2013 (103). HIV prevalence information categorised by healthcare provider was not available for England and therefore surrogate data on HIV prevalence (104) for Upper Tier Local Authorities (UTLA) (105) was obtained from Public Health England (PHE). The most recently available data at the time of the study design were from 2012. Data for 3-year average tuberculosis reports and rates for 2010-12 by English UTLA were provided by PHE (106). HIV prevalence information for 2012 was obtained for each Welsh (107) and Scottish (108) Health Board, and Northern Irish Health and Social Care Trust (HSCT) (109), with matched data extracted from 3-year average tuberculosis reports and rates for 2010-12 (110-112).

Each UTLA, Health Board and HSCT (hereafter referred to as 'geographical areas') was assigned a category dependent upon their local HIV prevalence per 1000 and TB incidence rate per 100,000 population respectively. HIV prevalence of >2 per 1000 or ≤2 per 1000 were designated High HIV and Low HIV, respectively. TB 3-year incidence rate of >20 per 100,000 or ≤ 20 per 100,000 were designated High TB and Low TB, respectively.

Each UTLA in England was then matched with the NHS Trust(s) providing health care in that geographical area. Several sources were used to enable the matching; a map from the Office of National Statistics showing every Local Authority (LA) in the UK; a comprehensive map detailing all NHS facilities in the UK (113), and individual NHS Trust websites.

The matching led to the identification of 174 geographical areas in the UK. 12 geographical areas had more than one organisation providing HIV care to the local population and in these situations, each organisation was considered separately. Thus the number of geographical areas was inflated to a total of 188.

3.2.5 Definition of compliance with BHIVA/NICE guidance on latent tuberculosis infection testing

Reported screening criteria, together with associated free text comments were assimilated in order to determine the proportion of geographical areas offering screening at different criteria thresholds.

3.2.6 Ethics approval

I discussed the questionnaire with the Nottingham 2 Research Ethics Committee (REC) who confirmed that this was an evaluation of service and no ethics approval was required.

3.3 Results

3.3.1 Survey response rate

Survey responses were obtained from 116 individuals, representing 162 geographical areas, since some respondents provided HIV care for more than one geographical area. The overall response rate was therefore considered to be 162/188 (86%). The questionnaire was completed online by 87/116 (75%) respondents, and via telephone interview by 29/116 (25%).

Of the 116 respondents, 81/116 (70%) were genitourinary medicine physicians, 30/116 (26%) were infectious diseases physicians, 3/116 (2.4%) were respiratory physicians, 1/116 (0.9%) was an HIV nurse specialist and 1/116 (0.9%) was an immunologist providing HIV care.

3.3.2 HIV and tuberculosis burden in all geographical areas

Of the 188 total geographical areas there was no difference in HIV/TB burden between those who did, and did not, respond to the survey ($p = 1.000$) (Table 3.1).

Table 3.1. HIV/TB categories of English Upper Tier Local Authorities, Welsh and Scottish Health Boards and Northern Irish Health and Social Care Trusts ('geographical areas')

HIV prevalence and TB incidence rate category	Responded to survey n (%)	Did not respond n (%)	Total n (%)
High HIV/High TB[1]	34 (21)	5 (19.2)	39 (20.7)
High HIV/Low TB	11 (6.8)	2 (7.7)	13 (6.9)
Low HIV/High TB	7 (4.3)	1 (3.9)	8 (4.3)
Low HIV/Low TB	110 (67.9)	18 (69.2)	128 (68.1)
Total[2]	162 (100)	26 (100)	188 (100)

[1]High HIV: >2/1000 population HIV prevalence; High TB: >20/100,000 population TB incidence; Low HIV: ≤ 2/1000 population HIV prevalence; Low TB: ≤ 20/100,000 population TB incidence
[2] Total number and percentage reflects the distribution of HIV/TB burden across all geographical areas

3.3.3 Size of HIV cohort in responding areas

The total number of patients reported as being treated within their HIV centres by the 116 respondents was 73,395 (90% of total HIV cohort reported by PHE in 2014). The median was 300, range 10-8,000 and inter-quartile range 170-700.

3.3.4 Coverage of screening HIV positive patients for latent tuberculosis infection

Only 93/162 (57.4%) of geographical areas reported offering any form of screening for LTBI to their HIV positive adult patients. There was no difference in the HIV/TB burden between the geographical areas who offered screening and those who did not (p=0.22) (Table 3.2).

Table 3.2. HIV/TB categories by latent tuberculosis infection screening

HIV prevalence and TB incidence rate category	Offer screening n (%)	Do not offer screening n (%)
High HIV/High TB[1]	17 (18.3)	17 (24.6)
High HIV/Low TB	8 (8.6)	3 (4.3)
Low HIV/High TB	2 (2.2)	5 (7.2)
Low HIV/Low TB	66 (71)	44 (63.8)
Total	93 (100)	69 (100)

[1]High HIV: >2/1000 HIV prevalence; High TB: >20/100,000 TB incidence; Low HIV: ≤ 2/1000 HIV prevalence; Low TB: ≤ 20/100,000 TB incidence

3.3.5 Selection of patients to screen for latent tuberculosis infection

Of the 93 geographical areas offering any kind of LTBI screening, 57/93 (61.3%) reported using the current blood CD4 count as a screening criterion, with 53/57 (93%) screening adults with a CD4 count of ≤200 cells/mm^3 and decreasing numbers of areas offering screening at higher CD4 counts (Table 3.3). 75/93 (80.6%) used the patient's country of origin as a screening criterion, with all screening those from high TB incidence countries, but fewer than two thirds screening from any other region. The duration of receipt of HAART treatment was the least utilised screening criterion, with only 52/93 (56%) geographical areas reporting this.

Table 3.3. Criteria used to guide screening for latent tuberculosis infection and screening tests utilised

Screening criteria and screening test strategies	Total n = 93 geographical areas offering screening n (%)	
Screening strategy		
CD4 count criteria used for screening	57	(61.3)
CD4 count ≤50 cells/mm^3	53/57	(93)
CD4 count ≤100	53/57	(93)
CD4 count ≤200	53/57	(93)
CD4 count ≤350	51/57	(89.5)
CD4 count ≤500	45/57	(79)
CD4 count >500	33/57	(57.9)
Other reported CD4 count criteria - Individual assessment	4/57	(7)
Country of origin criteria used for screening	75	(80.6)
High TB incidence country >40/100,000 pop.	75/75	(100)
Medium TB incidence country 20-40/100,000 pop.	49/75	(65.3)
Low incidence TB country <20/100,000 pop.	35/75	(46.7)
Other reported criteria – Eastern European countries	1/75	(1.3)
Duration receiving HAART criteria used for screening	52	(60)
Under 6 months	48/52	(92.3)
Under 1 year	42/52	(80.8)
Under 2 years	42/52	(80.8)
Other reported criteria – Individual assessment	4/52	(7.7)
Testing strategy[1,2]		
QuantiFERON-TB® (all types) testing alone	44	(47.3)
T-SPOT®.*TB* testing alone	42	(45.2)
Mantoux testing alone	7	(7.5)
QuantiFERON-TB® then T-SPOT®.*TB* if QuantiFERON-TB® negative or equivocal	5	(5.4)
Mantoux and QuantiFERON-TB® together	4	(4.3)
Mantoux then QuantiFERON-TB® if Mantoux negative	3	(3.2)
Mantoux and T-SPOT®.*TB* together	3	(3.2)
Other strategy – Chest radiograph	2	(2.2)
Mantoux then T-SPOT®.*TB* if Mantoux negative	1	(1.1)
Other strategy – IGRA type unknown	1	(1.1)
Other strategy – Not specified	1	(1.1)

[1]Respondents could select as many answers as were applicable, therefore total >100%

[2] Other combinations of tests listed in the survey have been omitted here as no respondents selected them; e.g. QuantiFERON-TB® and T-SPOT®.*TB* together

3.3.6 Methods of screening for latent tuberculosis infection

The most commonly reported screening methods (Table 3.3) were the individual use of different IGRA tests (with 44/93 (47.3%) and 42/93 (45.2%) of geographical areas using QuantiFERON-TB® and T-SPOT®.*TB* tests respectively.) Other screening methods or

combinations were utilised infrequently. Of note, tuberculin skin tests were used as a sole test by only 7/93 (7.5%) of respondents.

3.3.7 Adherence to national guidance

Only 33/93 (35.5%) and 6/93 (6.5%) reported complete adherence with BHIVA and NICE guidelines, respectively. No geographical area reported using any non-UK guidelines.

3.3.8 Screening strategies in patients with a CD4 count <200 cells/mm^3

9/93 (9.7%) geographical areas that offered LTBI screening reported using a different screening strategy for patients with a CD4 count <200 cells/mm^3. Five reported being more likely to use a T-SPOT®.*TB* than a QuantiFERON-TB® test, and four reported that they would use a Mantoux if the T-SPOT®.*TB* was negative.

3.3.9 Reasons for not screening

Of those geographical areas (n=69) not offering screening, an explanation was provided by 100% respondents (Table 3.4). The most common reason, in 31/69 (45%) was that the cohort of patients was considered to be at low risk of latent TB infection. 20/69 (29%) cited a lack of confidence in the existing guidelines, 12/69 (17.4%) reported that the tests were too expensive, with 10/69 (14.5%) and 8/69 (11.6%) reporting unavailability of T-SPOT®.*TB* and QuantiFERON-TB® Gold In-Tube test (or other version) respectively. Fewer numbers of geographical areas cited reasons such as wanting a cost-effectiveness analysis, or concern over chemoprophylaxis efficacy, toxicity/drug-drug interactions, and conflicting local advice.

Table 3.4. Reported reasons why latent tuberculosis screening is not offered

Reported reason why screening is not offered[1]	Total n = 69 geographical areas not offering screening n (%)
Cohort of patients is considered to be at low risk of latent TB infection	31 (44.9)
Lack of confidence in the existing guidelines	20 (29)
The tests are too expensive	12 (17.4)
T-SPOT®.*TB* test is unavailable	10 (14.5)
QuantiFERON-TB® Gold In-Tube test (or other version) is unavailable	8 (11.6)
Would not treat a positive result in an asymptomatic patient	7 (10.1)
Lack of physician or nursing time to arrange the tests	6 (8.7)
The guidelines are too complex	6 (8.7)
Mantoux test is unavailable	4 (5.8)
Wishing to wait for cost-effectiveness analysis to determine best approach	3 (4.3)
Concern over limited efficacy of the chemoprophylaxis	3 (4.3)
Non-compliance of guidelines	2 (2.9)
Concern about toxicity/drug-drug interactions from chemoprophylaxis	2 (2.9)
Would only test if recommended by local HIV network	2 (2.9)
Conflicting advice from respiratory physicians	1 (1.4)
Sensitivity and specificity of the tests uncertain	1 (1.4)

[1]Respondents could give multiple reasons, therefore total >100

3.3.10 Management of latent tuberculosis infection

88/93 (94.6%) geographical areas offering LTBI screening reported offering chemoprophylaxis to those with a positive result from IGRA, with or without Mantoux testing. The most common regimen used was six months isoniazid (62/88, 70.5%), followed by three months combined isoniazid/rifampicin (49/88, 55.7%), nine months isoniazid (5/88, 5.7%), and combined rifampicin/isoniazid/ethambutol (1/88, 1.1%).

In the free comments box, 11/88 (12.5%) geographical areas reported that local policy was to send HIV positive individuals with LTBI to another service for treatment, commonly to the local respiratory TB service. There were a large number of additional comments in support of using a regimen of six months isoniazid, with most citing increased evidence, support in published BHIVA or NICE guidelines, and favourable tolerance and lack of interactions with HAART as reasons for the use of this regimen. Comments in favour of using three months combined isoniazid/rifampicin included concerns about rates of isoniazid resistance in London, and familiarity with using this regimen in HAART-naïve individuals without the concern of potential drug-drug interactions.

5/93 (5.4%) geographical areas offering screening for LTBI, reported that chemoprophylaxis was not subsequently offered to those diagnosed with LTBI. The reasons for this were not clearly stated in three cases. Two areas reported that patients were observed closely for the development of active TB.

3.3.11 Future intention to offer screening and treatment for latent tuberculosis infection

Of the 69 geographical areas not currently offering LTBI screening for PLWH, 22/69 (31.9%) indicated that they were planning to do so in the future. The intended guidelines to be followed in the future, together with planned screening tests and treatment, are shown in Table 3.5.

Table 3.5. Intended future latent tuberculosis screening strategies

Planned screening guideline[1], testing strategy[1] and chemoprophylaxis strategy	Total n = 22 geographical areas intending to perform future screening n (%)
Screening guideline to be followed	
British HIV Association guidelines	16 (72.7)
NICE guidelines	8 (36.4)
Other – awaiting better/revised guidance	5 (22.7)
Scottish guidance (pending)	1 (4.5)
International guidelines	0 (0)
Testing strategy[2]	
Unsure of future screening strategy	9 (41)
T-SPOT®.*TB* only	7 (31.8)
QuantiFERON-TB® (all types) only	3 (13.6)
QuantiFERON-TB® then T-SPOT®.*TB* if QuantiFERON-TB® negative or equivocal	3 (13.6)
Mantoux then QuantiFERON-TB® if Mantoux negative	1 (4.5)
Mantoux and T-SPOT®.*TB* together	1 (4.5)
Chemoprophylaxis to be offered	
6 months isoniazid	11 (50)
Unknown future treatment regime	5 (22.7)
Other – awaiting further studies	3 (13.6)
4 months rifampicin or rifabutin	3 (13.6)
3 months isoniazid/rifampicin	1 (4.5)
9 months isoniazid	0 (0)

[1] Respondents could select as many answers as were applicable, therefore total >100%
[2] Other combinations of tests listed in the survey have been omitted here as no respondents selected them; e.g. QuantiFERON-TB® and T-SPOT®.*TB* together

3.4 Discussion

This national evaluation, which covers services caring for over 90% of HIV positive adults in the UK, is the first to evaluate LTBI screening in this population. It has revealed that LTBI screening practices are highly heterogeneous in terms of the criteria used to offer screening, and the tests utilised, and in the majority of cases, deviate from the published national guidance that was in place at the time, although these were themselves non-congruent. Additionally, screening policy was not dependent on the local burden of HIV-TB.

Tuberculosis control through the identification and treatment of people with latent infection is an increasingly important focus, with the 2016 updated NICE guidance

recommending expanding LTBI treatment in the HIV negative cohort from only those under the age of 35, to all those under 65 years of age (55). The global HIV epidemic has contributed significantly to the increased burden of TB (36, 47) and the need to manage LTBI amongst this population is imperative, despite its logistical challenges, especially in high-burden countries (89, 114, 115).

Previous evaluations of clinical practice in TB management have also revealed disparate guidance and varying clinical practice, although these studies have been limited in scope and size with a Belgian survey of HIV healthcare professionals, and a UK survey of paediatricians (116, 117) having only 55 and 13 respondents respectively. This questionnaire was more comprehensive in its scope, and obtained results from 116 HIV healthcare providers around the UK, who between them covered 162 out of 188 identified geographical areas, and yielded results which are representative of all parts of the UK, irrespective of HIV or TB disease burden.

Despite two national guidelines, a relatively low proportion (57.4%) of areas in the UK indicated that they currently perform any kind of systematic evaluation, although a further 14% have expressed a future intention to do so. The heterogeneity of testing approaches identified in this study suggests that there is uncertainty amongst HIV clinicians in the UK as to how to select individuals for screening. Over 80% of geographical areas who screen, use country of origin as a criterion, with all of these offering screening to those from high TB incidence countries, but less than half screening those from low incidence areas. The TB incidence rate in non-UK born individuals has been declining in the UK, in comparison to the rate in UK born individuals, which has remained static (118). A retrospective analysis of a London HIV cohort found that the majority of those who had developed active TB, who would not have been initially captured by LTBI screening using NICE or BHIVA guidance, were born in the UK (119).

Current blood CD4 count was used as a criterion by 61% of geographical areas that screen. Clearly the exact CD4 count levels at which screening was offered in line with the BHIVA algorithm would vary with the country of origin/time on HAART, although it is possible to draw some general conclusions. Over 90% of those geographical areas offered screening when the CD4 count was 200 cells/mm^3 or below, with gradually declining numbers offering screening to those at higher levels. Only 58% offered any

screening to those with CD4 counts above 500 cells/mm^3. The London cohort demonstrated that only 8% of HIV positive individuals developing TB, did so at a CD4 count above 500 cells/mm^3 (119), consistent with previous data (35, 42) including from the UK Collaborative HIV Cohort (UKCHIC) (35, 120), which also showed declining incidence of TB with higher CD4 counts. Although the UKCHIC report excluded all individuals who had died within 3 months of HIV diagnosis, and may therefore have potentially under-reported TB incidence, early deaths were presumably more likely to have been in severely immunosuppressed individuals (48).

This study highlights the fact that having two divergent guidelines may have been causing confusion as to which groups to screen, thereby underlining the need for further work in this area and consistency of approach. There needs to be a balance between identifying the highest-risk individuals and making screening guidance practicable to implement. Moreover, the potential cost-effectiveness of different screening methodologies need to be considered to enable resources to be targeted to those subgroups that will benefit most from screening, and treatment, of LTBI.

Among those screening, or intending to do so, the most commonly reported screening tool is an IGRA (with a roughly even split between T-SPOT®.*TB* and QuantiFERON-TB®), rather than TST, and only a small proportion of respondents in this survey used a different screening strategy in advanced immunosuppression.

Treatment of LTBI in HIV positive individuals with isoniazid preventive therapy is supported by a variety of trials performed in Sub-Saharan Africa and elsewhere (91, 95, 96). Isoniazid monotherapy and combinations with rifampicin or pyrazinamide are all similarly effective, although combination regimens carry an increased risk of adverse effects (89). This survey indicates that in practice, the predominant preferred treatment strategy in the UK is a six month course of isoniazid, avoiding drug-drug interactions with HAART, and in keeping with both NICE and BHIVA guidance. Shorter courses of rifamycins or combined rifampicin/isoniazid are also utilised in some areas, particularly in individuals not receiving HAART.

Interestingly, the most commonly reported reason for not offering LTBI screening in this evaluation was a perception that the cohort was at low risk of TB infection, although a

quarter of geographical areas not offering LTBI screening, are areas of high HIV prevalence/TB incidence. This suggests that there is potentially limited knowledge about the risk of TB and LTBI in general amongst the respondents. The next most reported explanation for not screening was a lack of confidence in the published guidance, with a smaller proportion stating that they considered the current guidelines to be too complex. Although not explicitly stated by the respondents, having two different published guidelines on the same topic may well cause confusion and uncertainty amongst clinicians as to which guidance to follow. Unavailability or high cost of screening tests was the next most reported explanation, raising questions about equitable resource allocation.

The predominant limitation of this study is that information about current LTBI screening and treatment practices, or future intentions, was provided by a single clinician in each geographical area. An assumption was made that other members of the clinical team would practice in the same manner, but there may be variation in clinical practice amongst different clinicians working in the same institution that would not have been identified. In addition, the number of HIV positive adult patients treated by the 116 respondents was self-reported and since some respondents provided data for more than one geographical area, this added to the difficulty in establishing exactly how many patients were treated in each area.

3.5 Conclusions

This national evaluation, covering services caring for over 90% of HIV positive adults in the UK, has revealed that screening for LTBI is highly variable, often deviates from national guidance and does not depend on the local TB-HIV burden. Many areas may be missing an opportunity to improve the health of their HIV cohorts by screening and treating to reduce the risk of active tuberculosis later on. It is clear that practitioners are using a variety of screening strategies in order to decide whom to screen. Having two differing published guidelines in the UK is potentially causing confusion. There is, therefore, an urgent need to prospectively assess, and compare, the impact, and cost-effectiveness, of different LTBI screening strategies for HIV positive individuals to inform the development of a uniform national guideline. Specific questions to be

addressed include whether screening of individuals born in low incidence countries is cost-effective, and the determination of the optimal screening strategy when there is widespread use of antiretroviral therapy in PLWH.

3.6 Publication arising from this work

White HA, Miller RF, Pozniak AL, Lipman MCI, Stephenson I, Wiselka MJ, Pareek M. Latent tuberculosis infection screening and treatment in HIV: insights from evaluation of UK practice. Thorax 2017; 72 (2): 180-182.

Chapter 4. Defining the risk of active tuberculosis in a cohort of HIV positive individuals in Leicester, UK

4.1 Introduction

Despite the apparent low levels of systematic LTBI screening occurring in the UK amongst PLWH, which I demonstrated through the national survey (121), it is well documented that these individuals are at much higher risk of progressing to active TB than other groups in the general population (36, 61, 122). Multiple studies have demonstrated that the risk is dependent upon a number of factors, principally concerned with HIV control and ethnicity/migration status, with remarkably little discordance between different studies.

The latest figures for Leicester (in 2017) show that the city has an HIV prevalence of 3.9 per 1000 population (in comparison to a prevalence in England as a whole of 2.3 per 1000), although there are areas of the city with a prevalence of >10 per 1000 population (123). Coupled with the high incident rates of active TB reported in Leicester (11) these figures render the city as being an ideal setting in which to study the relationship between TB and HIV in more detail.

As a precursor to undertaking a patient acceptability study into the screening and treatment of PLWH for latent TB, and implementing systematic screening in our cohort, I therefore first analysed the incidence of active TB across the entire cohort of patients who had sought HIV care in Leicester. The main objective was to define the risks of developing active TB, especially incident TB disease occurring after the diagnosis of HIV.

4.2 Methods

4.2.1 Creation of the patient database

Several sources were utilised in order to identify patients who had ever attended for HIV care in Leicester. These included patients recorded as having been registered with UKCHIC (120), and those recorded on our electronic HIV patient management system (Lilie Sexual Health Management System © 2018 Idox Health, UK). Lilie went live in November 2008, and the records for all active patients on two earlier electronic record systems were migrated across at that time. Confirmation of HIV sero-status was undertaken by cross-checking our electronic laboratory results programme, which commenced in 1998, and examining paper hospital records if the dates of clinic attendance pre-dated this time. All patients were considered for inclusion up to 30th June 2017.

4.2.2 Exclusions

Patients were excluded if; they were under the age of 16 years on 30th June 2017 or principally under the care of the paediatricians; if they were found actually to be HIV negative, or HIV positivity could not be definitely confirmed; or if their principal care was at another centre and they had only attended our centre briefly, for example, to replenish medication stocks. All other patients were included in the study.

4.2.3 Demographic details

Date of birth and gender at birth was recorded, together with NHS number where available, to verify records. NHS numbers not recorded on our local electronic systems were obtained from NHS Spine (124). Ethnicity and country of birth were ascertained from electronic hospital and HIV records, or paper hospital records, and ethnicity was coded according to the national NHS data dictionary (125). Countries of birth were further classified into regions according to the World Bank Analytical Grouping (126).

4.2.4 Ascertainment of tuberculosis status

Confirmation of active TB was undertaken wherever possible by cross-checking our electronic laboratory results programme, examining paper hospital records for patients who had received care pre-1998, and scrutinising transfer letters from other HIV centres. If an individual had had more than one episode of active TB, only the first episode was included.

The definition of active TB included the following; isolation of MTb from microbiological culture; AAFB positivity on sputum smears, even if culture negative, with other clinical or radiological evidence suggestive of tuberculosis; clinical or radiological evidence suggestive of tuberculosis and treated as such by the treating physician, even if MTb was not isolated.

The timing of active TB infection in relation to the HIV diagnosis was ascertained. Active TB occurring more than three months before the HIV diagnosis was classified as having occurred before HIV. Active TB diagnosed concomitantly with the HIV diagnosis, or within three months, was classified as having occurred with HIV, and active TB diagnosed more than three months after the HIV diagnosis was classified as having occurred after HIV (incident TB). The three month timeframe was selected in order to enable a reasonable period of time for clinicians to engage with the patient, undertake clinical and, where appropriate, radiological assessment, and also to account for the potential emergence of active TB as a result of Immune Reconstitution Inflammatory Syndrome (IRIS) following the initiation of HAART.

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

Additionally, cross-referencing with the national HIV dataset and TB surveillance system held at Public Health England (PHE) was undertaken at the start of March 2019,

to identify cases of active TB which had not been recorded in our medical notes or local TB surveillance system but which were recorded as having occurred when patients were under care elsewhere in the UK.

4.2.5 Dates of tuberculosis and HIV diagnosis

The date of HIV diagnosis was recorded as the first date upon which a positive HIV antibody or viral load test was taken in Leicester, or a date recorded in the medical notes if diagnosis was made elsewhere. If only the month was known then the date was recorded as the first day of the month, whereas if only the year was known then 15th July of that year was used as the diagnosis date.

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

4.2.6 HIV viral load thresholds for undetectable versus detectable viraemia

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

For the purposes of this study, I classified any PCR result reported as "<…." as an undetectable viral load, and any absolute value as a detectable viral load.

