Testing for tuberculosis infection in HIV infected individuals

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I, Santino Jacob Capocci, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

Aim:

To investigate the yield, and cost effectiveness of testing for TB in a contemporary, HIV-infected population.

Methods:

1. Economic modelling of three LTBI testing strategies of testing HIV clinic attendees using data from two successive periods from the Royal Free Hospital, using univariate, multivariate and probabilistic sensitivity (Monte Carlo) analyses.

2. A prospective cross-sectional study of extensive TB testing in HIV clinic attendees and economic modelling of 30 different strategies using similar methods.

Results:

1. From 2000-2010, testing people living with HIV for latent TB infection became progressively less cost-effective.

2. From the prospective study, 219 HIV-infected individuals were recruited between June 2013 and September 2014. No cases of active TB, two cases of subclinical TB and 14 cases of latent TB infection were detected. Modelling 30 differing strategies based on this data, strategies based on UK guidelines were no longer cost effective. Testing with a tuberculin skin test (TST) or single interferon gamma release assay (IGRA) in black Africans, or testing both black Africans and those from middle TB incidence countries with TST were the only cost-effective strategies at under £30,000/QALY. Probabilistic sensitivity analysis results found no testing to be most probably cost-effective up to a threshold of £30,000.

Conclusion:

TB testing has become increasingly less cost-effective over the past decade possibly due to increasing antiretroviral use and changing demographics. Even testing the most high-risk groups is now only marginally cost-effective at the NICE threshold.

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ABBREVIATIONS

AFB	Acid fast bacillus
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
BA	Black African
BCG	Bacille Calmette et Guerin
BHIVA	British HIV Association
CCA	Cost per case averted
CD4+	CD4 glycoprotein positive cells
CDC	Centre for Disease Control
CEA	Cost effectiveness analysis
CFP	Culture filtrate protein
CFU	Colony forming units
CHIC	Collaborative HIV Cohort
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computerised tomography
CXR	Chest X ray/Frontal chest radiograph
DCLO	Diffusion capacity of carbon monoxide
ECG	Electrocardiogram
EDTA	Ethylene-diamine-tetraacetic acid
ELISA	Enzyme-linked immunoassay
ELISPOTS	Enzyme-linked immunospots
EQ5D	EuroQol five dimensions questionnaire

ESAT	Early secretory antigenic target
FDG-PET	Fluorodeoxyglucose positron emission tomography
HIV	Human Immunodeficiency Virus
ICCA	Incremental cost per case averted
IDU	Injecting drug user
IFN	Interferon
IGRA	Interferon gamma release assay
IPT	Isoniazid preventive therapy
KS	Kaposi's Sarcoma
LI	Low [TB] incidence - <30/100,000
LIP	Lymphocytic interstitial pneumonia
LJ	Lowenstein-Jensen
LTBI	Latent tuberculosis infection
M. tuberculosis	*Mycobacterium tuberculosis*
MI	Middle [TB] incidence - 30-300/100,000
MSM	Men who sleep with men
NAAT	Nucleic-acid amplification test
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
PACS	Picture archive and communication system
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction
PPD	Purified protein derivative (tuberculin)
PPV	Positive predictive value

PY	Person-year
QALY	Quality Life Year
QFT	Quantiferon TB Gold
QOL	Quality of life
qPCR	Multiplex quantitative polymerase chain reaction
RHZE	Rifampicin, Isoniazid, Pyrazinamide, Ethambutol
RNA	Ribonucleic acid
SF36	San-Francisco 36 Quality of Life Questionnaire
SOCS1	suppression of cytokine signalling 1
sSA	Sub Saharan Africa
SSI	Statens Serum Institute
TB	Tuberculosis
Th1	T [thymus]-helper cell 1
TNF	Tumour necrosis factor
TSpot	T-Sport.TB test
TST	Tuberculin skin test
TU	Tuberculin units
UK	United Kingdom
US	United States of America
VNTR	Variable Nucleotide Tandem Repeat
WHO	World Health Organisation
XpertTB.RIF	GeneXpert MTB/RIF nucleic amplification test
ZN	Ziehl-Neelsen

CHAPTER 1: INTRODUCTION

1.1 Introduction

1.1.1 Tuberculosis and HIV

Tuberculosis disease (TB) and human immunodeficiency virus (HIV) infection vie as the biggest infectious causes of death worldwide. [1] After a fall in global incidence of TB for 100 years, it began to rise in the 1980s. This was predominantly due to the HIV epidemic, especially in the most southerly nations of Africa – where more than one in four adults are infected with HIV – leading to a lifetime risk of TB of more than 50% in some areas. [1] Unlike other parts of Europe, the incidence of TB disease in the United Kingdom (UK), and most notably in London, had been increasing up until 2011, and is only just starting to fall. HIV co-infection may have contributed to this. [2]

1.1.2 Natural history of HIV infection

The acquired immune deficiency syndrome (AIDS) was first described in 1981. [3] The HIV virus was discovered in 1983 and may have started infecting humans as early as in the first half of the twentieth century. [4-6]

HIV is usually acquired through sexual contact, infected blood through shared needles or blood products, or vertically from mother to child. [7] The natural history of infection in humans is an initial, usually temporary, fall in blood CD4+ T lymphocytes, which then somewhat recover in number, plateau (with sustained cell death and replication in near balance), until a fall (often years

later) leading to AIDS and then death. [8,9] HIV increases the risk and severity of several infections that are regulated by innate immunity (such as certain viruses, mycobacteria and fungi), and also malignancies, frequently associated with a viral co-factor, such as Kaposi's sarcoma (KS), lymphoma and cervical cancer. [10] The increased, sustained, systemic inflammatory response associated with HIV has also been implicated in an increase in coronary artery disease and, possibly in combination with recurrent infection due to the immunosuppression, certain respiratory illnesses such as chronic obstructive lung disease (COPD) and bronchiectasis. [11]

1.1.3 Natural history of tuberculosis infection

TB disease in humans is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) complex, which also includes species such as *Mycobacterium bovis*, *Mycobacterium canetti* and *Mycobacterium africanum*. The most frequent method of transmission in humans is via an aerosol route and usually person to person, where the bacillus is inhaled in 5-10 micrometre droplets and ingested by alveolar macrophages where it can evade killing. Whether the bacteria causes disease depends on factors in both the microbe and the host. [12] If not eliminated by the body, it can proliferate, then spread via dendritic cells to the pulmonary lymphatics and throughout the body via the bloodstream. [13,14] Locally, it can cause pulmonary disease and induces cytokines, attracting monocytes, macrophages and neutrophils to form a granuloma (although the histopathology of tissue infective with *M. tuberculosis* can vary depending on the organ involved and immune status of the person infected). [15-18] In up to a half of cases, there are extra pulmonary

manifestations (with or without pulmonary involvement), most frequently in lymph nodes, the central nervous system, abdomen or disseminated widely throughout the body. [19]