4.2.7 Ethics approval

Formal ethics approval was not required as this was considered a service evaluation. However, cross-referencing with the datasets from PHE was approved by the Caldicott guardians of both UHL and PHE after completion of a Data Impact Assessment Tool and Risk Evaluation. Individuals who were identified as having had active TB through matching with PHE datasets, but had had no previous record of this recorded in their medical notes, had this information about the TB diagnosis retrospectively entered into their medical notes to inform future care by their clinicians.

4.2.8 Statistical analysis

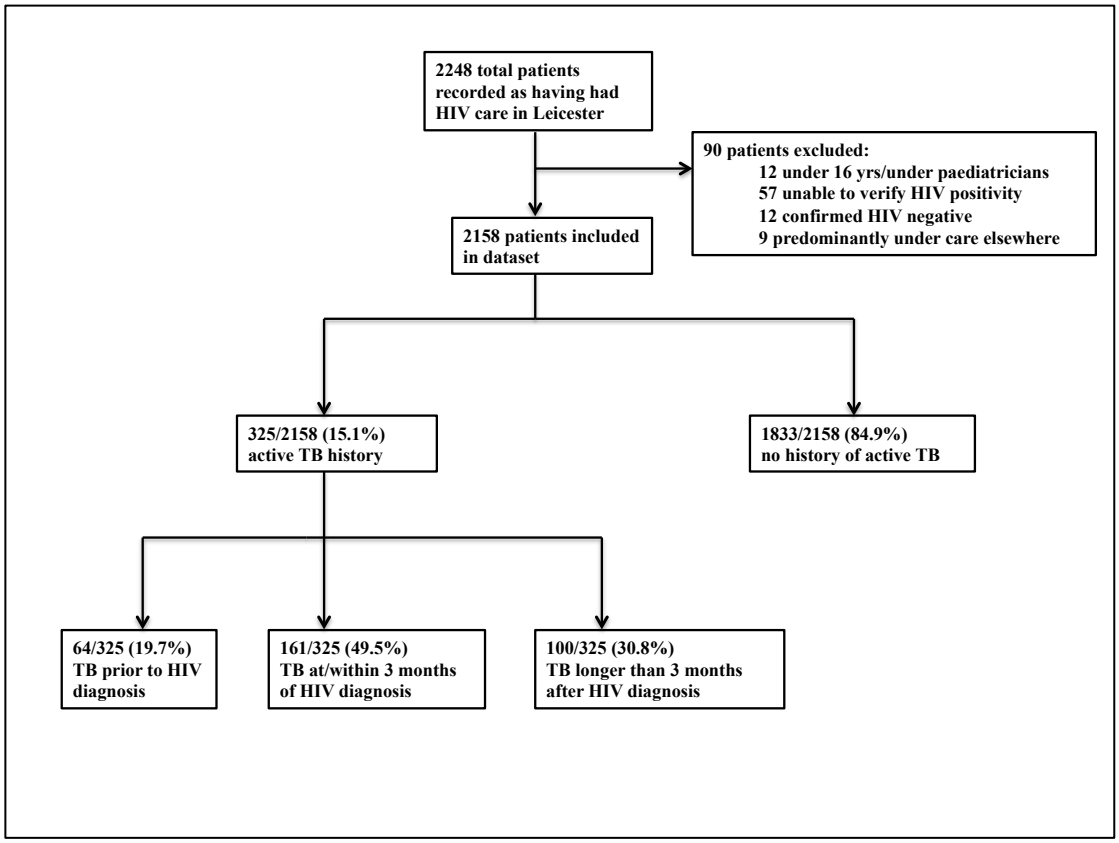
Continuous data were summarised with median and interquartile range (IQR) and categorical responses as proportions/percentages. Comparisons were made using Pearson's chi-square test (or Fishers exact test if appropriate). All statistical tests were considered significant when the p-value was ≤ 0.05. Logistics regression and Cox proportional hazard models were used to determine predictors of LTBI reactivation (patients with TB before HIV infection, or TB at the time of HIV diagnosis/within three months were removed from this analysis). TB incidence rate was calculated as the annual number of patients diagnosed with TB divided by the annual number of person years at risk of TB in the cohort. All data were analysed using Stata v15.1 (StataCorp, Texas, USA).

4.3 Results

4.3.1 Total cohort

The total cohort of patients recorded as having received care for HIV in Leicester was 2248. Ninety patients were excluded (Figure 4.1), leaving an active cohort of 2158.

Figure 4.1. Flowchart of HIV positive patients in tuberculosis cohort study



4.3.2 Demographics

The demographics of the total cohort are shown in Table 4.1. 1193/2158 (55%) of the total cohort was male, and patients were predominantly of black African ethnicity (1158/2158, 53.7%), with smaller proportions of white (647/2158, 30%) and South Asian (178/2158, 8.2%) ethnicities. 1502/2158 (70%) were born outside of the UK, and the majority (1959/2158, 90.8%) had been diagnosed with HIV in or after the year 2000.

Table 4.1. Demographics of the total HIV cohort

Variable	Total cohort n (%) n = 2158		Active TB as proportion of Total cohort n (%) (n=325)		Not had active TB as proportion of Total cohort n (%) (n=1833)	
Male gender	1193	(55.3)	146	(12.2)	1047	(87.8)
Median age at HIV diagnosis (IQR)	33	(27 - 40)	35	(29 - 41)	33	(27 - 40)
Ethnicity						
Black African	1158	(53.7)	238	(20.6)	920	(79.4)
South Asian	178	(8.2)	50	(28.1)	128	(71.9)
White	647	(30)	21	(3.2)	626	(96.8)
Mixed	29	(1.3)	4	(13.8)	25	(86.2)
Black Caribbean	21	(1)	1	(4.8)	20	(95.2)
Black Other	26	(1.2)	2	(7.7)	24	(92.3)
Other	53	(2.5)	5	(9.4)	48	(90.6)
Unknown	46	(2.1)	4	(8.7)	42	(91.3)
UK birth status						
UK born	569	(26.4)	13	(2.3)	556	(97.8)
Non-UK born	1502	(70)	302	(20.1)	1200	(79.9)
Unknown	87	(4)	10	(11.5)	77	(88.5)
Region of birth						
Sub-Saharan Africa	1210	(56.1)	254	(21)	956	(79)
South Asia	95	(4.4)	32	(33.7)	63	(66.3)
Europe & Central Asia	691	(32)	22	(3.2)	669	(96.8)
East Asia & Pacific	35	(1.6)	5	(14.3)	30	(85.7)
Latin America & Caribbean	22	(1)	1	(4.5)	21	(95.5)
Middle East & North Africa	10	(0.5)	1	(10)	9	(90)
North America	8	(0.4)	0	(0)	8	(100)
Unknown	87	(4)	10	(11.5)	77	(88.5)
Year of HIV diagnosis						
1983[1] – 1989	17	(0.8)	0	(0)	17	(100)
1990 – 1999	182	(8.4)	29	(15.9)	153	(84.1)
2000 – 2009	1381	(64)	244	(17.7)	1137	(82.3)
2010 – 2017[2]	578	(26.8)	52	(9)	526	(91)

IQR = Inter-quartile range.
[1] 1983 is the earliest year in which a patient in the total HIV cohort was diagnosed with HIV.
[2] Individuals were included up and including to 30th June 2017

4.3.3 Active tuberculosis diagnosis

A diagnosis of active TB was recorded for 325/2158 (15.1%) patients. The demographics of those with active TB in comparison with the total cohort are shown in Table 4.1. Notable results are that 238/1158 (20.6%) of the total black African cohort, and 50/178 (28.1%) of the total South Asian cohort, had had TB, in contrast to only

21/647 (3.2%) of the total white cohort. 302/1502 (20%) of the non-UK born population had had TB.

The cases of active TB were subdivided into those who had had active TB prior to their HIV diagnosis (64/325, 19.7%), concurrently with or within three months of the HIV diagnosis (161/325, 49.5%) or more than three months after the HIV diagnosis (100/325, 30.8%) (Figure 4.1). Concurrent TB/HIV diagnosis prevalence was calculated as 161/2158 (7.46%). The descriptions of each of these groups are shown in Table 4.2 and the temporal trend of TB diagnoses by year is shown in Figure 4.2.

Across all groups, there was a strong predominance of individuals who were born in countries where the TB incidence exceeds 150/100,000 population. Individuals who were concurrently diagnosed with TB and HIV had a predominance of pulmonary TB (108/161, 67.1% of cases) and 66/161 (41%) had a CD4 count of less than 100 cells/mm^3. Those who developed TB after HIV (incident TB) had a higher median CD4 count, 36/100 (36%) were virologically suppressed at the time of TB diagnosis, and there was a more even split between pulmonary (54/100, 54%) and extrapulmonary (46/100, 46%) disease. Around 9% of individuals developing TB with, or after their HIV diagnosis, had died by 30th June 2017.

Table 4.2. Description of those with HIV who developed tuberculosis

Variable	Timeline of TB infection		
	TB before HIV diagnosis n (%) n = 64	TB at HIV diagnosis n (%) n = 161	TB after HIV diagnosis n (%) n = 100
Male gender	34 (53.1)	69 (42.9)	43 (43)
Median age at HIV diagnosis (IQR)	35.5 (30 - 39.5)	35 (30 – 44)	32 (27.5 - 38.5)
Median age at TB diagnosis (IQR)	28 (24 – 35)	35 (30 – 43)	36 (31 – 43)
Ethnicity			
Black African	48 (75)	113 (70.2)	77 (77)
South Asian	12 (18.8)	29 (18)	9 (9)
White	2 (3.1)	11 (6.8)	8 (8)
Mixed	0 (0)	3 (1.9)	1 (1)
Black Caribbean	0 (0)	0 (0)	1 (1)
Black Other	0 (0)	1 (0.6)	1 (1)
Other	2 (3.1)	1 (0.6)	2 (2)
Unknown	0 (0)	3 (1.9)	1 (1)
UK birth status			
UK born	2 (3.1)	7 (4.3)	4 (4)
Non-UK born	60 (93.8)	149 (92.5)	93 (93)
Unknown	2 (3.1)	5 (3.1)	3 (3)
Region of birth			
Sub-Saharan Africa	50 (78.1)	122 (75.8)	82 (82)
South Asia	6 (9.4)	21 (13)	5 (5)
Europe & Central Asia	4 (6.3)	10 (6.2)	8 (8)
East Asia & Pacific	1 (1.6)	3 (1.9)	1 (1)
Latin America & Caribbean	0 (0)	0 (0)	1 (1)
Middle East & North Africa	1 (1.6)	0 (0)	0 (0)
North America	0 (0)	0 (0)	0 (0)
Unknown	2 (3.1)	5 (3.1)	3 (3)
TB incidence in country of birth			
<50/100,000 population	3 (4.7)	11 (6.8)	9 (9)
50 – 149/100,000 population	6 (9.4)	11 (6.8)	4 (4)
150 – 249/100,000 population	36 (56.3)	103 (64)	69 (69)
250-349/100,000 population	9 (14.1)	14 (8.7)	9 (9)
≥ 350/100,000 population	8 (12.5)	17 (10.6)	6 (6)
Unknown	2 (3.1)	5 (3.1)	3 (3)
Year of HIV diagnosis			
1983[1] – 1989	0 (0)	0 (0)	0 (0)
1990 – 1999	6 (9.4)	10 (6.2)	13 (13)
2000 – 2009	47 (73.4)	125 (77.6)	72 (72)
2010 – 2017[2]	11 (17.2)	26 (16.1)	15 (15)
Year of TB diagnosis			
1977[3] - 1979	1 (1.6)	0 (0)	0 (0)
1980 – 1989	7 (10.9)	0 (0)	0 (0)
1990 – 1999	24 (37.5)	12 (7.5)	2 (2)
2000 – 2009	29 (45.3)	124 (77)	58 (58)
2010 – 2017[2]	2 (3.1)	25 (15.5)	39 (39)
Unknown	1 (1.6)	0 (0)	1 (1)

Variable	TB before HIV diagnosis n (%) n = 64	TB at HIV diagnosis n (%) n = 161	TB after HIV diagnosis n (%) n = 100
HIV viral suppression at TB diagnosis	-		
Suppressed		1 (0.6)	36 (36)
Not suppressed		109 (67.7)	39 (39)
Unknown		51 (31.7)	25 (25)
CD4 count at TB diagnosis			
Median (IQR)	-	90 (40 - 240)	290 (120 - 370)
Range		0 - 1010	0 - 766
<50 cells/mm^3		46 (28.6)	9 (9)
51-99		20 (12.4)	8 (8)
100-199		19 (11.8)	7 (7)
200-349		28 (17.4)	29 (29)
350-499		5 (3.1)	14 (14)
≥500		4 (2.5)	8 (8)
Unknown		39 (24.2)	25 (25)
Site of TB infection			
Pulmonary	51 (79.7)	108 (67.1)	54 (54)
Extra-pulmonary	12 (18.8)	51 (31.7)	46 (46)
Unknown	1 (1.6)	2 (1.2)	0 (0)
TB culture positivity			
Culture positive	6 (9.4)	77 (47.8)	47 (47)
Culture negative	1 (1.6)	49 (30.4)	40 (40)
Unknown	57 (89.1)	35 (21.7)	13 (13)
Deceased from any cause[4]	3 (4.7)	14 (8.7)	9 (9)

IQR = Interquartile range

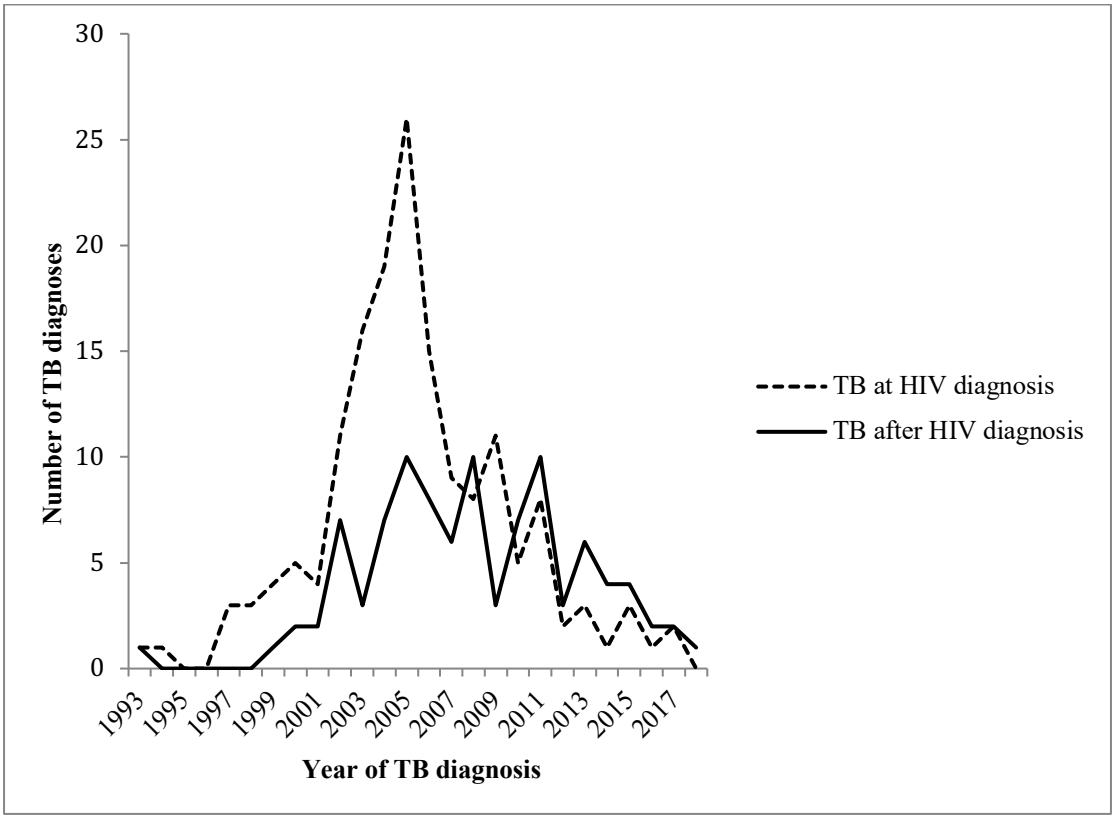
[1] 1983 is the earliest year in which a patient in the total HIV cohort was diagnosed with HIV.

[2] Individuals were included up and including to 30th June 2017.

[3] 1977 is the earliest year in which a patient was diagnosed with TB.

[4] At 30th June 2017.

Figure 4.2. Temporal diagnosis of tuberculosis amongst people living with HIV



4.3.4 Risk of developing active tuberculosis after HIV diagnosis

Univariate and multivariable logistics regression analyses were undertaken to establish associations with developing TB more than three months after a diagnosis of HIV (Table 4.3), in comparison to the cohort who had not developed TB. The regions of birth were collapsed due to small numbers, or no patients, in some regions. Ethnicity, UK birth status, and region of birth, were all closely linked to the incidence of TB in the country of birth, and were not taken forward into the multivariable analysis.

Age at HIV diagnosis was not significant in either the univariate or multivariable analysis, although the year of HIV diagnosis was. Gender was unrelated to TB risk in the multivariable model. The univariate model showed that being born abroad, and specifically in sub-Saharan Africa and the South Asia and East Asia & Pacific regions, and being of black African or South Asian ethnicities, were all factors significantly associated with developing TB. In the multivariable analysis, the association with TB

incidence in the country of birth, which was also noted as significant in the univariate model, was confirmed, as there was a significantly increased risk of developing TB after HIV diagnosis in individuals born in countries where the TB incidence was greater than 50/100,000 population, and particularly above 150/100,000 population. .

Table 4.3. Univariate and multivariable logistics regression for development of tuberculosis more than three months after HIV diagnosis

Variable		Observation (%)	Unadjusted OR (Univariate analysis)	p value	Adjusted OR2 (Multivariable analysis)	p value
Age at HIV diagnosis			0.99 (0.97 - 1.01)	0.38	1.002 (0.98 – 1.02)	0.84
Year of HIV diagnosis			0.93 (0.9 – 0.96)	<0.00001	0.91 (0.87 – 0.95)	<0.0001
Gender	Male	43/100 (43)	1		1	
	Female	57/100 (57)	1.77 (1.18 - 2.65)	0.0058	1.04 (0.67 – 1.62)	0.85
Ethnicity	Black[1]	79/100 (79)	1			
	South Asian	9/100 (9)	0.86 (0.42 – 1.75)			
	White	8/100 (8)	0.16 (0.07 – 0.32)			
	Mixed/Other/Unknown[2]	4/100 (4)	0.42 (0.15 – 1.18)	<0.0001		
UK birth status	Non-UK born	93/100 (93)	1			
	UK born	4/100 (4)	0.09 (0.03 – 0.25)			
	Unknown	3/100 (3)	0.5 (0.16 – 1.62)	<0.0001		
World Bank region of birth	Europe & Central Asia, North America and Latin America & Caribbean and Middle East & North Africa[3]	9/100 (82)	1			
	South Asia and East Asia & Pacific[4]	6/100 (6)	5.07 (1.76 – 14.56)			
	Sub-Saharan Africa	82/100 (9)	6.74 (3.36 – 13.5)			
	Unknown	3/100 (3)	3.06 (0.81 – 11.55)	<0.0001		
TB incidence in country of birth	<50/100,000 population	9/97 (9)	1		1	
	50 - 149/100,000 population	4/97 (4.1)	2.94 (0.89 – 9.71)		3.27 (0.97 – 11.07)	
	150 – 249/100,000 population	69/97 (71.1)	7.26 (3.6 – 14.66)		7.81 (3.72 – 16.36)	
	250 – 349/100,000 population	9/97 (9.3)	6.94 (2.69 – 17.9)		6.44 (2.45 – 16.95)	
	≥ 350/100,000 population	6/97 (6.2)	4.33 (1.51 – 12.4)	<0.0001	4.29 (1.47 – 12.57)	<0.0001

[1] 77/79 were black African. One was black Caribbean, and one was "other" black ethnicity.
[2] One was mixed ethnicity; two were "other" ethnicity and one was unknown ethnicity.
[3] 8/9 were from Europe and Central Asia; one was from Latin America & Caribbean; none were from Middle East & North Africa and none were from North America
[4] 5/6 were from South Asia; one was from East Asia & Pacific region

4.3.5 Cox proportional hazards model

Using the date of death, date of active TB diagnosis, or the end study date (1st March 2019) as the end point, the impact of factors on the time to developing active TB more than three months after a diagnosis of HIV was calculated using Cox proportional hazards (Table 4.4). The regions of birth were again collapsed. The total at-risk time was 22,346.771 person years. The incidence rate was 4.47 per 1000 person years.

The year of HIV diagnosis was again significant in both the univariate and multivariable models and showed that the development of TB became less common with the passage of time after HIV diagnosis. Gender was not significant in the multivariable model. Being born in countries where the TB incidence was greater than 50/100,000 population, and particularly above 150/100,000 population, led to the faster development of TB.

Table 4.4. Cox proportional hazards model for the time to development of tuberculosis after HIV diagnosis

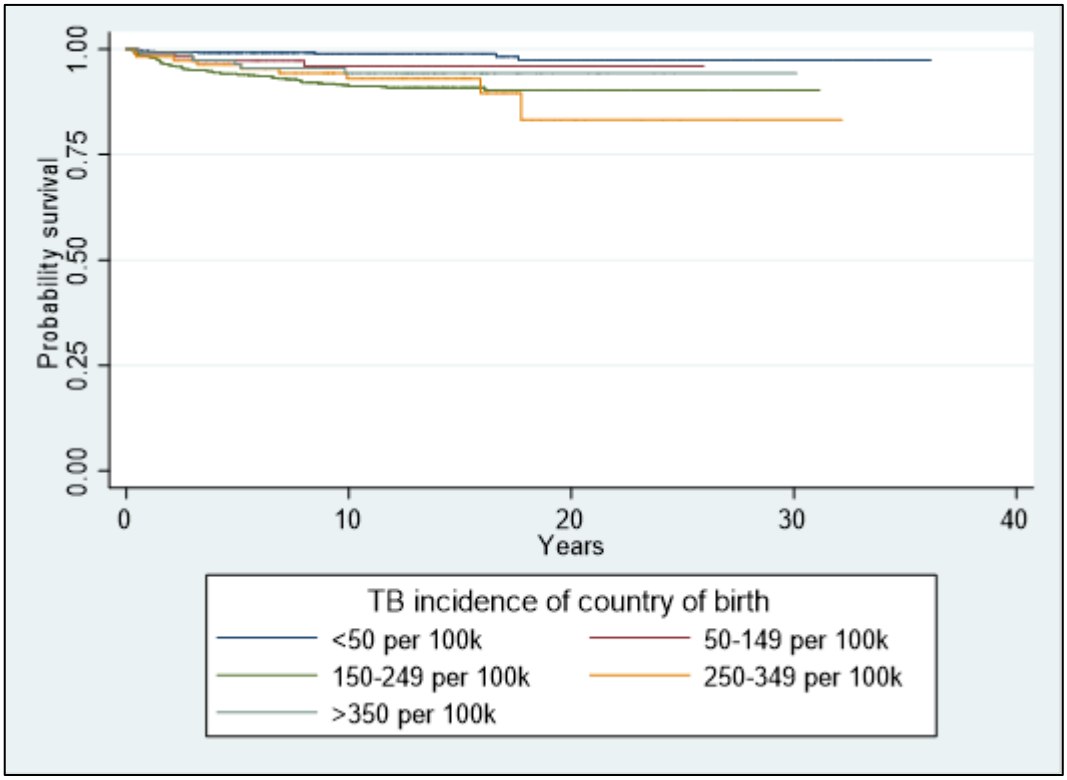
Variable		Observation (%)	Unadjusted OR (Univariate analysis)	p value	Adjusted OR2 (Multivariable analysis)	p value
Age at HIV diagnosis			0.998 (0.98 - 1.02)	0.83	1.00 (0.98 – 1.03)	0.71
Year of HIV diagnosis			0.96 (0.92 – 0.99)	0.0137	0.94 (0.896 – 0.978)	0.003
Gender	Male	43/100 (43)	1		1	
	Female	57/100 (57)	1.65 (1.11 - 2.46)	0.0122	1.01 (0.67 – 1.56)	0.92
Ethnicity	Black[1]	79/100 (79)	1			
	South Asian	9/100 (9)	0.85 (0.43 – 1.69)			
	White	8/100 (8)	0.17 (0.08 – 0.35)			
	Mixed/Other/Unknown[2]	4/100 (4)	0.44 (0.16 – 1.21)	<0.0001		
UK birth status	Non-UK born	93/100 (93)	1			
	UK born	4/100 (4)	0.099 (0.04 – 0.27)			
	Unknown	3/100 (3)	0.53 (0.17 – 1.67)	<0.0001		
World Bank region of birth	Europe & Central Asia, North America and Latin America & Caribbean and Middle East & North Africa[3]	9/100 (82)	1			
	South Asia and East Asia & Pacific[4]	6/100 (6)	5.1 (1.82 – 14.33)			
	Sub-Saharan Africa	82/100 (9)	6.15 (3.08 – 12.24)			
	Unknown	3/100 (3)	2.98 (0.81 – 11)	<0.0001		
TB incidence in country of birth	<50/100,000 population	9/97 (9.3)	1		1	
	50 - 149/100,000 population	4/97 (4.1)	2.84 (0.88 – 9.24)		3.1 (0.94 – 10.19)	
	150 – 249/100,000 population	69/97 (71.1)	6.73 (3.35 – 13.49)		7.14 (3.46 – 14.73)	
	250 – 349/100,000 population	9/97 (9.3)	6.17 (2.45 – 15.54)		5.9 (2.3 – 14.99)	
	≥350/100,000 population	6/97 (6.2)	3.93 (1.4 – 11.04)	<0.0001	3.96 (1.39 – 11.26)	<0.0001

[1] 77/79 were black African. One was black Caribbean, and one was "other" black ethnicity.
[2] One was mixed ethnicity; two were "other" ethnicity and one was unknown ethnicity.
[3] 8/9 were from Europe and Central Asia; one was from Latin America & Caribbean; none were from Middle East & North Africa and none were from North America
[4] 5/6 were from South Asia; one was from East Asia & Pacific region

4.3.6 Kaplan-Meier survival estimates

Figure 4.3 shows the Kaplan-Meier survival estimates for the development of incident TB, in relation to the categorical TB incidence rate in the country of birth.

Figure 4.3. Kaplan-Meier survival estimate curve for development of incident tuberculosis



4.4 Discussion

In this study I had the opportunity to investigate the associations with the development of TB in a large HIV cohort, in significant detail. Overall, more than 15% had had a diagnosis of TB at some stage, and the risk of developing active TB more than three months (incident risk) after the diagnosis of HIV was extremely high, at 4.47/1000 person years, which is higher than the range of 0.43 – 3 per 1000 person years reported in other studies of PLWH from elsewhere in the UK and other low TB incidence settings (46, 53, 66, 127, 128). Even though HIV/TB coinfection comprises only 3.8% of the overall cases

of TB in the UK (54), the documented post-HIV incidence in this current study far exceeds the risk of TB in the UK population as a whole (11) and my results therefore support the premise that TB/HIV coinfection is an important health problem, at least in some areas of the UK, which commands detailed research attention.

The definition of concomitant HIV/TB infection has varied amongst different studies, with some including TB cases diagnosed within one month after HIV diagnosis (46, 127), and another within three months (119). Nevertheless, prevalence of TB at, or shortly after, the time of HIV diagnosis was notably much higher in my study, at 7.46%, than in these other studies, where prevalence was reported as 0.9% - 2.6% (46, 127). Coupled with the high incidence rate for the development of TB later in the HIV disease course, this suggests that the Leicester HIV cohort may contain a higher proportion of individuals with risk factors for TB, than in other HIV cohorts elsewhere in low TB prevalence countries, and is in keeping with the overall high rates of TB seen in this city, in comparison to other areas of the UK (11).

In this cohort, early cases of TB/HIV coinfection occurred when individuals were immunosuppressed with a low CD4 count, and uncontrolled viraemia. Diagnosing HIV infection earlier is imperative in order to reduce the risk of complications and mortality (129). Figures from Leicester city show that 56.9% of new HIV diagnoses between 2015 and 2017 were made when the CD4 count was ≤ 350 cells/mm^3 (classified as "late" by PHE) (123), and there have been efforts made in Leicester to try and increase HIV testing in order to facilitate earlier diagnoses (130), especially as HAART is now known to be beneficial at all stages of the disease (98).

There are data showing that TB risk is higher in the early period following HIV seroconversion, potentially due to early depletion of MTB-specific CD4 cells in primary HIV infection (53), and also immediately after commencing HAART (53, 128), which may represent unmasking of TB due to immune reconstitution inflammatory syndrome (IRIS) (131). Other clinical groups have described intensive active TB case-finding amongst their newly diagnosed HIV patients (127).

Other studies have demonstrated that detectable viraemia is strongly associated with the risk of active TB (44, 49, 53, 127), and that HAART reduces this risk (132, 133) but not

back to baseline population levels (41, 42, 62). My data support this, since amongst the incident cases of TB that occurred more than three months after HIV diagnosis for which virological control data was available, it is notable that around 50% of cases occurred in individuals who were virologically suppressed.

There have also been previously noted strong associations with CD4 count, in that the incidence of TB is higher when the CD4 count is low, and TB risk declines as the CD4 count increments (42, 49, 53, 119, 127). In this study, the median CD4 count in those who had TB at the time of HIV diagnosis was 90 cells/mm^3, and over 52% had a CD4 count below 200 cells/mm^3, as one might expect for a cohort presenting with HIV who had already developed a complicating infection. Those who developed incident TB had a higher median CD4 count of 290 cells/mm^3, but still, fewer than a third of those for whom CD4 count data was available had a CD4 count of greater than 350 cells/mm^3, and only just over 10% had a CD4 count higher than 500 cells/mm^3. Therefore, my data supports the previously documented association between TB and low immunological recovery.

There was an interesting observation regarding the split between pulmonary and extrapulmonary disease in these cohorts, in that over time, the proportion of TB cases with isolated pulmonary disease seemed to diminish in favour of more cases of extrapulmonary disease. This has been noted previously, including in non-HIV cohorts (134, 135). The highest proportion of pulmonary disease was evident in the cohort who had had TB prior to HIV infection, although many of these cases were self-reported cases and so most clinical confirmatory details were lacking. It is known that HIV predisposes to greater extrapulmonary dissemination of TB due to reduced cell-mediated immunity (45, 134, 136), and that individuals of non-white ethnicity also have higher rates of extrapulmonary disease (134, 135), with an association noted with Vitamin D deficiency (135).

This study showed overwhelmingly that ethnicity, and country/region of birth, are the principal drivers for active TB amongst PLWH, and are represented by the TB incidence in the country of birth, reflecting TB exposure prior to migration to the UK. 20% of our total non-UK-born HIV cohort has had TB, in contrast to only 2.3% of our UK-born cohort. 20% of black Africans in this cohort have had TB, and at all time points of TB

diagnosis in relation to HIV, this ethnic group predominates and makes up the bulk of the cases, as has been seen in other studies (50, 51). The peak incidence of TB cases in this study occurred in 2005, corresponding with high migration from sub-Saharan Africa. Although we have a smaller cohort of Asian individuals with HIV, this group also has a high incidence of TB, with 28% having had TB. Several previous studies have categorised cohorts into "black", "white" and "other" (35, 127) which misses the nuances of ethnic diversity in general, and also within geographical areas in the UK, where there is often clustering of ethnic and cultural groupings.

The multivariable analyses for examining factors related to developing TB after HIV, and associations with the timing of TB after HIV, both showed that the TB incidence in the country of birth was statistically significant in determining subsequent incident TB and the time taken to develop TB, as has been documented by others (46) and the risk factors of ethnicity and country of birth are probably subsumed within this country of birth incidence risk. The incidence TB group of 150-249/100,000 population seemed to be the predominant group in both analyses, although this may be because the numbers of patients from countries with higher incidence levels in this study were smaller.

The other significant association in the multivariable models was with the year of HIV diagnosis, suggesting that for each year after the HIV diagnosis, there was a reduction in the risk of individuals developing TB. This may suggest improving management of patients with HIV, with increasingly more effective and tolerated HAART, even in those with resistant virus, and a focus on maintaining and improving other aspects of physical health (137).

A principal limitation of this study is that it is likely that the total number of adult patients recorded as having attended for HIV care at our centre is incomplete. Early patients would probably have had paper records only and many of these have unfortunately since been destroyed. The governance rules on retention of hospital records for patients with chronic conditions, which would include lifelong conditions such as HIV, have changed, and there is now a requirement to keep such records for 30 years (or 8 years after death) (138). We also found a number of individuals whose recorded name and date of birth on our HIV patient management system could not be matched with either our main hospital records or an NHS number. It is likely that many of these had given false details at the

point of HIV care, potentially due to concerns about stigma due to their HIV diagnosis. Additionally, there were apparently no diagnoses of active TB concurrently or after HIV diagnosis, in the 1980s, which seems rather improbable. There are likely to have been individuals diagnosed with TB in those early years, who later died, either from TB or some other cause related to HIV, in the time before HAART was available, who are not included in this data.

Additionally, we found multiple errors in the data that had been submitted to UKCHIC, which included duplicate records and errors in the date of HIV diagnosis and TB status, amongst others, which had to be corrected for this study. Matching with the PHE datasets would only have identified individuals who had had a diagnosis of active TB made in the UK and would not have identified those who had had a diagnosis made abroad. For all these reasons, it is therefore possible that the total number of individuals documented as having had a previous diagnosis of active TB is incomplete. Additionally, many of the cases of TB that occurred prior to HIV diagnosis had occurred abroad, were self-reported by individuals and so clinical verification was not possible. It is likely that some individuals may not have had TB, but another, clinically similar illness, diagnosed abroad, and equally likely that others will actually have been infected with HIV at the time, but were not tested.

4.5 Conclusions

Profiling the association between TB and HIV in this study has demonstrated that there are groups within the HIV cohort who were highly represented amongst those who developed incident TB disease, following the diagnosis of HIV. These are predominantly individuals from high burden TB countries who are potentially most likely to benefit from latent TB screening and treatment programmes. The next question to address is whether such programmes are acceptable to PLWH in the UK, and will ultimately result in high uptake and completion of chemoprophylaxis.

Chapter 5. Cohort questionnaire study investigating planned behaviour and uptake of latent tuberculosis screening/testing amongst people living with HIV

5.1 Introduction

As demonstrated in Chapter 4 and in other studies, populations of PLWH have high rates of active TB at all stages of their HIV infection, but are at risk of progressing from LTBI to active TB disease, even after HIV is diagnosed and treated (35, 36, 42). Treatment of LTBI with chemoprophylaxis is effective in reducing the risk of active TB disease in this population (44, 89) and as a result, LTBI screening and treatment of PLWH is advocated by a number of national and international organisations (55, 60, 139, 140). However, I also demonstrated in Chapter 3 that there is currently limited systematic screening of PLWH occurring in the UK (121).

To date, most studies investigating the provision of LTBI chemoprophylaxis in PLWH have been undertaken in high TB burden settings and focused primarily on quantitative analysis of isoniazid preventive treatment uptake. These show that treatment uptake is determined by factors such as understanding the diagnosis and the need for screening or treatment (100), and a positive influence of LTBI screening and treatment being offered as part of a package of HIV care (99). Self-perception of not being at risk of TB has also been noted previously in some patients (82). In addition these studies have shown that certain issues including fear of the diagnosis (100), fear of stigma (100), financial concerns and time availability (90) may adversely impact on treatment uptake. However, little is known about the factors determining planned and actual behaviour with respect to LTBI testing and treatment uptake. This is critical if LTBI screening and uptake is to be scaled up and implemented into routine clinical, programmatic, practice.

I therefore aimed to address this gap in the evidence-base by prospectively evaluating the planned, and actual behaviours of PLWH, with regards to LTBI screening and treatment.

5.2 Methods

5.2.1 Study design and setting

I designed and undertook a prospective study at the HIV clinic at the University Hospitals of Leicester (UHL) NHS Trust, Leicester. Following ethics approval, the Coventry and Warwickshire Partnership NHS Trust, Coventry was added as a second research site and the same study was conducted there by a colleague (Dr Amandip Sahota).

Patients were invited to complete a questionnaire and subsequently offered IGRA testing, and LTBI chemoprophylaxis, where clinically appropriate.

5.2.2 Study population, participants and methods of screening

Between April 2014 and September 2017 (inclusive), PLWH who were attending HIV services at one of the two participating centres were eligible to take part. The majority of questionnaires were distributed throughout 2014 and 2015. Inclusion criteria were; male and female adult patients (≥16 years); currently receiving care for HIV from one the two centres; from all ethnic backgrounds; irrespective of antiretroviral treatment or other medical comorbidities. In Leicester, patients with any CD4 count were included. In Coventry, only patients with CD4 counts below 500 were included, as funding for IGRA testing in that centre was dependent upon individuals meeting the NICE guidance in force at the time, which recommended screening only at CD4 counts below 500 (88). I excluded; known previous diagnosis of active or latent TB; residence in prison; a lack of capacity to consent to participate; non-English speakers without a translator in clinic; and where the treating clinician felt that participation would be detrimental to the wellbeing of the patient (such as acute distress associated with HIV diagnosis).

All sequential, eligible patients were approached as they attended for clinic follow-up, with no randomisation. The participant information leaflet made it apparent that individuals would be offered screening irrespective of whether they wished to participate in the questionnaire study.

5.2.3 Questionnaire design

An elicitation study to determine possible beliefs around LTBI testing and treatment was not performed. However, other studies on LTBI chemoprophylaxis were examined and common themes extracted, forming the basis of my questionnaire, which was designed around the psychological model of behaviour change, the Theory of Planned Behaviour. This model proposes that the intention of an individual to carry out certain behaviours is dependent upon three variables; the individual's overall attitude towards the behaviour; the actual or perceived influence of others (subjective norms); and the perceived control that the individual feels that they have over the behaviour. The theory has been widely utilised to investigate the acceptability of other health-related interventions (141-144).

The questionnaire asked a series of questions pertaining to the planned intentions of accepting screening/treatment, and potential influencing factors which had been identified from the literature. A five-point Likert-scale ranging from 1 (Strongly agree) through 2 (Agree), 3 (Uncertain), 4 (Disagree) and 5 (Strongly disagree) was used. Additional demographic questions, and questions asking whether individuals had previously been diagnosed with, or treated for, active or latent TB were included. There was a free text box to enable simple thematic analysis of general comments related to LTBI testing and treatment. Readability indices were obtained for written patient materials and all scored between 7.3-8.6 on the Flesch-Kincaid Grade (145).

I designed, and gave potential participants a personalised invitation letter, a study information leaflet, and a booklet that explained TB and LTBI, IGRA testing, chemoprophylaxis and potential side effects. Patients were asked to read these documents and then complete the questionnaire if they wished to participate (Appendix 2).

In Leicester, patients were approached by letter, sent either to their home address, or given directly to them in clinic. Letters were only sent to home addresses if the patient had previously given consent to receive written correspondence about their HIV diagnosis through the postal system.

In the early phase of the study it was apparent that only 13/26 (50%) of questionnaires sent to the home addresses had been returned. I therefore switched to approaching patients solely through the clinics, at the time that they attended for their routine appointments, in order to try and increase response rates.

5.2.4 Data collection

Demographic data were collected from the questionnaire or hospital records. I used a slightly modified version of the World Bank analytical grouping (126) to cohort countries together into specific regions of birth (all patients in the Europe/Central Asia group were actually from Europe). Ethnicity was coded according to the national NHS data dictionary (125).

5.2.5 IGRA testing and clinical management of positive results

In Leicester, I scrutinised the clinic lists in advance and checked the medical notes of each patient due to attend clinic (to exclude those who had had active TB or LTBI previously, and those who had already had LTBI screening). I placed IGRA kits in the notes, in order to prompt the clinician to offer testing in clinic. I booked T-SPOT®.*TB* tests in advance with the immunology department at UHL, as only eight (and later five) tests were able to be undertaken across all department in the entire hospital each week. Results were obtained and stickers placed in each set of notes where IGRA tests were positive, to remind the clinician to exclude active TB and offer chemoprophylaxis, where appropriate, at the next appointment. Similar oversight was undertaken in Coventry by Dr Amandip Sahota.

IGRA testing varied slightly between the two sites according to which tests were available locally. Coventry used T-SPOT®.*TB* tests for all patients, whereas Leicester used QuantiFERON-TB® Gold In-Tube Test (QFN-GIT) (and more latterly QuantiFERON-TB® Gold Plus (QFT-Plus)) for those with CD4 counts ≥200, and T-SPOT®.*TB* tests in conjunction with QuantiFERON-TB® tests for those with CD4 counts <200. All positive or borderline positive tests were classified as being positive, and

clinical review took place before LTBI treatment was offered. Clinicians were blinded to the questionnaire responses.

5.2.6 Statistical analysis

Power calculation was undertaken as follows. Assuming an estimated total population size of 1000 subjects meeting the inclusion criteria, of whom a hypothesised proportion of 50% indicate that they would accept screening for LTBI (with a margin of error of 5% around this proportion) and a design effect (deff) of 1, a total of 278 subjects would be required to be recruited. Assuming a response rate of 50% the sample size was inflated to 556.

Demographic characteristics were summarised using median for age and proportions/percentages for categorical variables; comparisons were made using the non-parametric Mann-Whitney U-test and Pearson's chi-square test (or Fishers exact test if appropriate) respectively. P-values of ≤ 0.05 were considered significant.

Responses to individual Likert-scale questions were excluded if none, or more than one, of the response options was ticked. I described the distribution of responses as proportions to gain an overall understanding of the views and beliefs of patients with respect to LTBI screening and treatment. Factors associated with the planned intention and actual behaviour to take up LTBI testing and treatment were examined using separate logistic regression analyses after amalgamating "strongly agree" and "agree" into one group, and the remainder into a separate group. Univariate and multivariable associations of demographic and influencing factors from the theory of planned behaviour domains associated with testing or treatment for LTBI were reported as crude, and adjusted, odds ratios (OR) and 95% confidence intervals. Statistical analyses were performed using Stata v14.0 (Statacorp, Texas, USA).

5.2.7 Consent and Ethics approval

As per our ethics approval, consent was presumed if the patient completed at least one question on the questionnaire (146) and returned it either in the pre-stamped envelope, or

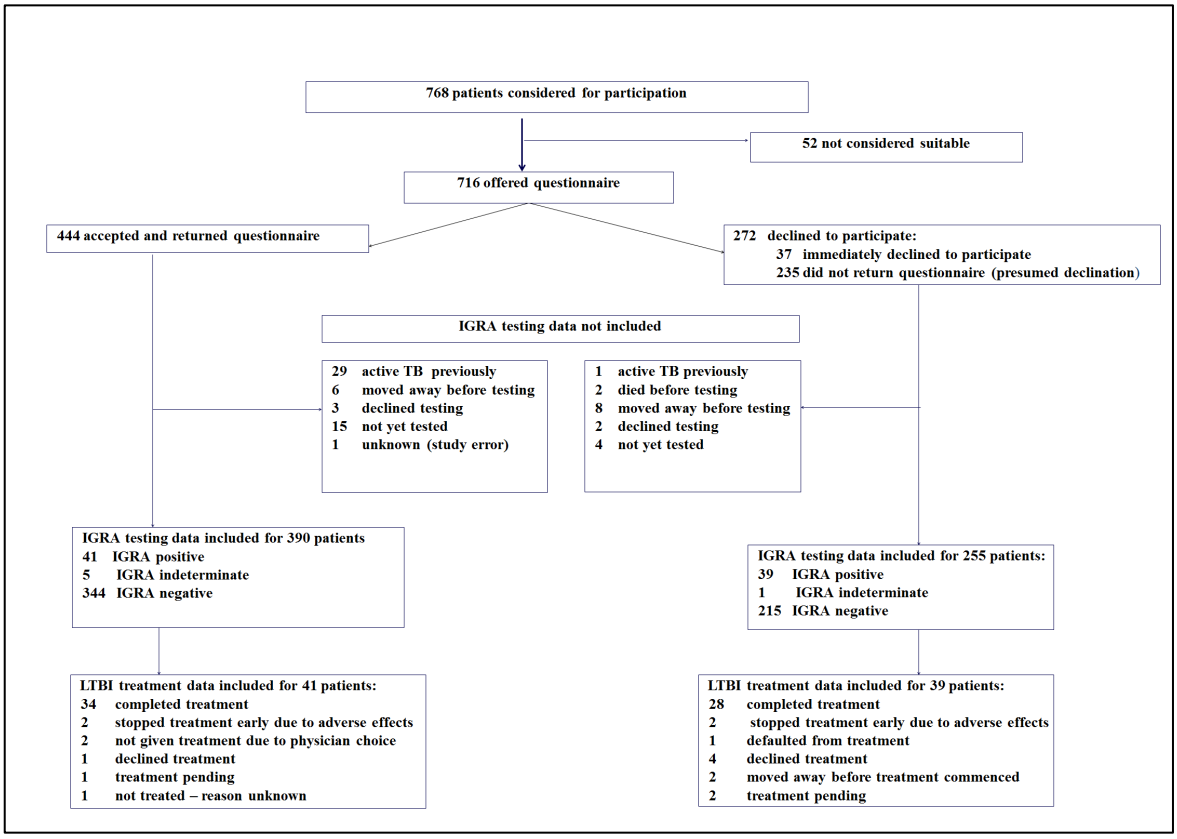
in person to a member of clinical staff. I submitted a proportionate ethics application for the study, which was granted by the National Research Ethics Service (NRES) Committee North West – Greater Manchester South (reference number 13/NW/0895).

5.3 Results

5.3.1 Response rate

768 patients were considered for participation (Figure 5.1). 52 were not suitable, and 716 were offered the questionnaire. 272/716 (38%) declined immediately, or failed to return the questionnaire and were presumed to have declined to participate. Overall 444/716 (62%) participated. 322/444 (72.5%) participated from Leicester and 122/444 (27.5%) from Coventry, but results were amalgamated for the purposes of analysis.

Figure 5.1. Flowchart of questionnaire participation and outcomes of LTBI screening and treatment



5.3.2 Demographics

Table 5.1 details the demographic data of the questionnaire respondents and non-respondents. 52.5% were black African and the cohort was relatively young, with median age 42 years. There was no significant difference between the cohorts in terms of age, sex or ethnicity.

Table 5.1. Demographics for questionnaire respondents and non-respondents

Variable	Questionnaire accepted n (%) n = 444	Questionnaire declined n (%) n = 272	p
Male sex	239 (53.8)	140 (51.5)	0.54
Median age	42	43	0.23
Ethnicity			
White	150 (33.8)	77 (28.3)	0.13
Black	234 (52.7)	163 (60)	0.06
Asian	39 (8.8)	28 (10.3)	0.5
Mixed/Other	21 (4.7)	4 (1.5)	0.02
Country of birth[1]			
Sub-Saharan Africa	249 (57.1)	-	
Europe	159 (36.5)	-	
South Asia	17 (3.9)	-	
Other	11 (2.5)	-	
Reported previous TB[2]	29 (6.5)	-	
Reported previous LTBI	0 (0)	-	
Acceptance of appropriate IGRA testing	390/393 (99.2)	255/257 (99.2)	0.95
Acceptance of LTBI treatment if LTBI diagnosed and treatment advised	36/37 (97.3)	31/35 (88.6)	0.15
Completion of treatment if LTBI treatment started	34/36 (94.4)	28/31 (90.3)	0.5

[1] 436 respondents stated their country of birth therefore this figure is used as the denominator for the country of birth figures. "Other" includes East Asia and Pacific, Latin America and Caribbean, Middle East and North Africa, and North America

[2] Excluded from IGRA testing

5.3.3 Mother tongue

430 respondents recorded their mother tongue/first language spoken at home (Table 5.2). 17 reported two mother tongues, and one respondent reported three mother tongues. There were 49 languages reported in total, the most common of which were English (193/430) and Shona (85/430). 23/49 languages were reported by only one respondent each as being their mother tongue.

Table 5.2. Mother tongue (first language) recorded by region of birth

Reported Mother tongue	Europe and Central Asia n = 157	South Asia n = 16	Sub-Saharan Africa n = 245	Other region of birth n = 10	Region of birth unknown n =2	Total numbers n = 430
Afrikaans			1			1
Akan			2			2
Arabic			2			2
Bengali	1					1
Chichewa			10			10
Chinese				1		1
Chwu (Ghanian)			1			1
Cypriot Turkish	1					1
Dutch	1					1
English	137	1	51	3	1	193
French			13			13
Greek	1					1
Gujurati	1	8	13			22
Hausa			1			1
Hindi		2				2
Igbo			1			1
Jola			1			1
Kikuyu			2			2
Kinyarwanda			1			1
Kirundi			2			2
Konkani		1				1
Krio			1			1
Lingala			1			1
Luganda	1		3			4
Luvenda			1			1
Moghamo			1			1
Ndebele			26			26
Persian				1		1
Polish	6					6
Portuguese	4	2	2			8
Punjabi		2				2
Romanian	2					2
Russian	2					2
Setswana			1			1
Shona			85			85
Shuwa-Arabic			1			1
Somali			6			6
Sotho			2			2
Spanish	1			1		2
Susu			1			1
Swahili			12		1	13
Thai				4		4
Tonga			1			1
Tigrinya			3			3
Tswana			2			2
Tumbuka			1			1
Xhosa			3			3
Yoruba			1			1
Zulu			8			8

5.3.4 Language translator

Only four respondents indicated that they had needed the assistance of a translator. The following languages were recorded; Shona (one), Punjabi (one), and Hindi/Gujurati (two). An English speaker was required by a further three respondents to help them understand and complete the questionnaire.

5.3.5 Length of time in the UK

The length of time that they had been in the UK, reported by the respondents, was categorised as per Table 5.3. The large number of respondents who did not complete this question meant that the numbers were too small to include in the univariate and multivariable analyses.