After 2-10 weeks a cell-mediated immune response occurs in most people and contains the infection. This relies on CD4+ and CD8+ T-cells that protect against intracellular pathogens, producing interferon-gamma in order to activate macrophages (mediated by tumour necrosis factor, TNF) to generate nitric oxide leading to cell death. [10,13,14] HIV infection impairs this mechanism as well as possibly affecting the interferon gamma-interleukin 2 axis (involved in T-cell proliferation), interleukin 27 production, and suppression of cytokine signalling 1 (SOCS1). These inhibit bacterial clearance and increase susceptibility to TB reactivation. [18]

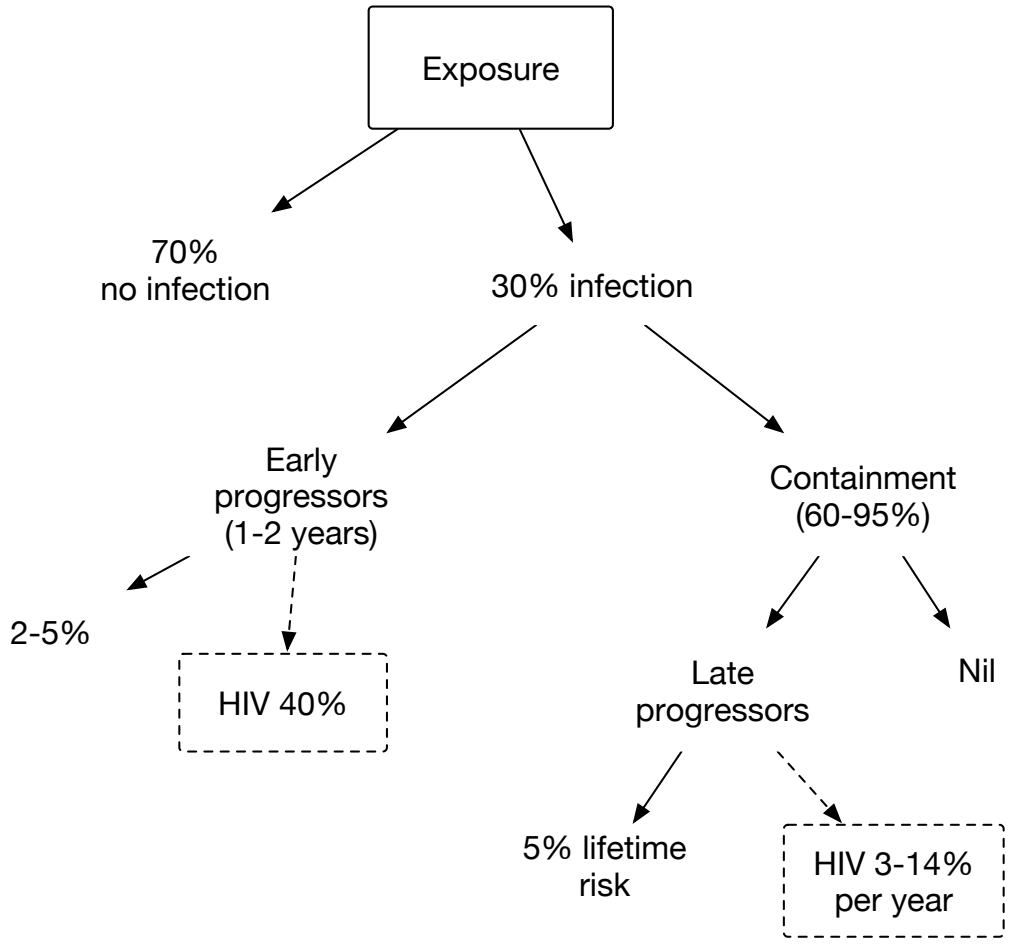
CD4+ T-cells and TNF are important in granuloma formation, and therefore HIV can affect how granulomata are formed or survive. [20] This could account for the atypical findings (fewer cavities on chest radiographs, lack of necrosis in pathological specimens) seen in patients with lower blood CD4 counts. [21]

TB has also been found to exacerbate HIV infection in humans by up-regulating replication in infected T-cells or macrophages, facilitating the late replication pathways of HIV, and help HIV evade type I interferon anti-viral signalling or upregulating SOCS1. [22-24]

1.1.4 Control of TB infection

The immune response to *M. tuberculosis* in humans can lead to various states of elimination or infection. Despite close contact with people infectious with TB

Figure 1.1.4 - Risk of infection after exposure - adapted from Glynn 2008 [25]



disease – the risk of developing TB disease varies depending on the infectiousness of patients and susceptibility of contacts – approximately 70% of adults exposed either are not infected with *M. tuberculosis* or clear the infection after exposure. [25,26] (Figure 1.1.4) Of the remaining 30%, approximately 5% develop primary

disease, perhaps associated with a fever, sometimes with chest pain, weight loss, sweats or cough, [17] whilst around 25% develop latent infection – where there is immune evidence of sensitisation, but individuals are asymptomatic and the bacillus cannot be isolated or cultured. At this point, the bacillus is thought to be contained in a granuloma, possibly in a dormant state or with low metabolic activity, [27] and preventing TB disease requires a balance of a healthy immune system with functioning CD4 T-cells. [28,29] In the general population, approximately 5-10% of people with latent infection will go on to reactivate and develop TB disease. This is often at a time associated with a decrease in cell-mediated immunity, for example, HIV infection, chronic renal impairment, immunosuppressive medications, malnutrition, chemotherapy, diabetes or age (immunosenescence). [18,30] This 'post-primary' TB tends to localise to a particular organ – in the case of pulmonary disease with chest radiographic changes (consolidation or cavitation) in the predominantly the lower segments of the upper lobe or upper segments of the lower lobes. There can be "atypical" changes, however – coexistent adenopathy, lower zone infiltrates, or disseminated disease – if there is weakened immunity. [15]