Table 5.3. Length of time in the UK as reported by the respondents

Years in UK	n	%
1-5 years	26	5.9%
6-10 years	50	11.3%
> 10 years	201	45.3%
Unknown	167	37.6%

5.3.6 Previous active TB or LTBI

29/444 (6·5%) respondents reported that they had been previously treated for active TB, although this information had not been recorded in their medical notes. These individuals were excluded from IGRA testing. No respondents indicated that they had had prior LTBI diagnosis or treatment.

5.3.7 Views about LTBI testing and intention to accept testing

The full Likert-scale questionnaire responses are in Appendix 3. Intention to accept LTBI screening was tested by the response to the first questionnaire statement, "I plan to accept a blood test for latent TB". 417/437 (95.4%) strongly agreed or agreed with this, and the

result was similar (390/408, 95.6%) when those who had already had active TB were excluded.

There was agreement that it was important to test, and important to know whether one had LTBI by 393/435 (90·3%) and 412/433 (95·2%) respectively, and a desire to know whether they had LTBI was expressed by 402/429 (93·7%). However, only 107/422 (25·4%) agreed with the statement that they were at risk of having been exposed to TB previously.

In terms of behavioural norms, there was a hierarchy in the proportions of respondents who felt that other individuals would wish them to undergo testing, ranging from 307/430 (71·4%) for their clinic doctor, to 232/427 (54·3%) for other significant individuals in their life, down to 165/428 (38·6%) for others attending the same clinic. High proportions of individuals expressed uncertainty as to whether these individuals would wish them to test. 99/424 (23·3%) felt that they would experience prejudice if they underwent testing.

There was high agreement with the concept of having control over the testing process and being able to decline the test (392/435, 90·1% and 395/434, 91% respectively).

5.3.8 Views about LTBI treatment and intention to accept treatment

Intention to accept chemoprophylaxis (if advised) was tested by the response to the twelfth questionnaire statement, "I plan to take treatment for latent TB…." and agreed to by 397/431 (92·1%). Similar to the intention to undergo testing, there was high agreement that treatment was important (415/432, 96·1%), but low agreement with the statement that they were at risk of developing active TB (101/407, 24·8%). The behavioural norms trends were similar, with the respondents agreeing that their clinic doctor, other significant individuals, and other clinic patients would wish them to receive treatment in 388/431 (90%), 318/425 (74·8%) and 233/429 (54·3%) cases respectively. Concern about prejudice was low at 90/419 (21·5%) and perceived control over treatment declination was high at 401/429 (93·5%).

5.3.9 Factors associated with intention to accept LTBI testing and treatment

Multivariable analysis (Table 5.4) of demographics showed that being female was significantly associated with an intention to accept testing whereas those from Sub-Saharan Africa or South Asia/Other region were less likely to intend to accept testing than those from Europe. Of all the questions pertaining to views that might influence the intention to accept, the only significant association was with the importance of testing to the individual.

On multivariable analysis, belief that treatment was important, being confident in the ability to take treatment and a belief that the clinic doctor would want the individual to be treated were associated with intention to accept chemoprophylaxis (Table 5.5).

Table 5.4. Univariate and multivariable regression analysis: factors associated with intention to accept LTBI screening

Variable		Expressed intent to test (%)	Unadjusted OR (Univariate analysis)	Adjusted OR2 (Multivariable analysis)	p
Age			1.03 (0.98 - 1.082)	1.06 (0.93 - 1.22)	0.34
Gender	Male	225/235 (95.74)	1	1	
	Female	192/202 (95.05)	0.85 (0.34 - 2.09)	20.63 (1.23 - 344.19)	0.04
World Bank region of birth	Europe	154/158 (97.47)	1	1	
	Sub-Saharan Africa	230/243 (94.65)	0.45 (0.14 - 1.43)	0.00230 (0.00002 - 0.27)	0.01
	South Asia and Other	27/28 (96.43)	0.70 (0.07 - 6.51)	0.00162 (0.00001 - 0.49)	0.03
Known TB contact	No	317/332 (95.48)	1 (1 - 1)	1	
	Yes	89/92 (96.74)	1.40 (0.39 - 4.95)	1.10 (0.07 - 15.8)	0.94
It is important that I have a blood test for latent TB			21.22 (7.66 - 58.78)	34.67 (4.36 - 275.71)	0.00
It is important that I know whether I have latent TB or not			9.16 (4.29 - 19.53)	1.67 (0.24 - 11.43)	0.60
I am at risk of having caught TB in the past			1.76 (1.12 - 2.78)	0.59 (0.21 - 1.63)	0.31
I want to know whether I have latent TB			7.63 (3.77 - 15.43)	2.88 (0.52 - 15.86)	0.22
My clinic doctor would expect me to be tested for latent TB			3.95 (2.37 - 6.60)	2.16 (0.53 - 8.74)	0.28
Other people attending the clinic would expect me to be tested for latent TB			2.09 (1.34 - 3.26)	0.52 (0.12 - 2.19)	0.38
I know people who would be prejudiced against me if I had a test for latent TB			1.32 (0.87 - 2.01)	2.70 (0.77 - 9.35)	0.12
Other significant people in my life would expect me to be tested for latent TB			1.98 (1.33 - 2.95)	1.58 (0.49 - 5.08)	0.44
I would feel able to tell my doctor if I did not want to have a test for latent TB			1.62 (1.05 - 2.49)	0.68 (0.08 - 5.86)	0.73
It is up to me whether or not to have a test for latent TB			1.65 (1.14 - 2.38)	1.04 (0.23 - 4.67)	0.96

Table 5.5. Univariate and multivariable regression analysis: intention to accept LTBI treatment

Variable		Expressed intent to accept treatment (%)	Unadjusted OR (Univariate analysis)	Adjusted OR2 (Multivariable analysis)	p
Age			1.01 (0.97 - 1.05)	0.97 (0.92 - 1.03)	0.40
	Male	221/234 (94.44)	1	1	
Gender	Female	176/197 (89.34)	0.49 (0.24 - 1.01)	0.91 (0.27 - 3.01)	0.89
World Bank region of birth	Europe	148/157 (94.27)	1	1	
	Sub-Saharan Africa	220/241 (91.29)	0.63 (0.28 - 1.42)	0.56 (0.15 - 2.08)	0.39
	South Asia and Other	26/27 (96.30)	1.58 (0.19 - 13.00)	1.44 (0.08 - 24.2)	0.80
	No	304/331 (91.84)	1	1	
Known TB contact	Yes	82/89 (92.13)	1.04 (0.43 - 2.47)	0.91 (0.19 - 4.29)	0.91
I am at risk of developing active TB			2.08 (1.40 - 3.10)	1.30 (0.72 - 2.33)	0.37
It is important for me to have treatment if I have latent TB			5.82 (3.22 - 10.50)	5.46 (1.92 - 15.49)	0.00
I want to have treatment for latent TB			3.31 (2.21 - 4.94)	1.89 (0.95 - 3.77)	0.07
My clinic doctor would expect me to take treatment for latent TB if she/he recommended it			4.08 (2.48 - 6.71)	3.01 (1.01 - 8.91)	0.05
Other people attending the clinic would expect me to take treatment for latent TB			1.74 (1.26 - 2.42)	0.52 (0.20 - 1.32)	0.18
Other significant people in my life would expect me to take treatment for latent TB			2.05 (1.50 - 2.79)	0.49 (0.19 - 1.23)	0.13
I know people who would be prejudiced against me if I took treatment for latent TB			1.14 (0.83 - 1.56)	1.49 (0.79 - 2.82)	0.21
I am confident that I could take the tablets every day for 6 months			5.54 (3.26 - 9.39)	6.51 (2.59 - 16.39)	0.00
Knowing the possible side effects of the tablets makes it more difficult for me to decide about taking the treatment			0.82 (0.59 - 1.13)	0.84 (0.46 - 1.52)	0.58
It is up to me to decide whether or not to have this treatment			0.92 (0.60 - 1.41)	0.76 (0.32 - 1.78)	0.54
I would feel able to tell my doctor if I did not want to have this treatment			0.91 (0.54 - 1.54)	0.27 (0.07 - 1.04)	0.06
Being pregnant or trying to get pregnant makes it more difficult for me to decide about taking the treatment (leave this question blank if not appropriate) **Females only analysed (n=75)**			0.85 (0.47 - 1.53)	-	

5.3.10 Actual LTBI testing, cascade of care and treatment uptake

Actual LTBI testing uptake was 390/393 (99·2%) of those for whom testing was appropriate and reasons for not offering testing are listed in Figure 5.1. Overall, only 3/444 (0·68%) questionnaire respondents declined IGRA testing and had answered the question about planned intention to accept LTBI screening as Agree, Uncertain, and Disagree, respectively.

Respondents and non-respondents to the questionnaire did not differ in terms of the proportion of each who accepted LTBI testing (p=0·9483) (Table 5.1).

41/390 (10·5%) respondents who were IGRA screened had a positive IGRA and 40/41 (97·5%) were diagnosed with LTBI after clinical and radiological assessment (Figure 5.1). It was unclear why the final patient was not assessed or offered treatment. 2/40 (5%) were not considered appropriate for treatment by their physician but all the others were offered treatment. One declined and had answered the questionnaire about planned intention to accept chemoprophylaxis as Strongly Disagree.

Questionnaire respondents and non-respondents did not differ in terms of the proportion who accepted LTBI treatment (if they were advised to do so by their treating clinician), or those who successfully completed treatment (p=0·15 and p=0·5 respectively) (Table 5.1).

5.3.11 Factors associated with actual LTBI testing and treatment uptake

Acceptance of LTBI testing was not significantly influenced by any demographic factor, and there was no association with any questionnaire responses (Table 5.6). The numbers who accepted and completed chemoprophylaxis were too small to enable any meaningful regression analysis to be conducted.

Table 5.6. Univariate and multivariable regression analysis: factors associated with actual acceptance of LTBI screening

Variable		Tested (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p
Age			1.02 (0.98 - 1.06)	1.03 (0.98 - 1.08)	0.16
Gender	Male	215/227 (94.71)	1	1	
	Female	175/188 (93.09)	0.75 (0.33 - 1.68)	0.75 (0.22 - 2.48)	0.64
World Bank region of birth	Europe	146/156 (93.59)	1	1	
	Sub-Saharan Africa	215/225 (95.56)	1.47 (0.59 - 3.62)	2.39 (0.66 - 8.57)	0.18
	South Asia and Other	22/26 (84.62)	0.37 (0.10 - 1.30)	0.86 (0.14 - 5.20)	0.88
Known TB contact	No	299/319 (93.73)	1	1	
	Yes	79/84 (94.05)	1.05 (0.38 - 2.90)	1.04 (0.26 - 4.16)	0.95
I plan to accept a blood test for latent TB			1.72 (1.04 - 2.83)	0.87 (0.31 - 2.43)	0.80
It is important that I have a blood test for latent TB			1.72 (1.07 - 2.75)	0.80 (0.25 - 2.55)	0.71
It is important that I know whether I have latent TB or not			2.04 (1.22 - 3.40)	1.32 (0.44 - 3.93)	0.61
I am at risk of having caught TB in the past			1.25 (0.83 - 1.88)	0.87 (0.49 - 1.55)	0.66
I want to know whether I have latent TB			2.41 (1.50 - 3.84)	1.50 (0.62 - 3.60)	0.36
My clinic doctor would expect me to be tested for latent TB			1.77 (1.17 - 2.66)	1.83 (0.91 - 3.65)	0.09
Other people attending the clinic would expect me to be tested for latent TB			1.31 (0.89 - 1.92)	0.97 (0.49 - 1.90)	0.93
I know people who would be prejudiced against me if I had a test for latent TB			1.20 (0.83 - 1.74)	1.03 (0.63 - 1.67)	0.90
Other significant people in my life would expect me to be tested for latent TB			1.36 (0.96 - 1.92)	1.05 (0.61 - 1.80)	0.85
I would feel able to tell my doctor if I did not want to have a test for latent TB			1.33 (0.86 - 2.03)	0.93 (0.44 - 1.99)	0.87
It is up to me whether or not to have a test for latent TB			1.55 (1.09 - 2.21)	1.49 (0.91 - 2.45)	0.11

5.3.12 Comments from respondents

69 individuals wrote comments in the free text box, which were grouped into themes (Appendix 4). 33 comments were supportive of testing and treatment; 12 indicated a desire for more information on some aspect of LTBI diagnosis or management; and 20 were comments of a general nature, mostly describing personal health experiences. Only four comments were not supportive of testing or treatment.

5.4 Discussion

The objective of this study was to explore in detail the intentions of PLWH towards accepting testing and treatment for LTBI. The results indicate that LTBI screening and treatment is highly acceptable to PLWH in the UK, thereby underpinning the expansion of LTBI screening and treatment as an important public health intervention across the UK, Europe and beyond, in order to reduce TB-associated morbidity and mortality in this high-risk population. I have previously demonstrated that there is currently limited LTBI screening occurring amongst PLWH in the UK (121). This is the first study to examine these issues in any real detail, although a range of LTBI chemoprophylaxis acceptance rates of between 17-87% in PLWH have been reported from elsewhere in the UK and other low TB incidence countries (75, 82, 102).

In this cohort, LTBI testing and chemoprophylaxis uptake was very high. Over 99% of questionnaire respondents accepted IGRA testing, and over 94% of those who were consequently diagnosed with LTBI and for whom chemoprophylaxis was recommended, successfully completed treatment. I have demonstrated that operationalising this screening is feasible as part of routine care in the UK, and that it is possible to do this without sustaining the losses noted by others during the cascade of care for LTBI screening and treatment (147).

It is likely that there were multifactorial reasons behind these results, including the fact that all patients were attending regular follow-up in our clinics, screening had been integrated into clinical pathways, and many of our HIV clinicians are infectious diseases clinicians experienced in TB and LTBI management. It is important that all

HIV clinicians receive training in the diagnosis and treatment of LTBI as part of the expansion of screening, especially in areas where HIV care is predominantly provided by genitourinary medicine physicians, who may have less clinical experience in tuberculosis.

Interestingly, 6% of individuals reported having had active TB previously, although this information was not documented in their medical notes. Almost all had had treatment for TB overseas, prior to their arrival in the UK. This serves to highlight the importance of ensuring that a complete medical history is taken by clinics at the point of initiating care of PLWH, in order to avoid unnecessary IGRA testing or inappropriate treatment.

I did not find that the intention to accept screening was influenced by subjective norms, including fear of prejudice, although this has been a concern reported previously (100), or by perceived control over the testing process. Modern approaches to care in terms of shared decision-making between clinicians and patients may influence the latter. Perceived risk of having been exposed to TB, or desire to know whether they had LTBI, did not influence the intention to accept testing either, but instead, it was the perception that the testing process was inherently important. This was also replicated in the intention to accept chemoprophylaxis results. Whether this stems from a true belief that TB is an important disease, or simply because information in the form of the study materials had been provided to them, is unknown. It is notable that relatively low proportions of respondents felt that they were at risk of having been exposed to TB, or of developing active TB, despite this being a well-known risk in HIV infection (35, 42, 48).

Women were more likely to express an intention to undergo IGRA testing in the multivariable model, although this was not replicated in the analyses of acceptance of testing, or intention to accept treatment, in which there was no sex discrepancy.

When it came to actually accepting IGRA testing, there appeared to be no specific influencing factors, as none of the psychological attribute questions, or demographic factors, significantly correlated with testing acceptance. There may well be some other, unexplored influence, such as the personal interaction with a clinician. Particularly

interesting are those individuals from Sub-Saharan Africa, and South Asia, who, in the multivariable analysis, were statistically less likely to express an intention to accept testing than those from other regions despite their high risk of having been exposed to TB. However, by the time of testing, there was no discrepancy, and a further qualitative study would be interesting, examining whether, and why, attitudes towards accepting LTBI screening alter after the clinical encounter. Any gender differences could also be explored, particularly as other psychological research indicates that further exploration is needed into why men may accept health interventions less frequently than women (148).

Self-belief in the ability to take LTBI treatment was one of the only factors significantly correlated with the intention to accept chemoprophylaxis. Over 95% of our HIV cohort is virologically suppressed on HAART and therefore ability to adhere faithfully to daily tablet treatment is already tried and tested. Although increasing number of daily medication doses has negatively influenced adherence in other studies (149), I demonstrated that over 94% of those given LTBI chemoprophylaxis did complete treatment. The only two individuals who did not complete chemoprophylaxis developed adverse effects from treatment that necessitated cessation. This suggests that PLWH who are offered LTBI treatment are confident and motivated in their adherence to medication and is an important point to consider when contemplating systematic screening.

One of the weaknesses of this study was that it only included individuals from two centres in the UK. Over half were from sub-Saharan Africa, although other respondents were from a diverse range of cultural backgrounds. It is possible that slightly different results may have been obtained if I had extended the questionnaire to other HIV centres, either nationally or internationally. The patient literature and questionnaire was written as simply as possible in English, in keeping with guidance from the NHS (150) and the National Institutes of Health (NIH) (151). The latter guidance recommends patient material should be written within the 7-8th reading grades, which I achieved as evidenced by the Flesch-Kincaid scores. I could potentially have had the questionnaire translated into different languages in order to make it easier for individuals to complete. That said, only 7/444 (1.6%) respondents indicated that they had required a translator of any kind.

There was an overall response rate of 62% to this questionnaire research, and evidence indicates that response rates may be increased through the use of digital questionnaires, small monetary incentives, provision of a pre-notification letter about the forthcoming questionnaire, and a reminder (152-154). The initial return rates of the questionnaire was much lower for those individuals who had the questionnaire sent to their home address, and indicates that this cohort of patients may respond best to being approached directly by a member of clinical staff at the time of attending for their routine follow-up appointments. Even though the questionnaire was anonymised, some individuals may have felt uncomfortable posting back a questionnaire dealing with potentially sensitive topics such as HIV and TB. Nevertheless, there were no significant differences in terms of acceptance of screening and treatment between the cohorts of questionnaire respondents and non-respondents, thus suggesting that this study cohort is representative of PLWH who attend for care at our centres.

5.5 Conclusions

In summary, I have demonstrated that LTBI screening and treatment is viewed positively by PLWH in the UK and that this positive intention translates to high levels of screening and chemoprophylaxis completion rates. This has important consequences for public health, and clinical teams implementing more widespread LTBI screening programmes in low TB burden countries. The perception of LTBI as being an important condition was evident in this research, but these attitudes may be influenced further by interaction with health professionals and would be an interesting area to pursue in future research.

Chapter 6. Programmatic latent tuberculosis infection screening and treatment of the HIV cohort in Leicester, UK

6.1 Introduction

The cohort data in Chapter 4 demonstrated the high risk of incident TB in PLWH, and the national survey showed for the first time that there was no widespread LTBI programmatic screening occurring in the UK amongst PLWH (121). I further demonstrated in Chapter 5 that screening and treatment is highly acceptable to this population, thereby supporting the current national and international guidelines that recommend screening in PLWH in low TB incidence countries such as the UK (55, 60, 139, 140). However, there is little previous 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 (67, 102), contained estimated data (68), or included fairly low numbers of patients (67, 82). In these cohorts, LTBI has been diagnosed in around 7-10% screened individuals (68, 82, 102).

Since this research started in 2014, several guidelines for LTBI screening in PLWH have been revised. The updated 2018 BHIVA guidance recommends offering 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 which are listed in the guidance (139). In contrast, the updated 2016 NICE guidance (55), the 2019 European Centre for Disease Control (ECDC) guidance for use in the European Union and European Economic Area (60), and the WHO guidelines for low tuberculosis burden countries (140) all recommend that all PLWH should be targeted for LTBI screening.

Only ad hoc LTBI screening amongst PLWH had been occurring in Leicester since the introduction of IGRA tests in the early 2000s. I therefore took a pragmatic approach and undertook to prospectively screen all remaining active patients in our HIV cohort

for LTBI, irrespective of ethnicity, country of birth, age, sex or co-morbidities. The aim was to produce data that could later be used to undertake a health economic analysis in order to try and determine which groups should be targeted for systematic screening on an ongoing basis and to establish which, if any, of the existing guidelines should be followed.

6.2 Methods

6.2.1 Study design and setting

This prospective LTBI screening programme was undertaken in the Leicester HIV cohort as described in Chapter 4. Leicester has amongst the highest rates of TB in the UK, with an average annual rate in the general population of 37.4/100,000 population over the years 2015-2017 (11). Rates of incident TB in our HIV cohort in Chapter 4 were found to be 4.47/1000 person years.

6.2.2 Study population and participants

Active HIV positive patients listed in the created database from Chapter 4 were used as the starting point for determining who should be screened prospectively (2014 onwards), or whose previous IGRA screening results (pre-2014) should be included in the results. Exclusion criteria were; those who had had active TB previously, irrespective of timing in relation to HIV diagnosis; those who had died without being screened; those who had moved away from Leicester or were lost to follow-up without being screened; those who had been treated for LTBI prior to their HIV diagnosis; those who had been treated for LTBI without an IGRA test being performed; those who had been treated for LTBI abroad.

6.2.3 Ethics and other approvals

No ethics approval was required as this was considered to be implementation of clinical care in line with national recommendations, and the cost of IGRA testing was borne by the HIV department. However, the proposal was submitted to, and approved by, the UHL Trust TB Board, and the UHL HIV department.

Approval was also gained from the UHL Microbiology department, since the implementation of mass screening would dramatically increase their workload in terms of processing QuantiFERON-TB® tests. The Immunology department were approached in November 2014 and asked whether it would be possible to increase the number of T-SPOT®.*TB* tests performed each week, from the eight offered at the start of screening in 2014, but declined. There was therefore competition with other areas of the hospital for T-SPOT®.*TB* testing throughout the screening period, and the number of available tests further decreased to five in 2016 due to laboratory staffing issues.

6.2.4 Methods of screening for LTBI

QuantiFERON-TB® Gold In-Tube Test (QFN-GIT) and T-SPOT®.*TB* tests had both been available in Leicester prior to 2014. The choice of tests utilised for the ad hoc LTBI screening in the HIV cohort that occurred prior to 2014 was dependent on physician choice.

QFN-GIT was the QuantiFERON-TB® in use in Leicester at the start of the systematic screening in 2014. This was phased out and replaced by QuantiFERON-TB® Gold Plus (QFT-Plus), between May 2016 – January 2017, with local verification demonstrating comparable results between the two (Hemu Patel, personal communication (155)). There was a cross-over period when both tests were in use.

QuantiFERON-TB® testing was predominantly used alone for those with CD4 counts ≥200, and T-SPOT®.*TB* tests in conjunction with QuantiFERON-TB® tests for those with CD4 counts <200 although there was occasional variation. Where possible, concomitant tests were performed on the same day. Occasionally, due to logistics, they were performed on different days, in which case a cut-off of 14 days was used when classifying them as having occurred concomitantly.

In the same way as I had for the patient questionnaire study, I scrutinised the clinic lists in advance and checked the medical notes of each patient due to attend clinic (to exclude those who had had active TB or LTBI previously, and those who had already had LTBI

screening). I placed IGRA kits in the notes, in order to prompt the clinician to offer testing in clinic and booked T-SPOT®.*TB* tests in advance with the immunology department.

6.2.5 Classification of IGRA results

Cut-off values for both tests reported by the manufacturers were used as the definition for positive or negative results.

The overall test result was classed as IGRA positive if; a sole IGRA, or both IGRA tests were positive in the event of two concurrent tests; or in the event of two concurrent tests, one was positive and one was negative. IGRA negative results were reported if a sole IGRA or two concurrent IGRA tests were negative. In the event of an indeterminate test, it was planned to ascertain why the IGRA was indeterminate and reach an overall decision based on this information, and the results of any other IGRA test, if performed.

The nearest previous CD4 count to the IGRA tests was used as the CD4 count classification at the time of the test. Individuals who had CD4 counts performed more than a year or so prior to the planned time of IGRA testing had testing withheld until a more recent CD4 count was available, in order to better inform the results.

6.2.6 Management of positive IGRA tests

I obtained each IGRA result and placed a sticker in the medical notes where IGRA results were positive to remind the clinician to exclude active TB and offer chemoprophylaxis, where appropriate, at the next appointment. The final decision about whether an individual had LTBI lay with the treating consultant and was made following clinical and radiological review. Six months of isoniazid was agreed by the HIV department at the start of the screening process to be the treatment of choice for individuals in receipt of HAART although individual clinicians made the final decision based on their own preferences.

The patient information leaflet created for the cohort questionnaire study was available in all clinic rooms for use in discussion with patients about screening and treatment.

6.2.7 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 Fishers exact test if appropriate). All statistical tests were considered significant when the p-value was ≤0.05. Logistics regression analysis was used to determine univariate and multivariable factors associated with IGRA positivity. All data were analysed using Stata v15.1 (StataCorp, Texas, USA).