1.1.5 Clinical consequences of HIV and TB interaction

HIV infection increases both the risk of primary disease and of reactivation of latent infection, especially in those with a detectable HIV viral load or with a lower blood CD4 lymphocyte cell count (referred to as CD4) of <200 cells/μL. [16,31] In early studies, this was up to forty times higher in tuberculin skin test (TST) positive, HIV-infected individuals than HIV-negative controls. [32]

Active TB disease can have a more indolent onset, affect other organ systems more frequently, and have more associated morbidity and mortality in those co-infected with HIV, plus there are often more adverse events related to TB treatment. [33] In TB endemic areas, such as subSaharan Africa, TB is the most common cause of death in people infected with HIV, even though the burden of TB in this group could still be underestimated. [1] Postmortem studies have shown evidence of TB in HIV patients – including in 46% of those thought to have died of other causes. [34,35] TB disease can also be 'unmasked' as the immune system reactivates after starting HIV (antiretroviral) medications (ART). This occured in 17% of those with TB just after starting ART in one London study – most notably in subjects with a low blood CD4 cell count and high plasma HIV viral load. [36] Explanations may be a sustained Th1 response, cytokine dysregulation and T-cell migration. [36-38] TB disease can also worsen during effective treatment. These paradoxical reactions can occur in individuals without HIV infection, but seem more common in HIV-infected patients just after starting antiretroviral therapy (ART). [36,39] There are also numerous interactions between antiretrovirals (ARV) and antituberculous medications. [33] Given that in low TB incidence areas, most TB is thought to be due to reactivation, preventing this by testing for and treating latent TB infection is attractive as a strategy, and has been recommended in HIV treatment guidelines since the late 1980s. [40-45]

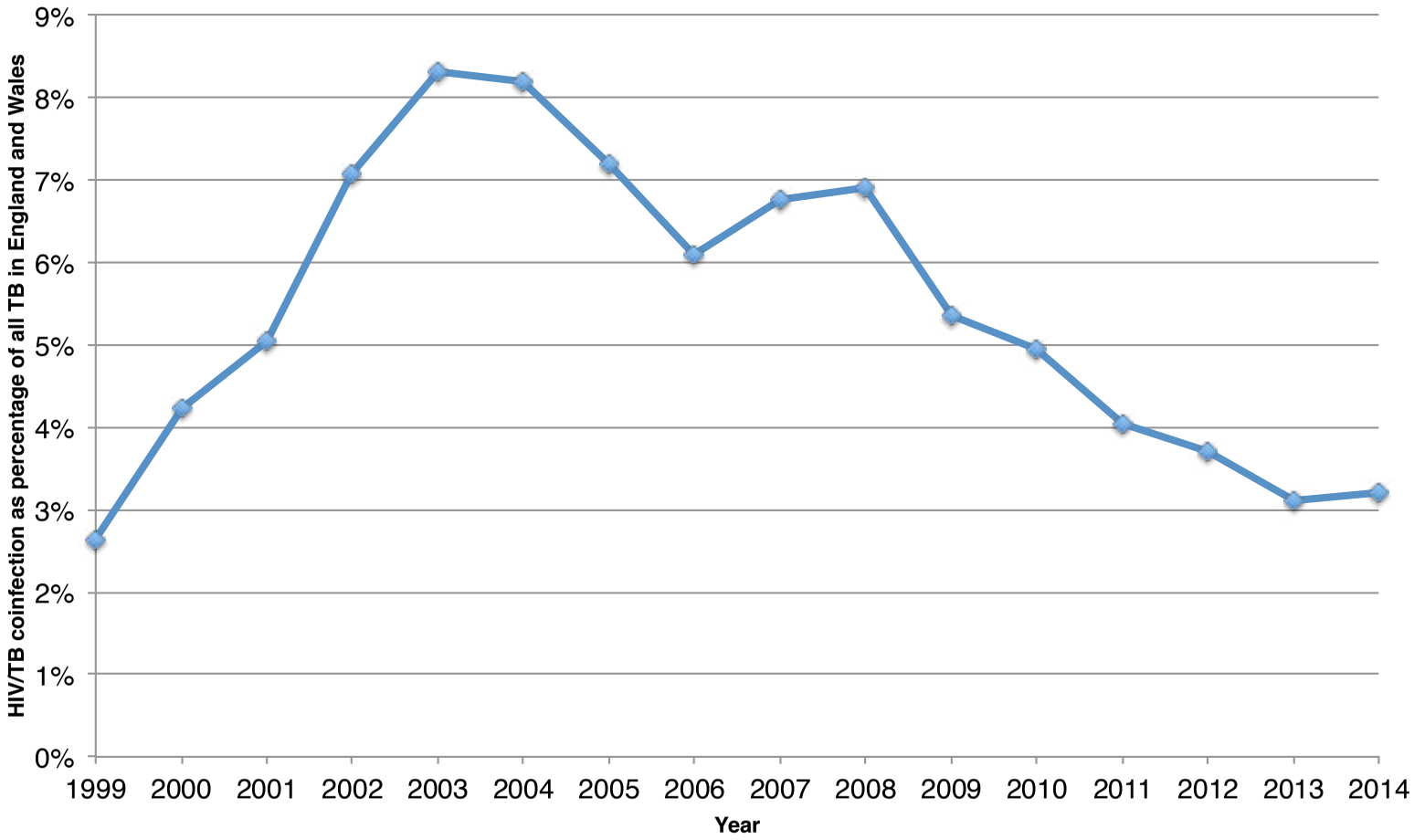
1.2 HIV epidemiology in the UK

In 2015 there were estimated to be approximately 101,000 people living with HIV in the UK, although around 13% would not be aware of their infection. In all, 47% of diagnoses are made in men who have sex with men (MSM), 28% in African-born men and women and approximately 2% in people with a history of injecting drug use (IDU). [46,47] The number of new HIV diagnoses in black Africans has fallen from around 5,000 in 2005 to 1000 in 2015, likely reflecting a change in migrant demographics, whilst the number in MSM have increased from 2,500 to around 3,000. [48] Effective combination antiretroviral therapy (ART) has been available from 1995 and led to a large fall in the number of people dying directly from HIV or AIDS-defining illnesses. There has been a debate as to when to start ART – toxicity has improved and studies suggest that early initiation of ART leads to preserved life and prevents HIV transmission. [49] Consequently, national and international guidelines have suggested treating HIV infection at higher CD4 thresholds, or even at HIV diagnosis. [44,49-51] This has led to an increase in the use of ART in people with known HIV infection, from 68% in 2003 to 95% in the UK in 2015. [46,47]

1.2.2 Epidemiology of HIV/TB co-infection in the UK

TB was the second most common AIDS-defining illness in the UK between 2010 and 2015. There were 205 diagnoses in 2014 (incidence rate of 203/100,00 compared to 10.5/100,000 in the general population), although the incidence of HIV/TB coinfection has fallen after a rise in the early 2000s. [47,52] In 2002 there were 3,020 diagnoses of TB per 100,000 HIV-infected adults in the UK and

Figure 1.2.2 - Incidence of HIV/TB as proportion of all TB in England and Wales (over 15s only). [55,58,59]



by 2011 this had fallen to 400 per 100,000. TB disease occurred most commonly in black African heterosexuals (incidence of 10.9/1000 compared to 3.1/1000 in white heterosexuals). [46] This fall coincided with a reduction in HIV diagnoses in the number of black African migrants from subSaharan Africa (sSA),[2,52] although increasingly widespread use of ART may also have decreased the number of people that develop active TB. [53,54]

As a proportion of all TB cases, HIV coinfected patients rose to 9% between 2000 and 2004, a level that plateaued and then fell to 4% by 2011 (Figure 1.2.2). [2,55] Similar trends were seen in Belgium and other parts of Western Europe. [56,57]

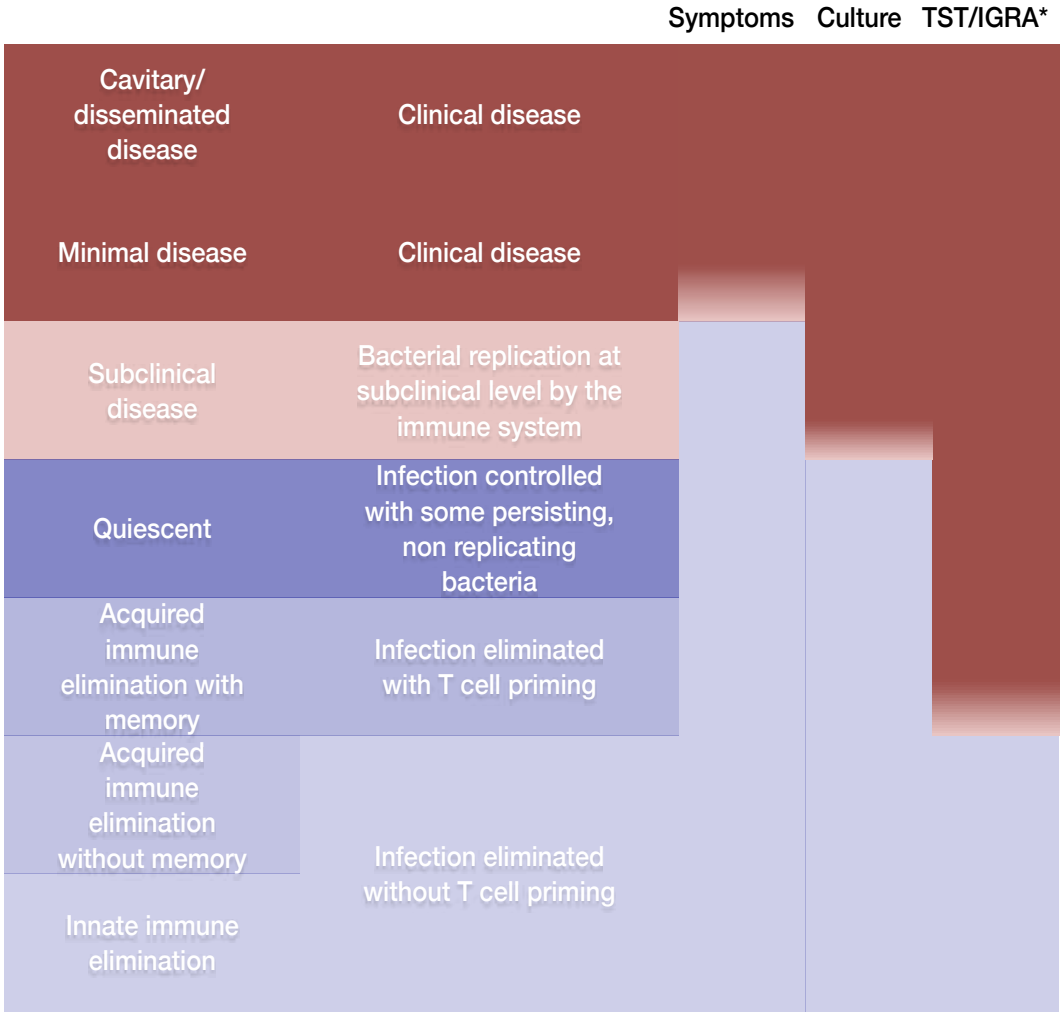
However, the majority of HIV/TB diagnoses were made in people not yet aware of their HIV status – between 2002-2010, 60% of HIV/TB co-infected adults were diagnosed with HIV and TB simultaneously. Most of these had blood CD4 cell counts of under 350 cells/μL. [52,54] This late presentation of HIV was reflected in an increased short and long-term mortality. [52]

1.3 Case definitions of active, subclinical, latent TB infection

The spectrum of TB disease seen in people with HIV has challenged the paradigm of two dichotomous states of active TB or latent infection. Instead, there appears to be a range from disseminated disease to full *M. tuberculosis* elimination with no immunological sensitisation, and include active disease, subclinical and latent infection (see Figure 1.3).

Active disease is characterised by symptoms such as fever, night sweats, and weight loss associated with localising symptoms such as cough or back pain, with consistent radiology and in many cases, the ability to culture sputum or

Figure 1.3: Spectrum of TB infection, adapted from Esmail et al. 2012 [66]



*TST/IGRA can be negative in active disease

tissue infected with *M. tuberculosis* (the gold standard). Subclinical infection is most commonly defined as a positive sputum culture, without symptoms, with or without X-ray changes consistent with TB disease. [12,60-62] To clarify the

pathophysiology between these states, 'incipient tuberculosis' has been used to describe a state in a subject with a strong immune response, where there are CXR changes (e.g. nodules), features of latent infection and high risk of reactivation. 'Subclinical tuberculosis' more describes active disease but without symptoms, most commonly in the immunocompromised. [12] In most cases, subclinical TB with HIV co-infection seems to be a temporary state, and left untreated, active disease frequently develops soon afterwards (75% between five days to two months in one South African study). [61] Latent TB infection (LTBI) is defined as an asymptomatic state with no consolidation or cavitation on CXR, an inability to culture sputum (or other tissue), but with a positive immune response (measured with an immunological test such as a tuberculin skin test, TST or Interferon-gamma release assay, IGRA) and described further below. [63]