6.2.8 Cost evaluation

A formal cost-effectiveness analysis was outside of the scope of this research. However, costs that took pathways of care into consideration, were calculated in order to compare different LTBI screening models. The following costs were used; local IGRA cost for each patient screened (£40); local chest X-ray cost for LTBI positive patient (£24); physician assessment at IGRA positive result and halfway through treatment and at the end of treatment (£134 each visit) (156); six months of isoniazid and pyridoxine treatment per patient provided VAT-free by outpatient pharmacy (£218.93); liver function test monitoring per patient (£2.18); local cost of one visit by TB nurses per patient (£89.52). The number of patients treated under each model took into account any cases of LTBI identified in this study who did not have chemoprophylaxis.

For the cost analysis, the number of patients who would have been screened in this cohort using the BHIVA guideline was inflated by 5% to take account of the fact that there would probably be additional patients from the countries where TB incidence <40/100,000 population, who had risk factors listed in the BHIVA guidance which would make them eligible for screening (139). These risk factors had not been collected prospectively since this study commenced in 2014, some years before the BHIVA guidance was amended.

6.3 Results

6.3.1 Uptake of screening

From a total cohort of 2158 patients who had ever been treated for HIV in Leicester, 966/2158 (44.8%) were excluded from screening based on the pre-defined exclusion criteria (Figure 6.1). The remaining 1192 patients were eligible for screening. 17/1192 (1.4%) patients were still untested at the end of this study on 1st March 2019. 8/1192 (0.7%) patients declined screening. Neither the untested patients nor the patients who refused screening have had their results included in any further analyses. This left 1167 patients who underwent LTBI screening.

6.3.2 Demographics

The demographics of the total cohort who were screened with an IGRA are shown in Table 6.1. 670/1167 (57.4%) were male. The median age at IGRA testing was 42 (IQR 36- 48), and median CD4 count was 510 (IQR 340- 680). Only 94/1167 (8%) were tested at a CD4 count of less than 200 cells/mm^3.

The dominant ethnic group were black Africans, who comprised 568/1167 (48.7%) of the cohort. The next largest ethnic group were white individuals (415/1167, 35.6%), followed by South Asians (104/1167, 8.9%). Similarly, 605/1167 (51.8%) were from sub-Saharan Africa, 450/1167 (38.6%) from Europe/Central Asia and 53/1167 (4.5%) from South Asia.

13/1167 (1.1%) had been diagnosed with HIV in the 1980s, and 74/1167 (6.3%) had been diagnosed in the 1990s.

Figure 6.1. LTBI screening and treatment cascade of care

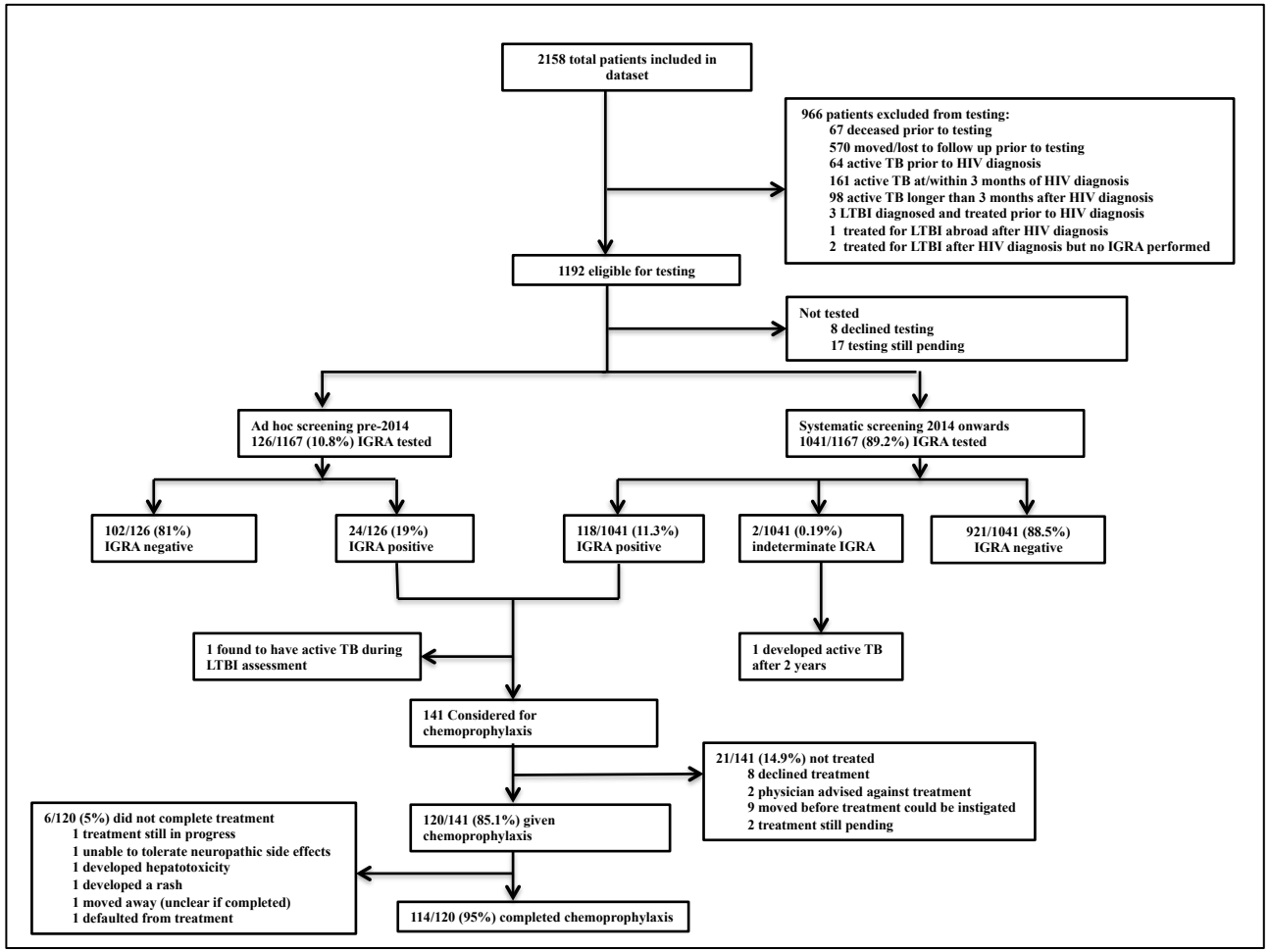


Table 6.1. Description of total cohort and those who were IGRA positive

Variable	Total screened cohort n (%) n = 1167	Proportion IGRA positive/total screened n (%) n = 142
Male gender	670 (57.4)	68 / 670 (10.1)
Female gender	497 (42.6)	74 / 497 (14.9)
Median age at IGRA testing (IQR)	42 (36 - 48)	42 (38 - 48)
Ethnicity		
Black African	568 (48.7)	107 / 568 (18.8)
South Asian	104 (8.9)	20 / 104 (19.2)
White	415 (35.6)	11 / 415 (2.7)
Mixed	17 (1.5)	0 (0)
Black Caribbean	16 (1.4)	1 /16 (6.3)
Black Other	10 (0.9)	0 (0)
Other	36 (3.1)	3 /36 (8.3)
Unknown	1 (0.1)	0 (0)
UK birth status		
UK born	384 (32.9)	11 (2.9)
Non-UK born	774 (66.3)	130 (16.8)
Unknown	9 (0.8)	1 (11.1)
Region of birth		
Sub-Saharan Africa	605 (51.8)	113 / 605 (18.7)
South Asia	53 (4.5)	8 / 53 (15.1)
Europe & Central Asia	450 (38.6)	16 / 450 (3.6)
East Asia & Pacific	25 (2.1)	3 / 25 (12)
Latin America & Caribbean	15 (1.3)	1 / 15 (6.7)
Middle East & North Africa	6 (0.5)	0 (0)
North America	4 (0.3)	0 (0)
Unknown	9 (0.8)	1 / 9 (11.1)
TB incidence in country of birth		
<50/100,000 population	471 (40.4)	17 / 471 (3.6)
50 - 149/100,000 population	65 (5.6)	14 / 65 (21.5)
150 – 249/100,000 population	481 (41.2)	88 / 481 (18.3)
250-349/100,000 population	70 (6)	12 / 70 (17.1)
≥ 350/100,000 population	71 (6.1)	10 / 71 (14.1)
Unknown	9 (0.8)	0 (0)
Year of HIV diagnosis		
1985[1] – 1989	13 (1.1)	3 /13 (23)
1990 – 1999	74 (6.3)	3 / 74 (4.1)
2000 – 2009	691 (59.2)	91 / 691 (13.2)
2010 – 2017[2]	389 (33.3)	45 / 389 (11.6)
Year of IGRA testing		
2003[3] – 2004	1 (0.1)	1 / 1 (100)
2005 - 2009	79 (6.8)	11 / 79 (13.9)
2010 – 2014	430 (36.8)	51 / 430 (11.9)
2015 - 2019[4]	657 (56.3)	79 / 657 (12)

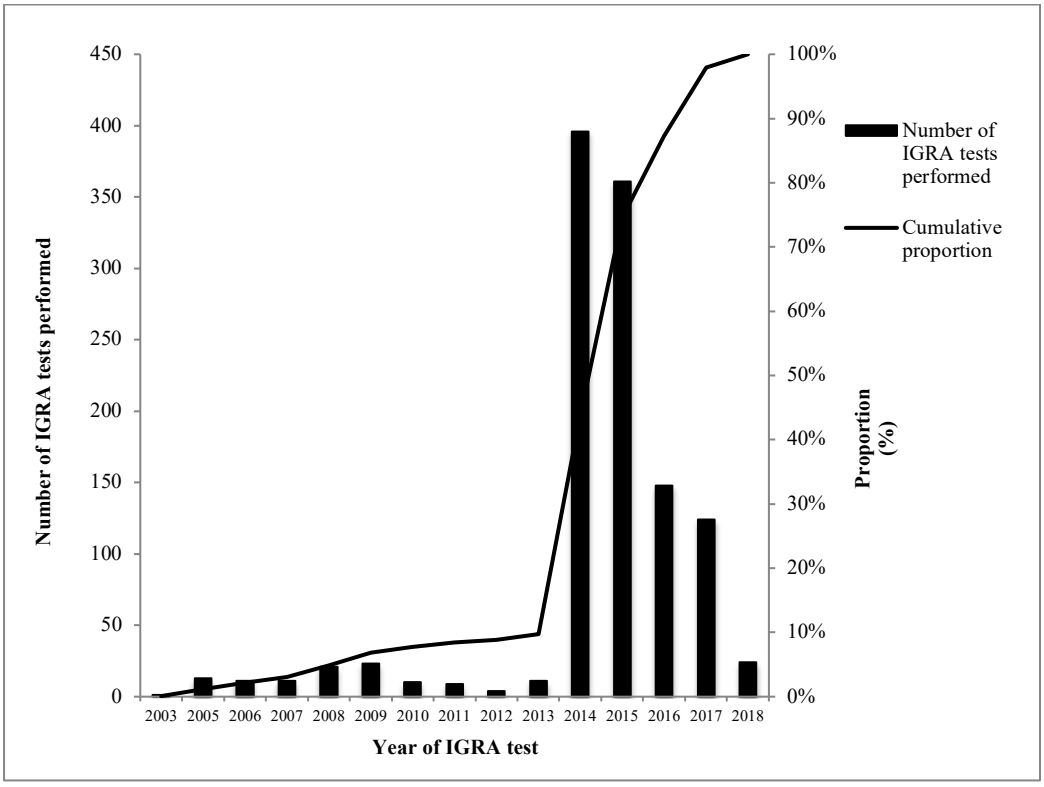
Variable	Total screened cohort n (%) n = 1167	Proportion IGRA positive/total screened n (%) n = 142
CD4 count at IGRA testing (cells/mm^3)		
Median (IQR)	510 (340 - 680)	530 (425 - 720)
Range	0 - 2260	90 - 1350
<50	25 (2.1)	0 (0)
51-99	25 (2.1)	1 /25 (4)
100-199	44 (3.8)	3 /25 (12)
200-349	211 (18.1)	18 / 211 (8.5)
350-499	266 (22.8)	41 / 266 (15.4)
>500	594 (50.9)	77 / 594 (13)
Unknown	2 (0.2)	2 / 2 (100)
Type of IGRA performed		
QuantiFERON-TB® tests[5] alone	1086 (93.1)	129 / 1086 (11.9)
QuantiFERON-TB® tests[5] & T-SPOT®.*TB*	27 (2.3)	2 / 27 (7.4)
T-SPOT®.*TB* alone	54 (4.6)	11 / 54 (20.4)

IQR = Interquartile range
[1]1985 was the earliest year in which a patient was diagnosed with HIV.
[2] Individuals were included up and including to 30th June 2017.
[3] 2003 was the earliest year in which a patient had an IGRA test.
[4]1st March 2019 was used as the cut-off for IGRA testing.
[5] QuantiFERON-TB® GIT or QuantiFERON-TB® Plus

6.3.3 Temporal changes in IGRA testing

Figure 6.2 shows the temporal changes in IGRA testing. The majority of tests were undertaken in 2014 and 2015 when this study began.

Figure 6.2. Temporal changes in IGRA testing



6.3.4 Positive IGRA results and LTBI diagnosis

Combining positive IGRA results from the ad-hoc screening which had occurred pre-2014, and those from the systematic screening programme from 2014 onwards, 142/1167 (12.2%) PLWH were classified as having a positive IGRA result (Figure 6.1 and Table 6.1). Overall, 130/774 (16.8%) of total non-UK born individuals were IGRA positive, in comparison to only 11/384 (2.9%) of UK-born individuals ($p<0.0001$). 113/142 (79.6%) were from sub-Saharan Africa. Only 17/471 (3.6%) patients from a country where the TB incidence was <50/100,000 population had a positive IGRA.

All patients 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 but with a detectable HIV viral load of 182 copies/ml. He had been a household contact of his partner who had had smear positive pulmonary TB. The patient complained of vague sweating symptoms, but had

no respiratory symptoms. A CT thorax revealed non-specific pulmonary nodules and small volume axillary lymphadenopathy, and he underwent a broncho-alveolar lavage which was culture positive for MTb.

6.3.5 Factors associated with positive IGRA screening results

Univariate and multivariable logistics regression analyses were undertaken to establish associations with a positive IGRA test (Table 6.2). The regions of birth were collapsed due to small numbers, or no patients, in some regions. Ethnicity, UK birth status, and region of birth, were all closely linked to the incidence of TB in the country of birth, and were not taken forward into the multivariable analysis.

Year of HIV diagnosis, age at IGRA testing and gender were not associated with IGRA positivity in either the univariate or multivariable analysis. The univariate model showed that being born abroad, and specifically in sub-Saharan Africa and the South Asia and East Asia & Pacific regions, and being of black African or South Asian ethnicities, were all factors significantly associated with having a positive IGRA. In the multivariable analysis, the association with TB incidence in the country of birth which was noted as significant in the univariate model, was confirmed, as there was a significantly increased risk of having a positive IGRA, amongst individuals born in countries where the TB incidence was >50/100,000 population.

Table 6.2. Univariate and multivariable logistics regression for having a positive IGRA test at LTBI screening

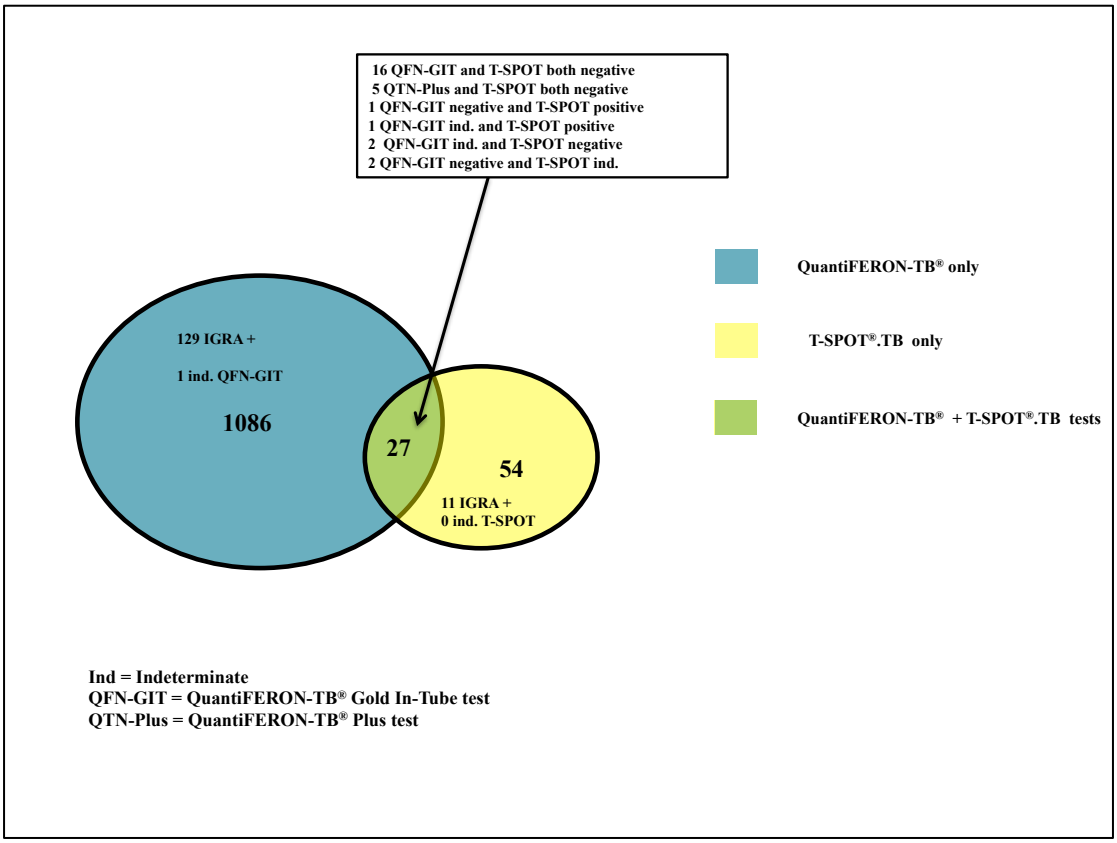
Variable		Observation (%)	Unadjusted OR (Univariate analysis)	p value	Adjusted OR2 (Multivariable analysis)	p value
Age at IGRA test			1.01 (0.99 – 1.02)	0.49	1.01 (0.99 – 1.03)	0.29
Year of HIV diagnosis			0.99 (0.96 – 1.02)	0.49	0.997 (0.96 – 1.04)	0.88
Gender	Male	68/142 (47.9)	1		1	
	Female	74/142 (52.1)	1.55 (1.09 – 2.2)	0.01	0.94 (0.64 – 1.37)	0.74
CD4 count at IGRA test			1.00 (1.00-1.00)	0.03		
Ethnicity	Black[1]	108/142 (76.1)	1			
	South Asian	20/142 (14.1)	1.07 (0.63 – 1.82)			
	White	11/142 (7.7)	0.12 (0.06 – 0.23)			
	Other	3/142 (2.1)	0.26 (0.08 – 0.86)	<0.0001		
UK birth status	Non-UK born	130/142 (91.5)	1			
	UK born	11/142 (7.7)	0.15 (0.08 – 0.27)			
	Unknown	1/142 (0.7)	0.62 (0.08-4.99)	<0.0001		
World Bank region of birth	Europe & Central Asia, North America and Latin America & Caribbean and Middle East & North Africa[2]	17/142 (12)	1			
	South Asia and East Asia & Pacific[3]	11/142 (7.7)	4.42 (1.99 – 9.85)			
	Sub-Saharan Africa	113/142 (79.6)	6.19 (3.66 – 10.47)			
	Unknown	1/142 (0.7)	3.37 (0.4 – 28.47)	<0.0001		
TB incidence in country of birth	<50/100,000 population	17/141 (12.1)	1		1	
	50 - 149/100,000 population	14/141 (9.9)	7.33 (3.41 – 15.73)		7.91 (3.63 – 17.23)	
	150 – 249/100,000 population	88/141 (62.4)	5.98 (3.5 – 10.22)		6.24 (3.56 – 10.93)	
	250 – 349/100,000 population	12/141 (8.5)	5.53 (2.51 – 12.15)		5.54 (2.49 – 12.32)	
	≥ 350/100,000 population	10/141 (7.1)	4.38 (1.92 – 10)	<0.0001	4.47 (1.93 – 10.31)	<0.0001

[1] 107 were Black African. One was Black Caribbean
[2] 16/142 were from Europe & Central Asia; 1/142 was from Latin America & Caribbean; none were from North America or the Middle East & North Africa
[3] 8/11 were from South Asia; 3/11 were from East Asia & Pacific region

6.3.6 Indeterminate IGRA results

Four patients (4/1027, 0.39%) had an indeterminate QFN-GIT test. Two patients (2/81, 2.5%) had an indeterminate T-SPOT®.*TB* test and no patients had an indeterminate QFT-PLUS test (Figure 6.3).

Figure 6.3. Venn diagram showing results of IGRA testing by type of test



A final classification was applied to each patient after considering the reason for the indeterminate test and any concomitant or subsequent test using a different IGRA (Table 6.3). For the purposes of analysis, indeterminate results were amalgamated with IGRA negative results.

Table 6.3. Indeterminate IGRA testing and clinical classification of patients

QuantiFERON-TB® test result	T-SPOT®.*TB* test result	Time period between tests	Nearest CD4 count to IGRA testing	Final classification	Clinical outcome
Indeterminate due to negative mitogen result	Positive	14 days (QFN first)	110	IGRA positive	Accepted chemoprophylaxis
Indeterminate due to negative mitogen result	Patient declined test	-	840	IGRA indeterminate	Watch and wait
Indeterminate due to negative mitogen result	Negative	8 days (QFN first)	100	IGRA negative	Watch and wait
Indeterminate due to mitogen result below threshold	Negative	14 days (QFN first)	240	IGRA negative	Watch and wait
Negative	Indeterminate due to severe lymphopaenia/ insufficient cells	0 days	60	IGRA indeterminate	Watch and wait – patient developed active TB 2 years later
Negative	Indeterminate due to positive control failure	0 days	130	IGRA negative	Watch and wait

QFN = QuantiFERON-TB®

6.3.7 Dual QuantiFERON-TB® and T-SPOT®.TB testing

27/1167 (2.3%) patients had concomitant QuantiFERON-TB® and T-SPOT®.TB testing (Figure 6.3). 21/27 (77.8%) of these were tested when their CD4 count was <200 cells/mm^3 and the remaining 6/27 (22.2%) were tested when their CD4 count was between 200-349 cells/mm^3. Two patients with dual testing had LTBI. The first had an indeterminate QFN-GIT due to a negative mitogen result and positive T-SPOT®.TB as detailed above, with a CD4 count of 100. The second had a negative QFN-GIT but positive T-SPOT®.TB at a CD4 count of 290. The numbers of patients having dual IGRA testing were too low to perform any concordance analysis. However, the range of CD4 counts at which both QuantiFERON-TB® and T-SPOT®.TB were concomitantly negative was 30-270 cells/mm^3.

6.3.8 Thresholds for TB incidence in country of origin and yield of IGRA positive results

The outcome of IGRA screening stratified by the TB incidence in the country of birth is shown in Table 6.4. All of the IGRA positive results in the TB incidence group 50-150/100,000 population occurred in individuals from sub-Saharan African countries. If screening was set at a threshold of including all those from countries where the TB incidence was >150/100,000, in addition to sub-Saharan African countries which have a lower TB incidence level, then 87.9% of all IGRA positive results would be diagnosed. In order to identify the remaining 12.1% of cases, the number of PLWH screened would need to increase by 69%, from 687 to 1158 patients. At this level, a significantly higher proportion of IGRA positive cases (as a proportion of those tested) would be identified than if the total cohort were screened ($p<0.0001$).

Table 6.4. Yield and percentage of IGRA positive results obtained by implementing LTBI screening at different TB incidence thresholds

Incidence of TB in country of birth	Number to be screened[1]	Proportion of total cohort to be screened (%)	Number IGRA positive[1]	Yield at that incidence level (proportion of those tested)	% IGRA positives identified if threshold set at this level
>350/100,000	71	6.1	10	14.1	7.1
>250/100,000	141	12.2	22	15.6	15.6
>150/100,000	622	53.7	110	17.7	78
>150/100,000 plus Sub-Saharan African countries	670	57.9	124	18.5	87.9
>50/100,000	687	59.3	124	18	87.9
Screen all[1]	1158	100	141	12.2	100

[1] Nine patients in the total cohort and one patient in the IGRA positive cohort were excluded as the country of birth was unknown

6.3.9 Application of different existing screening guidelines to this cohort

Patients from this study with a positive IGRA who were born in a country where the TB incidence was <40/100,000 population had their medical notes examined further to identify any additional risk factors which would have made them eligible for screening using the BHIVA guidance (139). These patients are detailed in Table 6.5. 7/17 (41.2%) had risk factors.