These states may not be so well defined – some patients have no symptoms, no radiological changes on CXR and negative sputum microbiology (thereby fitting criteria for latent infection), but may have increased lymph node metabolism on fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, and/or blood transcriptional upregulation similar to those with active disease. [64-66]

1.4 Treatment of active tuberculosis disease

Minimum standard treatment for drug-sensitive active TB disease consists of four antituberculous medications given for two months (rifampicin R, isoniazid H, ethambutol E, pyrazinamide Z, 2RHZE), followed by two drugs for four months (4RH). This regimen is associated with relapse rates of about 3% in people without HIV infection. [67] In HIV co-infected patients, the same short course (6 month)

TB treatment often need not be changed or prolonged, unless there is reduced absorption, drug interactions preclude it, or disseminated disease such as central nervous system involvement, and provided sputum becomes culture negative at two months. Adverse events, however, do seem to be more frequent in the HIV co-infected group. [33,43,68] In drug-resistant cases the treatment is more prolonged and regimens based on microbiological in-vitro sensitivities. [69,70]

1.4.2 Duration of latent TB chemoprophylaxis

Treatment with one or two anti-tuberculosis drugs in patients with evidence of LTBI (by TST) has been shown to reduce the risk of active TB disease in HIV-infected individuals by 62% in randomised controlled trials in high TB incidence countries. [71] TST seems to be a good predictor of effect – efficacy is 33% if TST is not used, and there is no significant benefit in those with a negative TST result. [71] The use of isoniazid alone has advantages as it has fewer drug interactions with ART and similar efficacy to other drug combinations. [71] Nine months treatment with isoniazid preventive therapy (IPT) has been recommended by the United States (US) Centers for Disease Control (CDC), but the optimal length of therapy probably depends on immune status and local tuberculosis prevalence. [41] In a South African study, six months was found to be as good as continuous treatment in those with CD4 >500 cells/μL, whilst in a Botswanan study, 36 months had more prolonged efficacy. [72-74] In lower TB incidence areas, and in individuals without HIV, the effect of IPT seems to last much longer – possibly due to the lower risk of person-to-person transmission. Six months has been suggested as a compromise between tolerability and efficacy. [75] There

have been very few cases of active TB in HIV-infected individuals who have completed LTBI prophylaxis in low TB incidence countries. [76-80]

Rifampicin alone (for four months), rifampicin and isoniazid in combination for three months, or rifapentin weekly with isoniazid for three months have been used successfully, although there are more drug interactions between ART and rifamycins. [81-83]

1.4.3 Protective effect of ART

Increasingly widespread ART use has had an effect on the incidence of TB in both high and low TB incidence areas. World Health Organisation (WHO) guidelines increased the threshold for initiation of ART from 200 to 350 cells/μL, and now suggest treating all infected individuals. [51,84,85]

A retrospective review in South Africa showed that the TB incidence rate fell significantly in people after starting ART, from 175/1000 person years (PY) without ART to 34, even in those with a blood CD4 count of <200 cells/μL. TB incidence also fell from 1995 onwards in those who acquired HIV by sexual transmission, IDU and in haemophiliacs. [86,87] Extrapolated data from South Africa showed a risk of TB up to 40x background in those with very low CD4 counts, but estimated a 1-5x increase in those with a CD4 >200 cells/μL. [88] In the UK, pooled epidemiological data showed a fall in TB incidence rate from 13.3/1000 PY to 1.8/1000 PY in individuals two years after starting ART. [31] In a national cohort between 2007-2011, black Africans treated with ART had a similar incidence of active TB to the background HIV negative population [59]

In a meta-analysis of ART use in predominantly high TB incidence areas, the

risk of TB fell by around 65% in all CD4 strata, and even more benefit was seen in those with CD4 <200 cells/μL with a reduction to one-sixth. [89] In the Temperano study (also in Africa), early initiation of ART led to a 60% reduction in those developing tuberculosis. [90]

1.5 Testing and screening methods for TB infection in patients with HIV

1.5.1 Testing in low resourced, high TB-HIV settings

TB control has long-relied on individuals presenting with symptoms and being investigated and then treated for TB. Two studies in India found that, despite regional chest radiograph (CXR) screening taking place, two-thirds of patients were aware of symptoms before TB was detected by screening. [91,92] This led to passive case detection becoming the norm for decades. TB transmission can occur between symptom onset (although possibly before) and starting treatment. In areas of high incidence of TB transmission and HIV, such as parts of subSaharan Africa, active case detection has been used, and is now recommended, as a public health measure. [1]

Country guidelines have varied, and given the costs required, routine radiology and sputum microscopy were not always available outside of large cities. Studies from the late 1990s tried to optimise symptom combinations to detect or rule out active TB in people with HIV before LTBI prophylactic treatment. [93-95] In the early 2000s, an increase in TB incidence was noted in individuals just after starting ART, and this was associated with a higher mortality. This made screening for TB even more crucial in ART clinics. [38,96-100]

Whether symptoms alone are useful for testing is questionable. Study results have been mixed – even in the highest TB incidence areas. In a study in Cape Town in patients with advanced HIV, two of: cough, night sweats, fever plus documented weight had a sensitivity of 100% and specificity of 88.1% for active tuberculosis. An absence of symptoms was able to rule out active TB in this group (with a negative predictive value of 100%). When added to the screening questionnaire, CXR did not improve its sensitivity (CXR was abnormal in only a third of subjects), although the study was criticised for not having microbiological outcomes in all subjects. [93]

In gold miners in South Africa worsening cough, night sweats and >5% weight loss had the highest sensitivity for active TB (75%). This increased further in individuals with a low blood CD4 cell count or abnormal CXR. [101] Many cases were still missed, however, if CXR screening was not used in combination. Another, more comprehensive, case-finding study in Cape Town, found that symptoms were not a useful screen for active TB disease, and that induced sputum for microscopy and culture, even in the absence of symptoms, was most effective, especially before starting IPT. [102]