Table 6.5. Patients from countries with low TB incidence who have a positive IGRA, with additional LTBI risk factors as detailed in BHIVA guidelines

Patient	Country of birth	TB incidence level in country of birth / 100,000 population	Additional risk factor as detailed in BHIVA guidelines
1	Grenada	2.3	Injecting drug use
2	UK	8.9	TB exposure as a child (father)
3	UK	8.9	TB exposure (father, brother)
4	UK	8.9	Possible TB exposure (cousin died of anorexia and a respiratory illness)
5	UK	8.9	Prolonged stays in India; previous injecting drug use
6	UK	8.9	No risk factors
7	UK	8.9	No risk factors
8	UK	8.9	No risk factors
9	UK	8.9	No risk factors
10	UK	8.9	No risk factors
11	UK	8.9	No risk factors
12	UK	8.9	No risk factors
13	France	9	No risk factors
14	Portugal	20	Recent TB exposure in a homeless hostel; Injecting drug use
15	Portugal	20	Injecting drug use
16	Portugal	20	No risk factors
17	Portugal	20	No risk factors

Table 6.6 compares the current UK and international guidelines which exist for LTBI screening in PLWH in low incidence TB countries, and details how many patients with LTBI from this current cohort would have been diagnosed as such if each guideline was followed. For comparison there is a threshold identified from this study of screening including all those born in a country where the TB incidence is >150/100,000 population in addition to those from any other sub-Saharan Africa country (the "Leicester model".

Table 6.6. Yield and percentage of IGRA positive results obtained by implementing LTBI screening using different guidelines

Guideline used	Number screened	Number IGRA positive	Yield (proportion of those tested)	% total IGRA positives identified (n=141)
This study (Leicester model): Patients from countries with TB incidence >150/100,000 population plus other Sub-Saharan Africa countries	670	124	18.5	87.5
2016 NICE guidelines (55)[1,2]	1158	141	12.2	100
ECDC guidelines for the European Union/European Economic Area (60)[1,2]	1158	141	12.2	100
WHO guidelines for low tuberculosis burden countries (140)[2]	1158	141	12.2	100
2018 BHIVA guidelines[3] (139)	698[4]	131	18.8	92.9

[1] These guidelines all mention dual use of IGRA/Mantoux testing in some, or all PLWH. Assumption made in this table that IGRA is as effective at diagnosing LTBI than Mantoux

[2] Recommends screening all PLWH

[3] 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 which are listed in the guidance

[4] This figure is an underestimate (includes all patients from countries where TB ≥40/100,000 population; plus 7 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)

Compared to the NICE, ECDC and WHO guidelines, using the Leicester model would lead to a significantly higher positivity rate in the proportion of cases tested ($p<0.0001$).

There was no significant difference between the Leicester model and the BHIVA guideline (p=0.95) in terms of the positivity rate in the proportion of cases tested, or the total number of individuals screened (p=0.29) but the number of patients screened from this cohort using the BHIVA guidance will be underestimated because BHIVA-cited risk factors for individuals from a country where TB incidence <40/100,000 population were not collected prospectively, and it is therefore unknown as to how many of the IGRA negative patients from these low incidence countries had risk factors which would have made them eligible for screening. There was no difference in the percentage of overall IGRA positive cases identified between the Leicester model and the BHIVA guideline (p=0.22).

6.3.10 Development of active TB following IGRA testing

In addition to the patient diagnosed with active TB immediately after IGRA testing, only one other patient has been diagnosed with active TB since undergoing IGRA testing. This individual had a negative QFN-GIT test, and an indeterminate T-SPOT®.*TB* test, performed on the same day, when his CD4 count was 60 but his HIV viral load was undetectable. He was classified as having an indeterminate IGRA result and no chemoprophylaxis was given. Two years later he developed fully sensitive active pulmonary TB.

6.3.11 LTBI chemoprophylaxis and cascade of care

All 141 patients with LTBI were considered for chemoprophylaxis. Treatment was not given in 21/141 (14.9%) cases. 8/141 (5.7%) declined chemoprophylaxis; treatment was not advised by the treating physician in 2/141 (1.4%) cases; 9/141 (6.4%) moved away before chemoprophylaxis could be given; and treatment is still pending in 2/141 (1.4%) (Figure 6.1). The remaining 120/141 (85.1%) patients all commenced chemoprophylaxis. 108/120 (90%) had isoniazid monotherapy. 12/120 (10%) had combined rifampicin/isoniazid.

114/120 (95%) of patients commenced on chemoprophylaxis completed treatment. One patient is still receiving chemoprophylaxis, one moved away and it was unclear whether

they completed chemoprophylaxis, and one defaulted from treatment (Figure 6.1). Only 3/120 (2.5%) had to stop treatment prematurely due to adverse drug effects.

6.3.12 Costs associated with IGRA screening and LTBI testing

Table 6.7 details the total cost of screening, together with the cost of treating each LTBI case identified using difference guidelines. The Leicester model proposed in this study was the cheapest overall and per case treated.

Table 6.7. Comparative costs associated with LTBI screening according to guideline followed

Guidance followed	Total cost £	Total cost/IGRA positives = cost per LTBI case £
2016 NICE, ECDC and WHO guidance (55, 60, 140)	138,033.60	978.96
2018 BHIVA guidance (139)[1]	115,483.20	881.55
Leicester model	108,884.00	878.10

[1] Estimated figures for total number to be screened as described in methods

6.4 Discussion

This study describes the largest prospective, systematic LTBI screening programme to have been implemented in PLWH, in a low TB incidence country, as far as I am aware from the published literature. It provides the basis for a health economic analysis to be undertaken on real-life data, including actual outcomes of screening and chemoprophylaxis uptake. Overall, 12.2% of screened patients had LTBI, confirming that there is significant potential to reduce the rates of incident TB amongst PLWH in the UK. I demonstrated in Chapter 4 that the rate of incident TB in this cohort is extremely high, and therefore it is imperative that the burden of LTBI amongst these individuals is addressed. I have shown that it is feasible to systematically screen large numbers of patients, that it is possible to achieve high levels of retention at each stage of the cascade of care and that a high proportion of individuals with LTBI can ultimately complete chemoprophylaxis successfully.

A previous cost-effectiveness analysis from London was largely theoretical, not based on prospective systematic screening, and used data from other centres to make assumptions about positivity rates, chemoprophylaxis uptake and treatment (119). The conclusion from that study was that a prospective health economic analysis would be helpful, examining LTBI screening and treatment in low incidence countries. This study provides the data to achieve this.

Only one patient in this study was found to have active TB during clinical evaluation of a positive IGRA test, in keeping with low numbers from another study (102) although proportions as high as 6% have been reported elsewhere (82). Only one additional patient, with an indeterminate IGRA test, has developed active TB since being screened for LTBI. Analyses of chemoprophylaxis in PLWH indicate that it reduces the risk of active TB by approximately one third (89) but long-term re-evaluation of the entire cohort who underwent systematic LTBI screening in this study would be important, to establish whether any more subsequent active TB cases occur at a later date, which would enable the efficacy of the screening and treatment programme to be further evaluated.

The most striking finding from this study is that the risk of having a positive IGRA test, and therefore the risk of being infected with TB, is dependent upon the incidence of TB in the country of birth. This factor was significant in both univariate and multivariable models. Black African or Asian ethnicity, non-UK birth status, and being born in sub-Saharan Africa or Asian regions are all significantly associated with LTBI positivity and are likely surrogate markers for TB incidence in the country of birth. A previous cohort study in low incidence settings also found that being from medium or high prevalence TB settings was associated with LTBI diagnosis in PLWH (82), and this was echoed in a meta-analysis which found that LTBI diagnosis was associated with black ethnicity and foreign-born origin (44). I found that almost 88% of IGRA positive cases could have been identified in this study by restricting screening to those from countries where the TB incidence was greater than 150/100,000 in addition to patients from other lower TB incidence sub-Saharan Africa countries. This strategy led to a significantly higher LTBI positivity rate in the proportion of cases tested than if all patients were screened, as is currently proposed in the ECDC, WHO and 2016 NICE guidelines (55, 60, 140). The estimated overall cost of the screening programme and cost of treating each LTBI diagnosis was also lower using the Leicester model. Although beyond the scope of this

work, a formal cost-effectiveness analysis examining screening from the NHS standpoint would be the most useful next step.

Other risk factors for LTBI in PLWH which are unrelated to the country of birth, may also apply to individuals from low TB incidence countries, and include financial poverty and low educational attainment (68) and risk factors for exposure to TB such as use of intravenous drugs and close proximity to known cases of TB (44). A New Zealand study diagnosed 11% of individuals from low incidence countries (all patients were from countries where incidence was <12/100,000 population) with LTBI (102) and found that many had additional risk factors for acquisition of TB, other than HIV infection. These results are much higher than in this current study, where only 17/471 (3.6%) of the entire tested cohort from a low TB incidence country (<50/100,000 population) had a positive IGRA and raises questions about whether guidelines set in one country may be applicable to others.

The updated 2018 BHIVA guidance recommends offering IGRA testing to PLWH from low TB burden countries (<40/100,000 population) only if additional risk factors for TB are present which are listed in the guidance (139). Since this study commenced in 2014, some years before the BHIVA guidance was updated, prospective data was not collected on additional TB risk factors cited in the BHIVA guidance and so I am unable to determine exactly how many patients in this research cohort would have been eligible for screening using the BHIVA model. However, applying the BHIVA risk criteria in the current study to the IGRA positive patients from low incidence countries revealed that only 7/17 (41.2%) of these would have been eligible for screening using the BHIVA model. By raising the threshold for screening, as in the potential current Leicester model, almost the same number of IGRA positive cases are identified as would be using the BHIVA model, but with a reduction in the total number of cases who are likely to require screening (given that the total number who would require screening using the BHIVA model is underestimated in this study). The previous cost-effectiveness analysis did find that a targeted approach to screening was more cost-effective, although was unlikely to pick up all IGRA positive patients (119). The list of risk factors cited in the BHIVA guidance may potentially still be too complex for HIV clinicians to remember in detail, as with the previous iteration of the guidance which used a combination of CD4 count,

TB incidence in the country of origin and length of time on HAART in order to determine who should undergo LTBI screening (87, 121).

NICE guidance indicates that HIV positive individuals with a CD4 count under 200 cells/mm^3 should be offered concurrent IGRA and Mantoux testing (55), and IGRA testing (with or without a concurrent Mantoux test) for all other PLWH. The ECDC guidance also recommend dual IGRA and Mantoux testing in PLWH (60) and the WHO guidelines recommends systematic testing of PLWH with either an IGRA or Mantoux test (140). My national survey of HIV clinicians indicated that Mantoux testing is very rarely undertaken in this setting (121) and that the majority of LTBI screening that exists in PLWH involves the use of an IGRA. Realistically, given the logistical issues of undertaking TST (67, 68), it is unlikely that Mantoux testing will feature highly in many future LTBI screening programmes for PLWH in the UK.

Screening in this study gave a definite IGRA result in almost all patients, with very few indeterminate results. Although the numbers of patients who had concomitant QuantiFERON-TB® and T-SPOT®.TB testing were too low to perform a formal concordance analysis between the two types of test, the majority (21/27, 77.8%) of patients had negative results for both tests, even at low CD4 counts. There has been no formal evaluation of QTN-Plus testing in PLWH and this would be a useful area to examine, now that the majority of the older QuantiFERON-TB® tests have been phased out. Of particular interest is whether this new IGRA and T-SPOT®.TB tests perform equally in those with advanced immunosuppression, given the varying concordance and correlations with CD4 counts seen in previous versions of the QuantiFERON-TB® tests (67, 69, 75, 78, 81, 82).

There were extremely low levels of patients who declined IGRA testing (8/1192, 0.67%) in this study, which was in keeping with the findings from my patient cohort questionnaire study, although a higher proportion of those with a positive IGRA did decline chemoprophylaxis here (8/142, 5.6%) than in the questionnaire study. The reasons behind declination are not well documented in the patient notes, and all were seen by other clinical colleagues, but would be an area to examine in the future, and to potentially readdress with individual patients at a later date.

Overall, 85.1% of individuals with a positive IGRA were commenced on chemoprophylaxis, which compares favourably with acceptance rates of between 17-87% from elsewhere in the UK and other low TB incidence countries (75, 82, 102).
95% of this cohort successfully completed treatment and adverse drug effects from chemoprophylaxis were severe enough in only 3/120 (2.5%) to necessitate cessation of therapy, supporting previous evidence showing that chemoprophylaxis regimens, and particularly isoniazid monotherapy regimens, are safe in PLWH (89, 97).

One limitation of this study was that the final conclusion of the laboratory report for each IGRA test was taken as absolute, and there was no scrutiny of the reported IGRA values for individual patients. Values reported which were close to the cut-off thresholds reported by the laboratories were not analysed in more detail, and the tests were not repeated although different results may have been obtained if they had. This would be an interesting aspect to look at in future, particularly if any individuals with negative IGRA tests later develop tuberculosis.

6.5 Conclusions

This large, prospective screening cohort shows that PLWH from high TB burden countries are at highest risk of having LTBI but that programmatic screening is achievable, and can lead to impressive outcomes in terms of chemoprophylaxis completion. It supports my previous data showing that screening and treatment is acceptable in this cohort and on a clinical level, has resulted in the successful treatment of 114 PLWH for LTBI, and therefore has potentially averted dozens of future active TB cases. The proposed model of screening all those from countries where the TB incidence is >150/100,000 population, in addition to individuals from other lower incidence sub-Saharan Africa countries, needs to be tested in a formal cost-effectiveness model in order to define the most appropriate future approach.

Chapter 7. Final conclusions

The aims of this research were fourfold. Firstly, to evaluate the epidemiology of active TB disease within a large HIV cohort in the UK, through detailed analysis of the patients who have sought HIV care in Leicester. Secondly, to gain understanding as to what current practice is in terms of implementation of LTBI screening amongst HIV cohorts through a national survey. Thirdly, to undertake a patient questionnaire cohort study in order to understand the planned behaviours and attitudes of PLWH towards LTBI screening and treatment. Finally, to implement programmatic screening amongst the Leicester HIV cohort, to treat all those with LTBI with chemoprophylaxis, and gain further understanding as to which groups of PLWH should be prioritised for screening. Four studies have been described herein, each pertaining to one of the stated aims, and have overall added to the body of knowledge which currently exists in this area of HIV clinical care. The overarching objective of this work was to raise the profile of LTBI within the HIV cohort, and amongst clinicians, and to ultimately reduce the burden of active TB within this population.

The national evaluation of practice covered services caring for over 90% of HIV positive adults in the UK (121) and was the first to evaluate LTBI screening practice in this population. It demonstrated that LTBI screening practices are highly heterogeneous in terms of the criteria used to offer screening, and the tests utilised, and there was little concordance with the published guidelines that were in place at the time, although these were themselves non-congruent. Additionally, screening policy was not dependent on the local burden of HIV-TB and there were areas in the UK with quite high local TB burden, but in which no screening programme was in place for PLWH. Considering their patients to be at low risk of developing TB was one of the predominant reasons cited by physicians to explain why programmatic screening was not undertaken, although my parallel TB cohort study revealed that TB risk was high overall in the Leicester HIV positive cohort, and this included risk of incident TB, occurring some months or years after the HIV was diagnosed. 325/2158 (15.1%) had had a diagnosis of TB at any stage of their lives, and the risk of incident TB was 4.47/1000 person years, which is higher than in several other studies in low TB burden settings (46, 53, 66, 127, 128).

A further survey of international HIV physicians or policymakers in other low TB incidence countries would be an interesting next step, in order to establish what screening programmes are in place elsewhere. Sharing experience of successful strategies on an international scale may be one way to encourage action in areas where screening is currently scant. Others have recognised that there have been missed opportunities to prevent active TB amongst their HIV positive cohorts through LTBI screening (157, 158).

The LTBI screening programme implemented amongst PLWH in Leicester, is the largest programmatic screening study undertaken in a low TB incidence country, that I am aware of, and resulted in 1167 patients undergoing IGRA screening, with 142/1167 (12.2%) IGRA positivity. Only 0.67% patients declined IGRA screening overall, and I demonstrated that it was possible to achieve high levels of testing and to retain patients throughout the cascade of care, ultimately achieving chemoprophylaxis completion in 95% of 120 individuals who were treated for LTBI. These high testing and completion outcomes support the results of the patient questionnaire study, in which PLWH expressed overwhelming support for LTBI screening and treatment through responding to a Likert-scale questionnaire. In that study, as in the larger, overarching, cohort screening programme, the support expressed in the questionnaire translated into positive action, with high uptake of screening and treatment. Both studies provide affirmation of the potential success of screening programmes, such that clinicians elsewhere in the UK and other low TB incidence countries should be encouraged by what is possible to achieve in their patient cohorts.

The proposed "Leicester model" for implementing targeted LTBI screening in PLWH is that individuals born in high TB incidence countries (>150/100,000 population) should be screened, alongside those born in all other sub-Saharan Africa countries, although the next clear step would be to undertake a formal cost-effectiveness analysis to determine the optimal screening threshold. This might then have implications for the next iterations of the national guidance provided by NICE and BHIVA.

A clinical by-product of this research was the successful treatment of 114 individuals for LTBI, which has the potential to reduce morbidity and mortality through averting future active TB diagnoses in our HIV cohort (128). The screening programme, which included

almost all of the current active HIV cohort in Leicester, was well received by my clinical colleagues working in the HIV department, and has resulted in heightened awareness amongst them, such that all newly diagnosed PLWH, and those transferred in from other centres are now undergoing LTBI screening as part of clinical care. This is in complete contrast to the ad hoc screening that occurred before 2014, in which only 126 individuals had been screened for LTBI. I am extremely proud of this achievement, which ultimately has improved the clinical care that we offer to our patients. A further analysis of the patients who underwent LTBI screening would be desirable, in a few years' time, in order to establish whether the TB incidence rate in this cohort has declined as a result of screening. This could include matching with the local TB surveillance system, or again, take the form of matching with the national TB dataset held at PHE.

Finally, there are ongoing innovative trials investigating shorter regimens for LTBI chemoprophylaxis that offer the potential for further simplification of treatment in the future, for example using weekly rifapentine-isoniazid dosing (97). The landscape of LTBI screening and treatment in PLWH is therefore not yet clearly set in the UK, although study evidence from this thesis provides further support for its prioritisation in HIV care.

Appendix 1. National survey of LTBI screening in PLWH: participant questions

Instructions

Thank you for participating in this survey. It should take no longer than 5 minutes to complete.

Location

1. Which organisation(s) do you work for, when providing HIV care?

(Select all that apply)

☐☐☐(Organisations listed in alphabetical order – respondents tick relevant boxes)

☐☐☐Other: (free text box)

Number of patients attending care

2. For approximately how many HIV positive adults (>16 years) does your organisation provide regular HIV care?

(Provide only one response)

(free text box)

Profession

3. In which of the following capacities do you work whilst caring for individuals with HIV infection?

(Select only one)

- ☐ As an infectious diseases physician
- ☐ As a genitourinary medicine physician
- ☐ As a respiratory physician
- ☐ As an HIV nurse specialist
- ☐ Prefer not to say
- ☐ Other

→ Question 5

→ Question 4

Other profession

4. In what other capacity do you work when caring for individuals with HIV?

(Provide only one response)

(free text box)

Current screening practices for latent tuberculosis

5. Does your organisation currently offer any form of latent tuberculosis screening to any HIV positive individuals?

(Select only one)☐

- ☐ Yes → Question 8
- ☐ No → Question 6

Reasons why LTBI screening is not offered

6. What are the reasons why your organisation does not currently offer screening for latent TB infection to HIV positive individuals?

(Select all that apply)

- ☐ Mantoux test is unavailable
- ☐ QuantiFERON Gold In-Tube test (or other version) is unavailable
- ☐ T-SPOT.TB test is unavailable
- ☐ The tests are too expensive
- ☐ Lack of physician or nursing time to arrange the tests
- ☐ Lack of confidence in the existing guidelines
- ☐ The guidelines are too complex
- ☐ Our cohort of patients is considered to be at low risk of latent TB infection
- ☐ We would not treat a positive result in an asymptomatic patient
- ☐ Other: (free text box)

Future intentions to offer screening

7. Does your organisation have any future plans to offer screening for latent TB infection to HIV positive individuals?

(Select only one)

- ☐ Yes → Question 37
- ☐ No → Question 43

BHIVA guideline

8. When screening for latent TB, does your organisation follow the BHIVA screening guidelines incorporated into the "British HIV Association guidelines for the treatment of HIV/TB coinfection" 2011 document?

(Select only one)

- ☐ Yes, in entirety → Question 26
- ☐ Yes, partially → Question 9
- ☐ No → Question 10

Partial use of BHIVA guidelines

9. Please explain how your organisation partially follows the 2011 BHIVA screening guidelines

(Provide only one response)

(free text box)

NICE guideline

10. When screening for latent TB in HIV positive individuals, does your organisation follow the guidelines included in the NICE (National Institute for Health and Care Excellence) "Clinical diagnosis and management of tuberculosis and measures for its prevention and control" 2011 document?

(Select only one)

- ☐ Yes, in entirety → Question 26
- ☐ Yes, partially → Question 11
- ☐ No → Question 12

Partial use of NICE guidelines

11. Please explain how your organisation partially follows the 2011 NICE screening guidelines

(Provide only one response)

(free text box)

International guideline use

12. Does your organisation follow any international guidelines when screening HIV positive individuals for latent TB?

(Select only one)

☐ Yes → Question 13

☐ No → Question 14

Explanation of international guidelines

13. Please explain which international guidelines your organisation follows

(Provide only one response)

(free text box)

Any other guideline use

14. Does your organisation follow any other guidelines when screening HIV positive individuals for latent TB?

(Select only one)

☐ Yes → Question 15

☐ No → Question 16

Explanation of other guideline use

15. Please explain which other guidelines your organisation follows

(Provide only one response)

(free text box)

Using CD4 count as a criterion

16. Is the CD4 count a criterion for offering screening for latent TB infection in your organisation?

(Select only one)

☐ Yes → Question 17

☐ No → Question 19

Specification of CD4 count used as a criterion

17. Which criterion do HIV positive individuals have to meet, in order to be offered latent TB screening in your organisation?

(Select only one)

☐ Screening offered only if CD4 count is 50 or below

☐ Screening offered only if CD4 count is 100 or below

☐ Screening offered only if CD4 count is 200 or below

☐ Screening offered only if CD4 count is 350 or below

☐ Screening offered only if CD4 count is 500 or below

→ Question 19

☐ Other (free text box) → Question 18

Further specification of CD4 count criterion

18. Please specify which alternative CD4 count criterion is used to offer screening in your organisation

(Provide only one response)

(free text box)

Using country of origin as criteria

19. Is the individual's country of origin a criterion for offering screening for latent TB infection in your organisation?

(Select only one)

☐ Yes → Question 20

☐ No → Question 22

Specification of country of origin as criteria

20. Which criteria are used when offering latent TB screening in your organisation?

(Select all that apply)

☐ Screening offered to those from sub-Saharan Africa

☐ Screening offered to those from the Indian sub-continent

☐ Screening offered to those from a country with a high incidence of TB (> 40 per 100,000 population)

☐ Screening offered to those from a country with a medium incidence of TB (20-40 per 100,000 population)

☐ Screening offered to those from a country with a low incidence of TB (< 20 per 100,000 population)

☐ Other (please specify): (free text box)

21. If you wish to, please add any additional comments about using countries of origin as criteria for offering screening

(Provide only one response)

(free text box)

Using duration of ARVs as a criterion

22. Is the duration of time an individual has received anti-retrovirals for, a criterion for offering latent TB screening in your organisation?

(Select only one)

☐ Yes → Question 23

☐ No → Question 25

Specification of duration of ARVs as a criterion

23. Which criterion do individuals have to meet in order to be offered latent TB screening in your organisation?

(Select only one)

☐ Screening offered to those receiving anti-retrovirals for under 6 months only

☐ Screening offered to those receiving anti-retrovirals for under a year only

☐ Screening offered to those receiving anti-retrovirals for under 2 years only

☐ Other (please specify): (free text box)

24. If you wish to, please add any additional comments about using the duration of anti-retroviral therapy as a criterion for offering screening

(Provide only one response)

(free text box)

Any other criteria for offering screening

25. If you wish to, please comment on any other criteria used by your organisation when deciding which HIV positive individuals to screen for latent TB

(Provide only one response)

(free text box)

Screening strategies

26. Which screening strategies for the diagnosis of latent TB infection are currently utilised in your organisation?

(Select all that apply)

- ☐ Mantoux testing alone
- ☐ QuantiFERON Gold In-Tube test alone
- ☐ T-SPOT.TB test alone
- ☐ Mantoux and sequential QuantiFERON Gold In-Tube test only if the Mantoux test is negative
- ☐ Both Mantoux and QuantiFERON Gold In-Tube test irrespective of the result of the Mantoux
- ☐ Mantoux and sequential T-SPOT.TB test only if the Mantoux test is negative
- ☐ Both Mantoux and T-SPOT.TB test irrespective of the result of the Mantoux
- ☐ QuantiFERON and sequential T-SPOT.TB if QuantiFERON is negative or equivocal
- ☐ T-SPOT.TB and sequential QuantiFERON if T-SPOT.TB is negative or equivocal
- ☐ Both QuantiFERON and T-SPOT together
- ☐ Mantoux, QuantiFERON and T-SPOT.TB together
- ☐ Other: (free text box)

27. If you wish to, please enter any comments you may have about the screening strategy used in your organisation

(Provide only one response)

(free text box)

Screening in low CD4

28. Is a different screening strategy utilised in individuals with a CD4 count under 200, compared to those with a CD4 count greater than 200?

(Select only one)

- ☐ Yes → Question 29
- ☐ No → Question 30

Explanation of differing strategy in low CD4 count

29. Please explain the difference in screening strategy offered for those with a CD4 count below 200

(Provide only one response)☐

(free text box)

Offering treatment

30. Are individuals diagnosed with latent TB infection (either through systematic screening or ad-hoc screening) offered treatment?

(Select only one)

- ☐ Yes → Question 34
- ☐ No → Question 31

Reasons why treatment is not offered

31. What are the reasons why your organisation does not currently offer treatment to HIV positive individuals diagnosed with latent TB infection?

(Select all that apply)

- ☐ Lack of confidence in the treatment guidelines

- ☐ Uncertainty as to which treatment regime to use
- ☐ Uncertainty as to the cost-effectiveness of treatment
- ☐ Treatment is too expensive
- ☐ Other: (free text box)

32. If you wish to, please elaborate further on the reasons why treatment is not offered in your organisation

(Provide only one response)

(free text box)

Survey end

33. Thank you very much for completing this survey.

(Select only one)

- ☐ Please take me to the end of the survey so that I can submit my answers

→ Question 44

Treatment regimes

34. Which of the following treatment regimes are offered in your organisation to HIV positive individuals diagnosed with latent TB infection?

(Select all that apply)

- ☐ 6 months of isoniazid
- ☐ 9 months of isoniazid
- ☐ 3 months of rifampicin and isoniazid
- ☐ Other (please specify): (free text box)

35. With reference to your previous answer, please comment on which treatment regime is preferred in your organisation, and why

(Provide only one response)

(free text box)

Survey end

36. Thank you very much for completing this survey.

(Select only one)

- ☐ Please take me to the end of the survey so that I can submit my answers

→ Question 44

Future screening plans

37. Upon which existing guidelines are you intending to base your future screening?

(Select all that apply)

- ☐ "British HIV Association guidelines for the treatment of HIV/TB coinfection" 2011
- ☐ NICE (National Institute for Health and Care Excellence) "Clinical diagnosis and management of tuberculosis and measures for its prevention and control" 2011
- ☐ International guideline (please specify which in the free text box)
- ☐ Planning systematic screening but not using any specific guideline
- ☐ Planning ad hoc screening only
- ☐ Other (please specify): (free text box)

Future screening plans 2

38. Which screening strategies for the diagnosis of latent TB infection will be planned for use in your organisation?

(Select all that apply)

- ☐ Mantoux testing alone
- ☐ QuantiFERON Gold In-Tube test alone
- ☐ T-SPOT.TB test alone
- ☐ Mantoux and sequential QuantiFERON Gold In-Tube test only if the Mantoux test is negative
- ☐ Both Mantoux and QuantiFERON Gold In-Tube test irrespective of the result of the Mantoux
- ☐ Mantoux and sequential T-SPOT.TB test only if the Mantoux test is negative
- ☐ Both Mantoux and T-SPOT.TB test irrespective of the result of the Mantoux
- ☐ QuantiFERON and sequential T-SPOT.TB if QuantiFERON is negative or equivocal
- ☐ T-SPOT.TB and sequential QuantiFERON if T-SPOT.TB is negative or equivocal
- ☐ Both QuantiFERON and T-SPOT together
- ☐ Mantoux, QuantiFERON and T-SPOT.TB together
- ☐ Unsure
- ☐ Other: (free text box)

39. If you wish, please comment further on the screening strategies which are planned in your organisation

(Provide only one response)

(free text box)

Future screening plans 3

40. Which of the following treatment regimes will your organisation offer to those HIV positive individuals diagnosed with latent TB infection?

(Select all that apply)

- ☐ 6 months of isoniazid
- ☐ 9 months of isoniazid
- ☐ 3 months of rifampicin and isoniazid
- ☐ Other : (free text box)

41. If you wish to, please comment on which treatment regime is planned for use in your organisation, and the reasons why

(Provide only one response)☐

(free text box)

Survey end

42. Thank you very much for completing this survey.

(Select only one)

- ☐ Please take me to the end of the survey so that I can submit my answers

Survey end

→ Question 44

43. Thank you very much for completing this survey.

(Select only one)

- ☐ Please take me to the end of the survey so that I can submit my answers

Comments

44. We welcome all comments about latent TB screening, either in your organisation, or in general. Please submit your responses. It may take take a few seconds to register your responses.

(Provide only one response)

(free text box)

Appendix 2. Patient questionnaire

Study number ☐

Questionnaire on latent TB testing and treatment

Please read the leaflet entitled "Latent tuberculosis (TB) testing" first.

We are doing a study to find out what people think about being tested for latent (dormant, sleeping) TB, and whether they would take treatment if it was recommended to them. We are asking all the patients attending our clinics what they think about this. We will use the information that people give us to try and work out what kind of tests and treatment should be offered to other people in the UK.

We are interested in your opinions and invite you to complete this questionnaire.

Completing the questionnaire is entirely voluntary and you do not have to put your name on the questionnaire. If the results are published then it will not be possible to identify anybody who has completed the questionnaire.

Your completed questionnaire will be held securely at the Leicester Royal Infirmary, and only the doctors and nurse involved in the study will have access to it.

None of your answers affects any care that you currently receive from the clinic.

Please ask if you would like more information about this questionnaire.

If you are happy to take part in this study then please complete the questions below. Your opinions are important to us and we aim to improve our service to you and others.

If a translator was used to assist in completing this questionnaire, please write which language was used for translation

_____

The next questions are about the blood test to see whether you have latent TB

Please tick <u>one</u> answer to indicate how strongly you agree or disagree with the statement

		Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
1	I plan to accept a blood test for latent TB (Taken at the same time as other blood tests in clinic)					
2	It is important that I have a blood test for latent TB					
3	It is important that I know whether I have latent TB or not					
4	I am at risk of having caught TB in the past					
5	I want to know whether I have latent TB					
6	My clinic doctor would expect me to be tested for latent TB					
7	Other people attending the clinic would expect me to be tested for latent TB					
8	I know people who would be prejudiced against me if I had a test for latent TB					
9	Other significant people in my life would expect me to be tested for latent TB					
10	I would feel able to tell my doctor if I did not want to have a test for latent TB					
11	It is up to me whether or not to have a test for latent TB					

The next questions are about the treatment you may be offered if you are diagnosed with latent TB
Please tick <u>one</u> answer to indicate how strongly you agree or disagree with each statement

		Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
12	I plan to take treatment for latent TB if it is recommended to me by my doctor (usually 4 tablets a day for 6 months)					
13	I am at risk of developing active TB					
14	It is important for me to have treatment if I have latent TB					
15	I want to have treatment for latent TB					
16	My clinic doctor would expect me to take treatment for latent TB if she/he recommended it					
17	Other people attending the clinic would expect me to take treatment for latent TB					
18	Other significant people in my life would expect me to take treatment for latent TB					
19	I know people who would be prejudiced against me if I took treatment for latent TB					
20	I am confident that I could take the tablets every day for 6 months					
21	Knowing the possible side effects of the tablets makes it more difficult for me to decide about taking the treatment					
22	It is up to me to decide whether or not to have this treatment					
23	I would feel able to tell my doctor if I did not want to have this treatment					
24	Being pregnant or trying to get pregnant makes it more difficult for me to decide about taking the treatment **(leave this question blank if not applicable)**					

25. Age _____ 26. **Male** ☐ **Female** ☐

27. Ethnicity (please tick one box)

White		**Black or Black British**	
British	☐	Caribbean	☐
Irish	☐	African	☐
Any other White background	☐	Any other Black background	☐
Mixed		**Asian or British Asian**	
White and Black Caribbean	☐	Indian	☐
White and Black African	☐	Pakistani	☐
White and Asian	☐	Bangladeshi	☐
Any other mixed background	☐	Any other Asian background	☐
Other Ethnic groups			
Chinese	☐	**Prefer not to say**	☐
Any other ethnic group	☐		

28. Which is your first language (mother tongue)? _____

29. Country of birth _____

30. If you were born outside of the UK, when did you move to the UK? _____

31. Have you ever been diagnosed with TB before? **Yes** ☐ **No** ☐

32. If you have been diagnosed with TB before, were you given treatment for TB?

Yes ☐ **No** ☐

33. Have you had treatment for latent (sleeping, dormant) TB before?

Yes ☐ **No** ☐

34. Do you know anyone who has had TB? **Yes** ☐ **No** ☐

35. If you know someone who has had TB, who was it? (You don't need to write their name – just state whether it was someone in your family e.g. mother, husband, or a work colleague, or close friend)_____

Please make any other comments you may have about latent TB testing or treatment

Thank you very much for completing this questionnaire
Please discuss any concerns you have about latent TB with your doctor

Appendix 3. Likert-scale questionnaire responses

	Strongly Agree n (%)	Agree n (%)	Uncertain n (%)	Disagree n (%)	Strongly Disagree n (%)
1. I plan to accept a blood test for latent TB (Taken at the same time as other blood tests in clinic)	266/437 (60.9)	151/437 (34.6)	13/437 (3.0)	3/437 (0.7)	4/437 (0.9)
2. It is important that I have a blood test for latent TB	239/435 (54.9)	154/435 (35.4)	34/435 (7.8)	7/435 (1.6)	1/435 (0.2)
3. It is important that I know whether I have latent TB or not	279/433 (64.4)	133/433 (30.7)	18/433 (4.2)	2/433 (0.5)	1/433 (0.2)
4. I am at risk of having caught TB in the past	51/422 (12.1)	56/422 (13.3)	204/422 (48.3)	72/422 (17.1)	39/422 (9.2)
5. I want to know whether I have latent TB	244/429 (56.9)	158/429 (36.8)	21/429 (4.9)	3/429 (0.7)	3/429 (0.7)
6. My clinic doctor would expect me to be tested for latent TB	150/430 (34.9)	157/430 (36.5)	105/430 (24.4)	12/430 (2.8)	6/430 (1.4)
7. Other people attending the clinic would expect me to be tested for latent TB	81/428 (18.9)	84/428 (19.6)	186/428 (43.5)	55/428 (12.9)	22/428 (5.1)
8. I know people who would be prejudiced against me if I had a test for latent TB	38/424 (9.0)	61/424 (14.4)	139/424 (32.8)	116/424 (27.4)	70/424 (16.5)
9. Other significant people in my life would expect me to be tested for latent TB	102/427 (23.9)	130/427 (30.4)	114/427 (26.7)	60/427 (14.1)	21/427 (4.9)
10. I would feel able to tell my doctor if I did not want to have a test for latent TB	191/434 (44)	204/434 (47)	22/434 (5.1)	10/434 (2.3)	7/434 (1.6)
11. It is up to me whether or not to have a test for latent TB	229/435 (52.6)	163/435 (37.5)	16/435 (3.7)	17/435 (3.9)	10/435 (2.3)
12. I plan to take treatment for latent TB if it is recommended to me by my doctor (usually 4 tablets a day for 6 months)	241/431 (55.9)	156/431 (36.2)	25/431 (5.8)	6/431 (1.4)	3/431 (0.7)
13. I am at risk of developing active TB	44/407 (10.8)	57/407 (14)	225/407 (55.3)	57/407 (14)	24/407 (5.9)
14. It is important for me to have treatment if I have latent TB	258/432 (59.7)	157/432 (36.3)	12/432 (2.8)	5/432 (11.6)	0/432 (0)
15. I want to have treatment for latent TB	160/417 (38.4)	145/417 (34.8)	96 /417 (23.0)	9/417 (2.2)	7/417 (1.7)

16. My clinic doctor would expect me to take treatment for latent TB if she/he recommended it	187/431 (43.4)	201/431 (46.7)	35/431 (8.1)	6/431 (1.4)	2/431 (0.5)
17. Other people attending the clinic would expect me to take treatment for latent TB	103/429 (24)	130/429 (30.3)	139/429 (32.4)	42/429 (9.8)	15/429 (3.5)
18. Other significant people in my life would expect me to take treatment for latent TB	156/425 (36.7)	162/425 (38.1)	70/425 (16.5)	25/425 (5.9)	12/425 (2.8)
19. I know people who would be prejudiced against me if I took treatment for latent TB	42/419 (10)	48/419 (11.5)	164/419 (39.1)	101/419 (24.1)	64/419 (15.3)
20. I am confident that I could take the tablets every day for 6 months	213/427 (49.9)	159/427 (37.2)	49/427 (11.5)	4/427 (0.9)	2/427 (0.5)
21. Knowing the possible side effects of the tablets makes it more difficult for me to decide about taking the treatment	49/425 (11.5)	108/425 (25.4)	138/425 (32.5)	99/425 (23.3)	31/425 (7.3)
22. It is up to me to decide whether or not to have this treatment	191/430 (44.4)	199/430 (46.8)	15/430 (3.5)	16/430 (3.7)	9/430 (2.1)
23. I would feel able to tell my doctor if I did not want to have this treatment	195/429 (45.5)	206/429 (48)	17/429 (4.0)	9/429 (2.1)	2/429 (0.5)
24. Being pregnant or trying to get pregnant makes it more difficult for me to decide about taking the treatment (please leave blank if not applicable)	21/111 (18.9)	21/111 (18.9)	44/111 39.6)	14/111 (12.6)	11/111 (9.9)

Appendix 4. Free text comments about LTBI screening and treatment

Supportive of testing

- It would help those with the disease to be treated
- Prevention is better than curing
- Testing is a must. Treatment is only a must if TB is found.
- Testing for TB is an appropriate thing to do as this is a preventive measure for illness and spread of TB
- It is a good idea to be tested so that I know my position
- Have done TB before and I don't mind having it done again. Is very good for people to know about it
- I want no iff I have TB
- To my opinion I find it's a very good thing for me to be tested TB
- I think it is a very good thing to be tested for latent TB because that would stop it spreading
- Great that you are undertaking the initiative to test patients – thanks
- It is good to have tested for TB because are moving every day you don't know who got it
- It good to be trated if they found it
- Good idea!!! Especially as my temperature seems to rise at night
- I feel it is important to get treatment against TB during its latent stage to avoid or reduce lung damage or spreading the others hence adding the costs on NHS bill
- Thanks for giving nice opportunity
- Thank you for working on TB. Coming from Sub Saharan African I've seen its edvastating effects. Thank You
- It should be compulsory and so should HIV test if it has to be combated
- I have had TB tests before but it would be good to find out that I am clear of any TB
- The testing is good, feel all questions right
- Good to have one
- I personally think it should not be optional, everyone who attends clinic must be tested
- It is very important to be tested on every possible illness/disease
- It is such a good idea for you to offer this test and treatment if needed
- I am willing to get tested
- If I've got it I expect to be treated and I'd agree to be, if not then great!
- I think it is good being tested
- I think it will important to me to know if I have got latent TB so I can get treatment for it Earlier!
- This is a really good project, cause it can help us
- I would like to say thank you very much for offering me a TB blood test
- I believe that it is important to know the risk of infection to all and the honest medical treatment to combat disease and educate
- Will be happy to take the treatment if I have TB

- This is a goodpractice to do this test well done.
- It is good to know if you have or not, so that you will be giving the treatment, also to not affect people

Wanting to know more

- I am not sure what latent TB is and is there any difference between TB and latent TB
- Would want to know more
- If I take the vaccine which I believe I did, can I still get it? How long does the vaccine last for?
- Is this all at once [in reference to treatment] spread throughout the day? What about interactions
- I have no knowledge of this treatment and therefore no information on its side effects
- I do feel that while I have answered 'uncertain' to many questions, much would need to be discussed in person before any treatment regime. The test I have no issues with
- Testing is OK. Is testing positive then I would need more informsation on possible side effects and if dormant what are the chances of break out
- What are the side effects of the drugs for treatment of TB
- I have no opinion on the side effects of TB treatment because I have no information about it
- I am not sure I know what TB is or the side effects of any medication
- Need to know about the latent TB please
- If one tests positive for latent TB, how long does it take for it to become active if one doesn't get medication and is it a fatal disease or not??

Concerns about testing or treatment

- If it is not a disease which spreadys quickly, I don't see the importance of having treatment and medication
- Need time to think about it
- See no reason why it should be made compulsory
- Do not understand/believe in latent TB bussiness. If you had TB previously and treated with full course with no break.

General comments

- I have come across patients suffering from TB and have them care, toileting, bathing and many more. I worked as Health Care Assistant for more than 10 years
- I suffer from peripheral neuropathy (side effects of my anti-retroviral drugs) which causes me a lot of pain in my hands and feet
- Working in a college would provide a greater risk of contracting TB (multi-cultural environment)

- I have travelled to South America (Colombia) several times which I believe is an at risk country for contracting TB
- I was tested for TB at Wexham hospital in 2006 when I fell ill but it turned out to be cancer and I tested HIV positive
- No comments all good
- Signature
- I just hope I have not got TB
- I was tested for TB after that (negative)
- Side effects (vomiting) and meds taking at present for HIV
- As I have Hep C I am concerned of the effect of treatment on my liver. Also I understand that as I have been cured of TB as a child I have immunity
- I didn't even know there was a 'latent state' of TB
- Because they didn't have treatment, they ended up dying
- Never heard of it, this is my first time
- Father has been told he 'may have' latent TB
- This is my first time to read about latent TB
- I took injection for TB when I was little
- I don't know much about latent TB but I am former patient of active TB
- Was told I ad TB event hough all the test results and scans did not confirm that. I took the treatment for 6 months but the symptoms that made the Dr to say I had TB is still there, i.e. a lump on the right side of my neck.
- I have been tested by Helena @ LRI 12.5.1

References

1. Orgeur M, Brosch R. Evolution of virulence in the Mycobacterium tuberculosis complex. Curr Opin Microbiol. 2018 Feb;41:68-75.

2. Thwaites G. Mycobacterial infections. In: Farrar J, Jungians T, Halloo D, Hotez P, Kang G, White N, editors. In: Manson's Tropical Infectious Diseases. 23rd ed. ed. Elsevier; 2014. p. 468-505.

3. Koch R. Die aetiologie der tuberculosis. Berlin Klinisch Wochenschau. 1882;19:221-30.

4. Osoba AO. Microbiology of tuberculosis. In: Madkour MM, editor. Tuberculosis. Berlin, Heidelberg: Springer; 2004.

5. United Nations. The Sustainable Development Goals Report 2018. New York: United Nations; 2018.

6. GBD Tuberculosis Collaborators. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. Lancet Infect Dis. 2018 Mar;18(3):261-84.

7. World Health Organization. Global Tuberculosis Report 2017. 2017, WHO.

8. United Nations. The Millennium Development Goals Report 2015. New York: United Nations; 2015.

9. Glaziou P, Floyd K, Raviglione M. Trends in tuberculosis in the UK. Thorax. 2018 Aug;73(8):702-3.

10. Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. BMC Med. 2016 Mar 23;14:48,016-0595-5.

11. Public Health England. Reports of cases of tuberculosis to enhanced tuberculosis surveillance systems: UK. 2000 to 2017. London, UK: Public Health England; 2018.

12. Thomas HL, Harris RJ, Muzyamba MC, Davidson JA, Lalor MK, Campbell CNJ, et al. Reduction in tuberculosis incidence in the UK from 2011 to 2015: a population-based study. Thorax. 2018 Aug;73(8):769-75.

13. Adam BU, Cosford P, Anderson SR, Abubakar I. Sustaining tuberculosis decline in the UK. Lancet. 2017 Mar 25;389(10075):1176-7.

14. Aldridge RW, Zenner D, White PJ, Muzyamba MC, Loutet M, Dhavan P, et al. Prevalence of and risk factors for active tuberculosis in migrants screened before entry to the UK: a population-based cross-sectional study. Lancet Infect Dis. 2016 Aug;16(8):962-70.

15. Latent TB Infection (LTBI): testing and treatment. [Internet].; 2016 []. Available from: https://www.gov.uk/government/publications/latent-tb-infection-ltbi-testing-and-treatment.

16. Riley RL, Mills CC, O''Grady F, Sultan LU, Wittstadt F, Shivpuri DN. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. Am Rev Respir Dis. 1962 Apr;85:511-25.

17. Mack U, Migliori GB, Sester M, Rieder HL, Ehlers S, Goletti D, et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur Respir J. 2009 May;33(5):956-73.

18. Hunter RL, Actor JK, Hwang SA, Karev V, Jagannath C. Pathogenesis of post primary tuberculosis: immunity and hypersensitivity in the development of cavities. Ann Clin Lab Sci. 2014 Fall;44(4):365-87.

19. Ehlers S. Lazy, dynamic or minimally recrudescent? On the elusive nature and location of the mycobacterium responsible for latent tuberculosis. Infection. 2009 Apr;37(2):87-95.

20. Tufariello JM, Chan J, Flynn JL. Latent tuberculosis: mechanisms of host and bacillus that contribute to persistent infection. Lancet Infect Dis. 2003 Sep;3(9):578-90.

21. Philips JA, Ernst JD. Tuberculosis pathogenesis and immunity. Annu Rev Pathol. 2012;7:353-84.

22. Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J. 2010 Nov;36(5):1185-206.

23. Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG, et al. Incipient and Subclinical Tuberculosis: a Clinical Review of Early Stages and Progression of Infection. Clin Microbiol Rev. 2018 Jul 18;31(4):10.1128/CMR.00021,18. Print 2018 Oct.

24. Lonnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Soc Sci Med. 2009 Jun;68(12):2240-6.

25. Mabud TS, de Lourdes Delgado Alves M, Ko AI, Basu S, Walter KS, Cohen T, et al. Evaluating strategies for control of tuberculosis in prisons and prevention of

spillover into communities: An observational and modeling study from Brazil. PLoS Med. 2019 Jan 24;16(1):e1002737.

26. Menzies D, Joshi R, Pai M. Risk of tuberculosis infection and disease associated with work in health care settings. Int J Tuberc Lung Dis. 2007 Jun;11(6):593-605.

27. Stead WW, Senner JW, Reddick WT, Lofgren JP. Racial differences in susceptibility to infection by Mycobacterium tuberculosis. N Engl J Med. 1990 Feb 15;322(7):422-7.

28. Crowle AJ, Elkins N. Relative permissiveness of macrophages from black and white people for virulent tubercle bacilli. Infect Immun. 1990 Mar;58(3):632-8.

29. O'Leary SM, Coleman MM, Chew WM, Morrow C, McLaughlin AM, Gleeson LE, et al. Cigarette smoking impairs human pulmonary immunity to Mycobacterium tuberculosis. Am J Respir Crit Care Med. 2014 Dec 15;190(12):1430-6.

30. Rees D, Murray J. Silica, silicosis and tuberculosis. Int J Tuberc Lung Dis. 2007 May;11(5):474-84.

31. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis. 2004 Mar;8(3):286-98.

32. Pizzol D, Di Gennaro F, Chhaganlal KD, Fabrizio C, Monno L, Putoto G, et al. Tuberculosis and diabetes: current state and future perspectives. Trop Med Int Health. 2016 Jun;21(6):694-702.

33. Dobler CC, Cheung K, Nguyen J, Martin A. Risk of tuberculosis in patients with solid cancers and haematological malignancies: a systematic review and meta-analysis. Eur Respir J. 2017 Aug 24;50(2):10.1183/13993003.00157,2017. Print 2017 Aug.

34. Dobler CC, McDonald SP, Marks GB. Risk of tuberculosis in dialysis patients: a nationwide cohort study. PLoS One. 2011;6(12):e29563.

35. Grant AD, Bansi L, Ainsworth J, Anderson J, Delpech V, Easterbrook P, et al. Tuberculosis among people with HIV infection in the United Kingdom: opportunities for prevention? AIDS. 2009 Nov 27;23(18):2507-15.

36. Corbett EL, Watt CJ, Walker N. The Growing Burden of Tuberculosis: Global Trends and Interactions with the HIV Epidemic. Arch Intern Med. 2003;163:1009-21.

37. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983 May 20;220(4599):868-71.

38. Centers for Disease Control (CDC). Pneumocystis pneumonia--Los Angeles. MMWR Morb Mortal Wkly Rep. 1981 Jun 5;30(21):250-2.

39. Centers for Disease Control (CDC). Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California. MMWR Morb Mortal Wkly Rep. 1981 Jul 3;30(25):305-8.

40. Sheppard HW, Ascher MS. The natural history and pathogenesis of HIV infection. Annu Rev Microbiol. 1992;46:533-64.

41. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. 1989 Mar 2;320(9):545-50.

42. Gupta RK, Rice B, Brown AE, Thomas HL, Zenner D, Anderson L, et al. Does antiretroviral therapy reduce HIV-associated tuberculosis incidence to background rates? A national observational cohort study from England, Wales, and Northern Ireland. Lancet HIV. 2015 Jun;2(6):e243-51.