In Ethiopia, cough lasting over two weeks only detected a third of patients with active TB, although 75% had both cough and fever. [103] In a South-East Asian study investigating the optimal combination of symptoms in ART-naive HIV clinic attendees, high negative predictive values (96–98%) but fairly poor positive predictive values (21–24%) were found using combinations of two or more symptoms including: cough, fever, drenching night sweats, loss of appetite and lymphadenopathy. [94] Sensitivity improved with CXR screening. In 2011,

in a strategy designed to increase the uptake of IPT, a presence of any of: current cough, fever, night sweat or weight loss (with CXR in higher TB prevalence areas) was adopted by the WHO as a screening algorithm. This had a sensitivity of 79% and negative predictive value of 97.7%. [104] All HIV-infected individuals in high TB incidence areas with no symptoms were recommended to start IPT. A review by Rangaka in South Africa soon after found a lower sensitivity than published associated with this strategy, and consequently a high number of people with active TB were started, possibly incorrectly, on IPT. [104,105] Despite its widespread use, testing using symptoms plus sputum smear microscopy only also seems inadequate for detection of active TB. [106] One reason why symptoms may not be reliable is because of the surprising number of patients (between 4-40%) with otherwise undiscovered asymptomatic (subclinical) TB in ART clinics throughout high TB incidence countries. [60-62,97,107,108] Some patients with subclinical infection are also sputum mycobacteria-smear positive (more so in those with low blood CD4 cell counts). If TB transmission occurs in this state of infection, earlier detection from active case finding might also prevent transmission. [109]

1.5.2 Role of chest radiographs

Although radiographic changes in TB-HIV confection can be characteristic for TB, especially at higher CD4 cell counts, atypical appearances or multiple abnormalities can occur in those with poorer immunity. For example, individuals with ≤200 blood CD4+ cells/μL were more likely to have lymphadenopathy, pleural effusion or infiltrates, compared to those with ≥200 blood CD4+ cells/μL

who were more likely to have cavitation. [21,110] Chest radiographs in HIV-TB co-infection can be normal in smear-negative TB disease. One study in Malawi (70% HIV seroprevalence in the cohort) showed 21% of those with normal/minimally abnormal CXR developed culture-positive pulmonary TB. [111] Another, investigating Ugandan HIV inpatients (with a median blood CD4 of 64 cells/μL) rather than screening asymptomatic clinic attendees, showed that CXR often missed smear-negative disease. [112] When used in isolation as a screening tool in South Africa, CXR had a positive predictive value of 22% and negative predictive value of 90% for active disease. [113] Ten patients in one study (with median blood CD4 70 cells/μL) in New York had normal CXR, four of whom were sputum smear positive. [21] Similar results were seen in San Francisco. [114]

1.5.3 Role of microscopy and culture

Sputum microscopy (Auramine or Ziel-Nielsen, ZN) is used routinely in parts of the world for fast detection of mycobacteria. Microscopy alone has reported in a systematic review to miss up to a third of TB cases, [115] although a more recent study based in an ART clinic in Durban (median CD4 100 cells/μL) showed only 9% of culture-positive TB cases were smear-positive. [113] Microscopy also requires significant resource to be performed safely, such as a Category 3 lab in order to protect laboratory staff.

Despite being the gold standard for diagnosis, microbiological culture is often too expensive to be routine in many countries with high TB prevalence. Culture is usually performed using solid (Lowenstein-Jensen, LJ) or liquid media – the latter has reduced the time to positive culture from six to three weeks. Approximately

one to ten colony forming units (cfu) of *M. tuberculosis* are required for sputum positivity on liquid culture, compared to around 100 with polymerase chain reaction (PCR – such as the XpertTB.RIF), 1000 for auramine and 10,000 for ZN staining. The sensitivity of each test is affected by this. Positive sputum culture has also been reported in children recently exposed to TB and thought to be excreting bacilli, although with no later evidence of infection. [116,117] Sputum culture may be negative for *M. tuberculosis* despite a positive smear for acid-fast bacilli (AFB) in non-tuberculous mycobacterial infection or when there has been aggressive sputum decontamination.

Sputum analysis usually requires patients to be productive. Diagnostic yield improves with a larger volume of sputum (up to 5ml) as does testing two samples for culture, even in asymptomatic patients where it increased sensitivity by 22% in one study from South Africa and by 17% in SE Asia. [118-121]

In individuals that cannot spontaneously produce sputum, sputum induction has been shown to be safe and almost as effective as bronchoscopy, although it still requires strict infection control measures to prevent transmission to staff and other patients. [122,123]

1.5.4 Role of Xpert MTB.RIF

Xpert MTB.RIF (Cepheid, USA) is a semi-automated, nucleic-acid amplification test (NAAT) in a cartridge-based system (that can also be used for other microbiological PCR assays). It uses a molecular beacon assay with fluorescent markers to detect five regions in the rpo-gene (specific for *M. tuberculosis* and very few other mycobacteria) which will also show variations consistent with

rifampicin resistance. [124] Rifampicin resistance is nearly always associated with isoniazid resistance. As it takes as little as two hours, the Xpert MTB.RIF is marketed as a fast and reliable test for drug sensitive and multidrug resistant tuberculosis. Standard liquid culture takes around 12 days. [125] In studies from Peru, Azerbaijan, South Africa and India, a single sputum PCR diagnosed 98.2% of smear-positive cases, 72.5% of smear-negative cases with a specificity of 99.2%. [124,126] It has been shown to be cost-effective as a diagnostic test in many high and medium TB incidence countries, and in the USA. [127,128] It has been assessed as part of a screening strategy in HIV-infected patients in Durban, South Africa (median blood CD4 100 cells/μL in the cohort), where its positive predictive value (PPV) when screening for active TB in an ART clinic was 29% and negative predictive value (NPV) 86%, more accurate than the combination of cough and acid fast bacillus (AFB) smear (the previous national recommended strategy for excluding active TB). However, it missed half of the cases of smear negative, culture positive TB disease, which would most likely be subclinical. [113,129]

1.5.5 Testing for active and latent TB in the UK and low TB incidence countries

The UK and other low TB incidence countries use active case finding amongst other high TB incidence groups, most notably with homeless people, where screening with chest radiographs has been the most popular initial test. [130,131]

CXR has also been used to screen new arrivals, but surprisingly little active TB was detected (0% in one recent multicentre study). [132] Almost three-quarters of cases of TB disease in the UK are in people born abroad, but only 15% are in

recent migrants making reactivation of latent infection a more likely cause than importing active disease. [19] Preventive strategies in low TB incidence countries are therefore increasingly focused on the detection of latent infection with an aim to prevent subsequent reactivation. Given people with HIV are at higher risk of TB reactivation, and those who know their status tend to be in engaged in long-term care, to test for and treat LTBI seems even more attractive in this group. [31,76] There are also reports of subclinical TB in HIV clinics in the UK and Western Europe. [77]