43. Alvaro-Meca A, Rodriguez-Gijon L, Diaz A, Gil A, Resino S. Incidence and mortality of tuberculosis disease in Spain between 1997 and 2010: impact of human immunodeficiency virus (HIV) status. J Infect. 2014 Apr;68(4):355-62.

44. Winter JR, Adamu AL, Gupta RK, Stagg HR, Delpech V, Abubakar I. Tuberculosis infection and disease in people living with HIV in countries with low tuberculosis incidence. Int J Tuberc Lung Dis. 2018 Jul 1;22(7):713-22.

45. von Reyn CF, Kimambo S, Mtei L, Arbeit RD, Maro I, Bakari M, et al. Disseminated tuberculosis in human immunodeficiency virus infection: ineffective immunity, polyclonal disease and high mortality. Int J Tuberc Lung Dis. 2011 Aug;15(8):1087-92.

46. Norrby M, Wannheden C, Ekstrom AM, Berggren I, Lindquist L. Incidence of tuberculosis and the need of prophylactic treatment in persons living with HIV in Stockholm during the era of anti-retroviral therapy 1996-2013. Infect Dis (Lond). 2018 Nov - Dec;50(11-12):807-16.

47. Getahun H, Gunneberg C, Granich R. HIV Infection-Associated Tuberculosis: The Epidemiology and the Response. Clin Infect Dis. 2010;50(S3):S201-7.

48. Zenner D, Abubakar I, Conti S, Gupta RK, Yin Z, Kall M, et al. Impact of TB on the survival of people living with HIV infection in England, Wales and Northern Ireland. Thorax. 2015 Jun;70(6):566-73.

49. Podlekareva DN, Efsen AM, Schultze A, Post FA, Skrahina AM, Panteleev A, et al. Tuberculosis-related mortality in people living with HIV in Europe and Latin America: an international cohort study. Lancet HIV. 2016 Mar;3(3):e120-31.

50. Maniewski U, Payen MC, Delforge M, De Wit S. Is systematic screening and treatment for latent tuberculosis infection in HIV patients useful in a low endemic setting? Acta Clin Belg. 2017 Aug;72(4):238-41.

51. Rice B, Elford J, Yin Z, Kruijshaar M, Abubakar I, Lipman M, et al. Decreasing incidence of tuberculosis among heterosexuals living with diagnosed HIV in England and Wales. AIDS. 2013 Apr 24;27(7):1151-7.

52. Martin-Echevarria E, Serrano-Villar S, Sainz T, Moreno A, Casado JL, Dronda F, et al. Development of tuberculosis in human immunodeficiency virus infected patients receiving antiretroviral therapy. Int J Tuberc Lung Dis. 2014 Sep;18(9):1080-4.

53. Lodi S, del Amo J, d'Arminio Monforte A, Abgrall S, Sabin C, Morrison C, et al. Risk of tuberculosis following HIV seroconversion in high-income countries. Thorax. 2013 Mar;68(3):207-13.

54. Public Health England. Tuberculosis in England 2017 Report (presenting data to the end of 2016). Public Health England, UK: 2017.

55. National Institute for Health and Care Excellence. Tuberculosis. NG33 London. . 2016.

56. Baxter S, Goyer E, Chambers D, Johnson M, Preston L, Booth A. Interventions to improve contact tracing for tuberculosis in specific groups and wider populations: an evidence synthesis. Health Serv Reliv Res. 2017;5(1).

57. Vynnycky E, Keen AR, Evans JT, Khanom S, Hawkey PM, White RG, et al. Mycobacterium tuberculosis transmission in an ethnically-diverse high incidence region in England, 2007-11. BMC Infect Dis. 2019 Jan 7;19(1):26,018-3585-8.

58. Wingfield T, MacPherson P, Cleary P, Ormerod LP. High prevalence of TB disease in contacts of adults with extrapulmonary TB. Thorax. 2018 Aug;73(8):785-7.

59. World Health Organization. The End TB Strategy: Guidelines on the management of latent tuberculosis infection. Geneva, Switzerland: WHO; 2015.

60. Rosales-Klintz S, Bruchfeld J, Haas W, Heldal E, Houben RMGJ, van Kessel F, et al. Guidance for programmatic management of latent tuberculosis infection in the European Union/European Economic Area. Eur Respir J. 2019 Jan 17;53(1):10.1183/13993003.02077,2018. Print 2019 Jan.

61. Vynnycky E, Fine PE. Lifetime risks, incubation period, and serial interval of tuberculosis. Am J Epidemiol. 2000 Aug 1;152(3):247-63.

62. Horsburgh CR,Jr. Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med. 2004 May 13;350(20):2060-7.

63. Nachiappan AC, Rahbar K, Shi X, Guy ES, Mortani Barbosa EJ,Jr, Shroff GS, et al. Pulmonary Tuberculosis: Role of Radiology in Diagnosis and Management. Radiographics. 2017 Jan-Feb;37(1):52-72.

64. Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, Kampmann B, et al. Interferon-gamma release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. Eur Respir J. 2011 Jan;37(1):88-99.

65. Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev. 2014 Jan;27(1):3-20.

66. Elzi L, Schlegel M, Weber R, Hirschel B, Cavassini M, Schmid P, et al. Reducing tuberculosis incidence by tuberculin skin testing, preventive treatment, and antiretroviral therapy in an area of low tuberculosis transmission. Clin Infect Dis. 2007 Jan 1;44(1):94-102.

67. Cheallaigh CN, Fitzgerald I, Grace J, Singh GJ, El-Eraki N, Gibbons N, et al. Interferon gamma release assays for the diagnosis of latent TB infection in HIV-infected individuals in a low TB burden country. PLoS One. 2013;8(1):e53330.

68. Reaves EJ, Shah NS, France AM, Morris SB, Kammerer S, Skarbinski J, et al. Latent tuberculous infection testing among HIV-infected persons in clinical care, United States, 2010-2012. Int J Tuberc Lung Dis. 2017 Oct 1;21(10):1118-26.

69. Ramos JM, Robledano C, Masia M, Belda S, Padilla S, Rodriguez JC, et al. Contribution of interferon gamma release assays testing to the diagnosis of latent tuberculosis infection in HIV-infected patients: a comparison of QuantiFERON-TB Gold In Tube, T-SPOT.TB and tuberculin skin test. BMC Infect Dis. 2012 Jul 31;12:169,2334-12-169.

70. Nikolova M, Markova R, Drenska R, Muhtarova M, Todorova Y, Dimitrov V, et al. Antigen-specific CD4- and CD8-positive signatures in different phases of Mycobacterium tuberculosis infection. Diagn Microbiol Infect Dis. 2013 Mar;75(3):277-81.

71. Barcellini L, Borroni E, Brown J, Brunetti E, Codecasa L, Cugnata F, et al. First independent evaluation of QuantiFERON-TB Plus performance. Eur Respir J. 2016 May;47(5):1587-90.

72. Siegel SAR, Cavanaugh M, Ku JH, Kawamura LM, Winthrop KL. Specificity of QuantiFERON-TB Plus(R): a new generation Interferon-gamma release assay. J Clin Microbiol. 2018 Sep 19.

73. Ryu MR, Park MS, Cho EH, Jung CW, Kim K, Kim SJ, et al. Comparative Evaluation of QuantiFERON-TB Gold In-Tube and QuantiFERON-TB Gold Plus in Diagnosis of Latent Tuberculosis Infection in Immunocompromised Patients. J Clin Microbiol. 2018 Oct 25;56(11):10.1128/JCM.00438,18. Print 2018 Nov.

74. Hoffmann H, Avsar K, Gores R, Mavi SC, Hofmann-Thiel S. Equal sensitivity of the new generation QuantiFERON-TB Gold plus in direct comparison with the previous test version QuantiFERON-TB Gold IT. Clin Microbiol Infect. 2016 Aug;22(8):701-3.

75. Sultan B, Benn P, Mahungu T, Young M, Mercey D, Morris-Jones S, et al. Comparison of two interferon-gamma release assays (QuantiFERON-TB Gold In-Tube and T-SPOT.TB) in testing for latent tuberculosis infection among HIV-infected adults. Int J STD AIDS. 2013 Oct;24(10):775-9.

76. Rivas I, Latorre I, Sanvisens A, Dominguez J, Tor J, Prat C, et al. Prospective evaluation of latent tuberculosis with interferon-gamma release assays in drug and alcohol abusers. Epidemiol Infect. 2009 Sep;137(9):1342-7.

77. Talati NJ, Seybold U, Humphrey B, Aina A, Tapia J, Weinfurter P, et al. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. BMC Infect Dis. 2009 Feb 10;9:15,2334-9-15.

78. Richeldi L, Losi M, D'Amico R, Luppi M, Ferrari A, Mussini C, et al. Performance of tests for latent tuberculosis in different groups of immunocompromised patients. Chest. 2009 Jul;136(1):198-204.

79. Miller R, Mahungu T, Young M, Mercey D, Morris-Jones S, Benn P. Comparison of two interferon-gamma release assays (Quantiferon-TB Gold In-Tube and T-Spot.TB) in screening for latent tuberculosis infection (LTBI) among HIV-infected adults attending an inner London HIV clinic. Thorax. 2011;66 (Suppl 4):A72-73.

80. Santin M, Munoz L, Rigau D. Interferon-gamma release assays for the diagnosis of tuberculosis and tuberculosis infection in HIV-infected adults: a systematic review and meta-analysis. PLoS One. 2012;7(3):e32482.

81. Oliveira SMDVL, Trajman A, Paniago AMM, Motta-Castro ARC, Ruffino-Netto A, Maciel ELN, et al. Frequency of indeterminate results from an interferon-gamma release assay among HIV-infected individuals. J Bras Pneumol. 2017 May-Jun;43(3):215-8.

82. Kall MM, Coyne KM, Garrett NJ, Boyd AE, Ashcroft AT, Reeves I, et al. Latent and subclinical tuberculosis in HIV infected patients: a cross-sectional study. BMC Infect Dis. 2012 May 4;12:107,2334-12-107.

83. Machingaidze S, Verver S, Mulenga H, Abrahams DA, Hatherill M, Hanekom W, et al. Predictive value of recent QuantiFERON conversion for tuberculosis disease in adolescents. Am J Respir Crit Care Med. 2012 Nov 15;186(10):1051-6.

84. Pareek M, Abubakar PJ, Garnet GP, Lalvani A. Tuberculosis screening of migrants to low-burden nations: insights from evaluation of UK practice. Eur Respir J. 2011;37:1175-82.

85. Horne DJ, Narita M, Spitters CL, Parimi S, Dodson S, Limaye AP. Challenging issues in tuberculosis in solid organ transplantation. Clin Infect Dis. 2013 Nov;57(10):1473-82.

86. Lee MR, Huang YP, Kuo YT, Luo CH, Shih YJ, Shu CC, et al. Diabetes Mellitus and Latent Tuberculosis Infection: A Systematic Review and Metaanalysis. Clin Infect Dis. 2017 Mar 15;64(6):719-27.

87. Pozniak AL, Coyne KM, Miller RF, Lipman MC, Freedman AR, Ormerod LP, et al. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. HIV Med. 2011 Oct;12(9):517-24.

88. National Institute for Health and Clinical Excellence. Tuberculosis - Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. Clinical guideline 117. . 2011.

89. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD000171. doi(1):CD000171.

90. Hiransuthikul N, Nelson KE, Hiransuthikul P, Vorayingyong A, Paewplot R. INH preventive therapy among adult HIV-infected patients in Thailand. Int J Tuberc Lung Dis. 2005 Mar;9(3):270-5.

91. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014 Aug 23;384(9944):682-90.

92. Chehab JC, Vilakazi-Nhlapo K, Vranken P, Peters A, Klausner JD. Survey of isoniazid preventive therapy in South Africa, 2011. Int J Tuberc Lung Dis. 2012 Jul;16(7):903-7.

93. Durovni B, Cavalcante SC, Saraceni V, Vellozo V, Israel G, King BS, et al. The implementation of isoniazid preventive therapy in HIV clinics: the experience from the TB/HIV in Rio (THRio) study. AIDS. 2010 Nov;24 Suppl 5:S49-56.

94. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Mosimaneotsile B, et al. Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana: a posttrial observational analysis. AIDS. 2015 Jan 28;29(3):351-9.

95. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New Regimens to Prevent Tuberculosis in Adults with HIV Infection. N Engl J Med. 2011;365(1):11-20.

96. Golub JE, Cohn S, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. Clin Infect Dis. 2015 Feb 15;60(4):639-45.

97. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Ann Intern Med. 2017 Aug 15;167(4):248-55.

98. INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug 27;373(9):795-807.

99. Bark CM, Morrison CS, Salata RA, Byamugisha JK, Katalemwa NH, Mugerwa RD, et al. Acceptability of treatment of latent tuberculosis infection in newly HIV-infected young women in Uganda. Int J Tuberc Lung Dis. 2010 Dec;14(12):1647-9.

100. Munseri PJ, Talbot EA, Mtei L, Fordham von Reyn C. Completion of isoniazid preventive therapy among HIV-infected patients in Tanzania. Int J Tuberc Lung Dis. 2008 Sep;12(9):1037-41.

101. Shayo GA, Moshiro C, Aboud S, Bakari M, Mugusi FM. Acceptability and adherence to Isoniazid preventive therapy in HIV-infected patients clinically screened for latent tuberculosis in Dar es Salaam, Tanzania. BMC Infect Dis. 2015 Aug 26;15:368,015-1085-7.

102. Gow N, Briggs S, Nisbet M. Screening for latent tuberculous infection in people living with HIV infection in Auckland, New Zealand. Int J Tuberc Lung Dis. 2017 Sep 1;21(9):1008-12.

103. National HIV surveillance tables. HIV: surveillance, data and management. [Internet].; 2014 [updated 5th September 2018; cited 11th September 2014]. Available from: https://www.gov.uk/government/statistics/hiv-data-tables.

104. Public Health England. Data from the Survey of Prevalent HIV Infections Diagnosed (SOPHID). Diagnosed HIV Prevalence Upper Tier Local Authorities in England. . 2012.

105. NHS Data Model and Dictionary Service: Supporting information: Local authority [Internet].; 2019 [updated 04/25; cited 22nd April 2016]. Available from: http://www.datadictionary.nhs.uk/data_dictionary/nhs_business_definitions/l/local_authority_de.asp?shownav=0.

106. Local Government Association: Tackling tuberculosis. Local government's public health role [Internet].; 2018 [updated 03/23; cited 27th May 2019]. Available from: https://www.local.gov.uk/tackling-tuberculosis-local-governments-public-health-role.

107. Public Health England. Data from the Survey of Prevalent HIV Infections Diagnosed (SOPHID), Diagnosed HIV Prevalence in Local Authorities (Wales). . 2012.

108. Public Health England. Data from the Survey of Prevalent HIV Infections Diagnosed (SOPHID). Diagnosed HIV Prevalence in Health Boards: Scotland. . 2012.

109. Public Health England. Data from the Survey of Prevalent HIV Infections Diagnosed (SOPHID), Diagnosed HIV Prevalence in Local Authorities (Northern Ireland). . 2012.

110. TB Section, Centre for Infectious Diseases Surveillance and Control, Public Health England. Three-year average tuberculosis case reports and rates by Health Board, Wales, 2005-2012. . 2013.

111. Public Health Agency. Epidemiology of Tuberculosis in Northern Ireland. Annual Surveillance Report. . 2012.

112. TB Section, Centre for Infectious Disease Surveillance and Control, Public Health England. Three-year average tuberculosis case reports and rates by Health Board, Scotland, 2005-2012. . 2013.

113. Wilmington Healthcare Limited, cartographer. Binley's NHS Map of the UK 2013-14 [map]. ; 2013.

114. Kasprowicz VO, Churchyard G, Lawn SD. Diagnosing Latent Tuberculosis in High-Risk Individuals: Rising to the Challenge in High-Burden Areas. The Journal of infectious diseases. 2011;20(4):S1168-78.

115. Ait-Khaled N, Alarcon E, Bissell K. Isoniazid preventive therapy for people living with HIV: public health challenges and implementation issues. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2009;13(8):927-35.

116. Wyndham-Thomas C, Schepers K, Dirix V, Mascart F, VAN Vooren JP, Goffard JC. Implementation of latent tuberculosis screening in HIV care centres: evaluation in a low tuberculosis incidence setting. Epidemiol Infect. 2015 Jul 27:1-9.

117. Turkova A, Welch SB, Paton JY, Riordan A, Williams B, Patel SV, et al. Management of paediatric tuberculosis in leading UK centres: unveiling consensus and discrepancies. Int J Tuberc Lung Dis. 2014 Sep;18(9):1047-56.

118. Public Health England. Tuberculosis in the UK: 2014 report. London. . 2014.

119. Capocci S, Smith C, Morris S, Bhagani S, Cropley I, Abubakar I, et al. Decreasing cost effectiveness of testing for latent TB in HIV in a low TB incidence area. Eur Respir J. 2015 Jul;46(1):165-74.

120. The UK Collaborative HIV Cohort Study. [Internet].; 2018 [cited 20th November 2018]. Available from: http://www.ukchic.org.uk.

121. White HA, Miller RF, Pozniak AL, Lipman MC, Stephenson I, Wiselka MJ, et al. Latent tuberculosis infection screening and treatment in HIV: insights from evaluation of UK practice. Thorax. 2017 Feb;72(2):180-2.

122. Sester M, van Leth F, Bruchfeld J, Bumbacea D, Cirillo DM, Dilektasli AG, et al. Risk assessment of tuberculosis in immunocompromised patients. A TBNET study. Am J Respir Crit Care Med. 2014 Nov 15;190(10):1168-76.

123. Public Health England. Leicester local authority HIV, sexual and reproductive health epidemiology report (LASER): 2017. London, UK: Public Health England; 2018.

124. NHS Digital. Spine. [Internet].; 2019 [updated 05/08; cited 27th May 2019]. Available from: https://digital.nhs.uk/services/spine#use-spi.

125. NHS Data Model and Dictionary Services. Ethnic category code. [Internet].; 2019 [updated 04/25; cited 27th May 2019]. Available from: http://www.datadictionary.nhs.uk/data_dictionary/attributes/e/end/ethnic_category_code_de.asp?shownav=1.

126. The World Bank. How does the World Bank classify countries? [Internet].; 2018 [cited 27th May 2019]. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/378834-how-does-the-world-bank-classify-countries.

127. Manavi K, Hodson J. An observational study on the incidence of tuberculosis among a cohort of HIV infected adults in a setting with low prevalence of tuberculosis. HIV Clin Trials. 2016;17(5):181-8.

128. Sterling TR, Lau B, Zhang J, Freeman A, Bosch RJ, Brooks JT, et al. Risk factors for tuberculosis after highly active antiretroviral therapy initiation in the United States and Canada: implications for tuberculosis screening. J Infect Dis. 2011 Sep 15;204(6):893-901.

129. British HIV Association, British Association of Sexual Health and HIV, British Infection Society. UK National Guidelines for HIV Testing 2008. . 2008.

130. Palfreeman A, Nyatsanza F, Farn H, McKinnon G, Schober P, McNally P. HIV testing for acute medical admissions: evaluation of a pilot study in Leicester, England. Sex Transm Infect. 2013 Jun;89(4):308-10.

131. Manabe YC, Breen R, Perti T, Girardi E, Sterling TR. Unmasked tuberculosis and tuberculosis immune reconstitution inflammatory disease: a disease spectrum after initiation of antiretroviral therapy. J Infect Dis. 2009 Feb 1;199(3):437-44.

132. Golub JE, Pronyk P, Mohapi L, Thsabangu N, Moshabela M, Struthers H, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS. 2009 Mar 13;23(5):631-6.

133. Jones JL, Hanson DL, Dworkin MS, DeCock KM, Adult/Adolescent Spectrum of HIV Disease Group. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent Spectrum of HIV Disease Group. Int J Tuberc Lung Dis. 2000 Nov;4(11):1026-31.

134. Yang Z, Kong Y, Wilson F, Foxman B, Fowler AH, Marrs CF, et al. Identification of risk factors for extrapulmonary tuberculosis. Clin Infect Dis. 2004 Jan 15;38(2):199-205.

135. Pareek M, Innes J, Sridhar S, Grass L, Connell D, Woltmann G, et al. Vitamin D deficiency and TB disease phenotype. Thorax. 2015 Dec;70(12):1171-80.

136. Patel AK, Thakrar SJ, Ghanchi FD. Clinical and laboratory profile of patients with TB/HIV coinfection: A case series of 50 patients. Lung India. 2011 Apr;28(2):93-6.

137. British HIV Association, British Association of Sexual Health and HIV, British Infection Society. BHIVA guidelines for the routine investigation and monitoring of adult HIV-1 -positive individuals. . 2016.

138. Information Governance Alliance. The Records Management Code of Practice for Health and Social Care. Information Governance Alliance (for the Department of Health); 2016.

139. British HIV Association. British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2018. . 2018 (interim update 2019).

140. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J. 2015 Dec;46(6):1563-76.

141. Andrew BJ, Mullan BA, de Wit JB, Monds LA, Todd J, Kothe EJ. Does the Theory of Planned Behaviour Explain Condom Use Behaviour Among Men Who have Sex with Men? A Meta-analytic Review of the Literature. AIDS Behav. 2016 Dec;20(12):2834-44.

142. Juraskova I, O'Brien M, Mullan B, Bari R, Laidsaar-Powell R, McCaffery K. HPV vaccination and the effect of information framing on intentions and behaviour: an application of the theory of planned behaviour and moral norm. Int J Behav Med. 2012 Dec;19(4):518-25.

143. Zhang Z, Zhu Y, Zhang L, Wan H. What factors influence exclusive breastfeeding based on the theory of planned behaviour. Midwifery. 2018 Jul;62:177-82.

144. Mtenga SM, Exavery A, Kakoko D, Geubbels E. Social cognitive determinants of HIV voluntary counselling and testing uptake among married individuals in Dar

es Salaam Tanzania: Theory of Planned Behaviour (TPB). BMC Public Health. 2015 Mar 4;15:213,015-1545-4.

145. Kincaid JP, Fishbourne RP, Rogers RL, Chissom BS. Derivation of new readability formulas (automated readability index, fog count and flesch reading ease formula) for Navy enlisted personnel. Naval Air Station: Memphis: Chief of Naval Technical Training; 1975. Report No.: Research Branch Report 8-75.

146. National Patient Safety Agency, NHS Research Ethics Service. Information sheets and consent forms - Guidance for researchers and reviewers [Internet].; 2011 [cited 27th May 2019]. Available from: https://www.lancashirecare.nhs.uk/media/Publications/R_and_D/Guidance/Template%20Consent%20Forms%20and%20Information%20Sheets.pdf.

147. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016 Nov;16(11):1269-78.

148. Smith JA, Braunack-Mayer A, Wittert G. What do we know about men's help-seeking and health service use? Med J Aust. 2006 Jan 16;184(2):81-3.

149. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001 Aug;23(8):1296-310.

150. Department of Health. NHS Toolkit for producing patient information. 2003. Report No.: Version 2.0.

151. National Institutes of Health. How to write easy-to-read health materials [Internet].; 2017 [updated 06/28; cited 27th May 2019]. Available from: https://medlineplus.gov/etr.html#organize.

152. Ebert JF, Huibers L, Christensen B, Christensen MB. Paper- or Web-Based Questionnaire Invitations as a Method for Data Collection: Cross-Sectional Comparative Study of Differences in Response Rate, Completeness of Data, and Financial Cost. J Med Internet Res. 2018 Jan 23;20(1):e24.

153. Koitsalu M, Eklund M, Adolfsson J, Gronberg H, Brandberg Y. Effects of pre-notification, invitation length, questionnaire length and reminder on participation rate: a quasi-randomised controlled trial. BMC Med Res Methodol. 2018 Jan 5;18(1):3,017-0467-5.

154. Robb KA, Gatting L, Wardle J. What impact do questionnaire length and monetary incentives have on mailed health psychology survey response? Br J Health Psychol. 2017 Nov;22(4):671-85.

155. Patel H. Verification report protocol for the introduction of the QuantiFERON (QFT)-Plus, which will replace the current QFT Gold In Tube (GIT) blood collection

tubes and the use of lithium heparin (LiHe) as a pre-step to the incubation of the QFT-Plus test. April 2016.

156. NHS Improvement. Annex A: The National Tariff Workbook [Internet].; 2019 [cited 25th May 2019]. Available from: https://improvement.nhs.uk/resources/national-tariff/#h2-201920-national-tariff-payment-system.

157. Rickman HM, Miller RF, Morris-Jones S, Kellgren L, Edwards SG, Grant AD. Missed opportunities for tuberculosis prevention among patients accessing a UK HIV service. Int J STD AIDS. 2018 Jan 1:956462418773010.

158. Pettit AC, Barkanic G, Stinnette S, Rebeiro P, Blackwell R, Raffanti SP, et al. Potentially preventable tuberculosis among HIV-infected persons in the era of highly active antiretroviral treatment. Int J Tuberc Lung Dis. 2009 Mar;13(3):355-9.