1.5.6 TB testing strategies in HIV infected individuals

Two sets of UK guidelines for TB testing in people living with HIV were published in 2011, although they have differing testing algorithms. [42,43] The National Institute for Health and Care (then Clinical) Excellence (NICE) guidelines (for England and Wales) from 2011 suggests only testing those with blood CD4 cell count of under 500/μL - with a single IGRA with or without TST if blood CD4 is 201-499, and both TST and IGRA in those with a blood CD4 <200 cells/μL. LTBI treatment should be considered in those with either positive test. [43,133] This guideline was updated in 2016 and suggested IGRA and TST in those with blood CD4 <200 cells/μL and IGRA with or without TST in all others, with the intention to treat with preventive therapy in all those with one positive test. [134]

The British HIV Association (BHIVA) guidelines advise only testing if intending to treat, and only target the highest risk patients (depending on the place of birth, blood CD4 cell count and time on ART). This guideline was based

Table 1.5.6: TB testing guidelines in various low TB incidence countries

	BHIVA 2011	NICE 2011	NICE 2016	EACS 2015	ASHM Australia 2015	Canada CDR 2002	Victoria 2014	US CDC
Citation	[42]	[43]	[134]	[44]	[135]	[136]	[138]	[41]
Place	UK	England and Wales	England and Wales	Europe	Australia	Canada	Victoria State, Australia	United States
TST	-	CD4 <200 (optional 200-500)	CD4 <200 (otherwise optional)	CD4 >400	-	All (annual if high risk)	All	All (annual if high risk)
IGRA	Depending on place of birth/CD4/ on ART	CD4 <500	In all	Selected high risk (if available in country)	If from high TB country, previous exposure	-	All	All (annual if high risk)
CXR	Symptoms	Symptoms	Symptoms	All	CD4<200, TB exposure, high TB country, symptoms	All	High TB countries, symptoms	All
Sputum/ induction	Symptoms	Symptoms	Symptoms	-	-	If fibrosis on CXR, CD4 <200	-	If fibrosis on CXR, CD4 <200
LTBI preventive therapy*	Any positive IGRA	Consider if any positive test/ contacts	Any positive test	Any positive test	Any positive test	Positive TST (consider IGRA), contacts,	Any positive test	Any positive test, fibrosis on CXR or CD4 <200

*if no evidence of active TB disease.
CD4 - blood CD4+ lymphocyte cell count (cells/μL)

predominantly on the Swiss and CHIC data sets. [31,42,76] The United States Centre for Disease Control (CDC) advise the most comprehensive strategy with testing for LTBI in all HIV infected individuals at HIV diagnosis, plus retesting in certain groups. [41] Other strategies are listed in Table 1.5.6. WHO have suggested that systematic testing and treatment for LTBI should be performed in people living with HIV in low TB burden countries. [45]

1.5.7 TB elimination

An ambitious target of TB elimination (<1 case per million per year) has been set by the WHO for 2050. [1] Modelling has suggested that in the absence of a new vaccine or shorter treatment for active TB, mass latent TB chemoprophylaxis may be the only way to reduce TB burden. [139]

Some US states already have declining notification rates and are on target for elimination. Many European countries have elimination plans where this is felt to be achievable, although TB incidence is too high to be thought to be achievable in many, including the UK. [140,141]

1.6 Diagnosis of LTBI

Latent TB infection is defined by a lack of symptoms and persistent immune response to and inability to culture *M. tuberculosis*. Its presence has to be inferred using surrogate markers, predominantly immunological tests of sensitisation. Both the TST and IGRA rely on cell-mediated immunity to recognise a mycobacterial antigen and then invoke a reaction (either in vivo or in vitro). The tests cannot distinguish between active disease from latent infection, the time of TB

exposure or predict risk of reactivation. [142] There is no gold standard with which to compare the two tests – TST do not have optimal sensitivity (there can be an anergic response, increasing in frequency as cell-based immunity deteriorates) nor specificity (cross-reaction with environmental mycobacteria and BCG vaccine). IGRA have a positive control, which helps to distinguish true from false negatives, but there is still a false positive rate, and each IGRA can (and often) give discordant results to each other and the TST. [143-146] TB infection seems to behave in a dynamic rather than dichotomous state. A more pragmatically useful screening test for LTBI would identify those at highest risk of progression to active disease, or specifically those with active disease or subclinical TB requiring four-drug treatment and where less drug for less time may risk drug resistance and treatment failure. Findings from transcriptomics studies or PET scanning look promising, but they are not yet in a convenient or commercially available form. [64,65]

1.6.2 Use of TST

The tuberculin skin test (TST) relies on a delayed (type IV) hypersensitivity reaction to an intradermal injection of tuberculin protein (most commonly purified protein derivative – PPD), extracted from killed *Mycobacterium tuberculosis*. It has been in use for over 100 years, initially as an attempted vaccine and then as a test to sensitisation to *M. tuberculosis*. It requires interpretation between 48-72 hours and any raised induration be marked and measured. The interpretation is subjective. Trained health care professionals are usually responsible for recording the result, although some studies show a relatively good correlation between

patients and clinicians interpretation. [147,148]

The TST can react to previous BCG (Bacille Calmette et Guerin) vaccination also to other, environmental mycobacteria. A phenomenon called 'boosting' also occurs when a repeat TST is performed (especially within four weeks) and lead to a false positive result. Various formulations of PPD are available globally, although the Danish Staten Serum Institute preparation has widely been used in the UK.

In non-HIV-infected adults and children, regardless of previous BCG vaccination in the UK, a reaction of ≥5mm is used as a cut-off to maximise sensitivity. [134,149]

A lower TST sensitivity and anergy (no reaction) are associated with HIV infection, especially in those with lower blood CD4 cell counts. [150] Studies just after the discovery of HIV showed a higher incidence of active TB in individuals with anergy to PPD when compared to HIV patients with a 1-4mm response. [151,152] Anergy testing was often performed simultaneously on the other forearm, usually using candida or mumps antigen. This regimen was abandoned by 1997 as the strategy was found to be flawed as anergy to mumps or candida did not correlate with anergy to PPD. The interpretation may also have been affected by boosting. [78,153,154] In vitro testing since then has also shown that interferon-gamma secretion from HIV-infected CD4 cells is lower than from non-HIV infected cells, despite the improvements in blood CD4 counts seen in patients after starting ART. [155]

1.6.3 Use of IGRA

IGRA were developed around twenty years ago to detect a T-cell immune response to tuberculosis antigens in vitro, which is quantified by measuring interferon-gamma (INF-gamma) release. [156] The response was initially to two TB mitogens - CFP (culture filtrate protein) 10 and ESAT (early secretory antigenic target) 6. These are still used in commercial tests – the Quantiferon-TB Gold test (QFT, Qiagen) uses an enzyme-linked immunoassay (ELISA) to detect the IFN-gamma, whereas the TSpot.TB (Oxford Immunotec) assay uses enzyme-linked immunospots (ELISPOTS). [157] Other mycobacteria that express these antigens are *M. kansasii*, *M. szulgai*, *M. marinum*, *M. riyadhense* and virulent strains of *M. bovis*. Its advantages over the TST are that it requires one visit, there is no boosting phenomenon, and there is less confounding with BCG cross-reactivity. The tests require at least 24 hours incubation, and the QFT requires three tubes of blood (one nil control, one for TB antigens, one for mitogen). Like TST, IGRA can be negative in those with active TB. [158,159] The sensitivity in low/middle-income countries for active TB was 61% for QFT and 72% for TSpot. [159]

1.6.4 IGRA indeterminate responses

An IGRA is reported as indeterminate when there is a failure of the control (i.e. QFT nil tube result is >8 IU/ml or positive control <0.5 IU/ml more than the nil tube; there is excess spot production in the nil TSpot control or inadequate in the positive control). Often this is caused by technical reasons (e.g. insufficient mixing in the bottles when the blood is added), preexisting interferon gamma in the sample, or immunosuppression. [160,161] In a meta-analysis of IGRA use in HIV-infected subjects, TSpot were indeterminate in 2% (range 0-10%) on average

in studies from low/middle-income countries and 5% (1-9%) in high-income countries. QFT were indeterminate in 4% in high-income countries, and more likely in those with blood CD4 < 200 cells/μL [162]

1.6.5 IGRA CONCORDANCE

As there is no gold-standard comparator, IGRA have been compared to known risk of previous TB exposure, to TST results, and to the risk of progression to active disease. Although TST and TSpot were concordant in a meta-analysis in 89% cases (with significant heterogeneity) in high-income countries and between TST and QFT in 94%, the concordance was much lower in those with positive results. In multiple studies, poor concordance has been shown between TST and either IGRA – slightly more frequently leading to IGRA+, TST- results. [146,163-167] In one US study, only 1 in 27 patients (median CD4 334 cells/μL) with a positive test had agreement in all three. [163] Results from Quantiferon GOLD In-Tube and Quantiferon GOLD have even differed, despite using similar methods and the same mitogens. [162,168]

1.6.6 IGRA VARIABILITY

More recent studies show that IGRA results can vary on serial testing. Causes are speculated to be possible dynamic immunological processes, random within-person variation or problems with test reproducibility. [169] In a Norwegian study, despite no known interim TB exposure, 7% of negative QFTs became positive at one year, and half of these then reverted to negative by two years, whilst six of 17 positive results became negative. None of these subjects had had

LTBI prophylaxis. [80] In a US study, 80% of positive QFT in non-TB exposed HIV patients reverted to negative, as did a quarter of the results in patients from high-risk countries. [170] The phenomenon has also been seen in HIV-uninfected healthcare workers. [169]

1.6.7 Positive progression rates for IGRA and TST

In a meta-analysis comparing IGRA to TSTs for risk of progression to active TB (in HIV-negative and positive groups combined), IGRA had an NPV of 99.8% (QFT) and 97.8% (TSpot). TST, in one available study, had an NPV of 99.7%, making any of the three tests useful for ruling out LTBI in the majority of patients. The positive progression rate (risk of developing active TB) at 19-24 months for immigrants or contacts with a positive IGRA in European studies was 2.8-14.3% in those with a positive QFT, 3.30-10% with positive TSpot and 2.3-3.3% with positive TST. [145]

There have been five studies from Europe specifically in patients with HIV, where those with a positive IGRA and not treated with chemoprophylaxis were followed up for subsequent TB. These showed a progression rate of between 0 and 10% in those with a positive IGRA. The NPV with IGRA was 98.2-100%. A Norwegian study (in a population with high ART uptake) had no cases of subsequent TB – even in those with a positive IGRA (positive and negative predictive values of 0%). [80] A pan-European study, however, showed an NPV of 99.48% with TSpot. [171] A large Swiss study between 1996-2006 used TST. They calculated a progression rate of 6.5% (16/246) in those with a positive TST over a median 4.6 years. This equated to an incidence rate of 15.9 per 1000 person years. In those with a negative TST, the progression rate was 0.26% over five

Table 1.6.7: Progression rates for IGRA in European studies (includes HIV and non-HIV for comparison)

	Brock/ Soborg	Clark	Aichelburg	Pullar	Sester	Diel	Kit
	HIV infected					HIV neg contacts	
Year published [Reference]	2006 [172] 2015 [173]	2007 [174]	2009 [175]	2014 [80]	2015 [171]	2011 [144]	2010 [176]
Year of recruitment	2004-2005	2004-2006 likely	2006-2007	2009-2010	2008-2011	2005-2008	2005-2007
Study group	HIV + clinic attendees	HIV + clinic attendees	HIV + clinic attendees	HIV + clinic attendees	Immunosuppressed (plus control group)	HIV neg contacts	TST+ve close contacts (HIV neg)
Total number	590	47 asymptomatic (201 total)	830	298	768 (HIV)	1335	327
% high TB incidence (BA)	13%	51% total (not randomised)	11.1%	73%	7.8%	NA (but 41% non German origin)	17.4%
Median CD4 of entire cohort	523 mean (± 278)	213 (77-367)	194 (81-300)	Not mentioned	Not mentioned	NA	NA
TST pos	Not mentioned	Subset	Subset	24%	14%	Varied (65.2%)	All
IGRA pos (IGRA)	22/542 (4.6%) QFT	20 Elispot	44 QFT	64 QFT and TSpot (25 untreated)	81 QFT, 103 T.Spot	314/1414 (22.2%) QFT; 198/954 (20.8% in those with both tests)	178 QFT
Number with active TB at inclusion	1	NA	15.9% (7/44)	11% (7 - 4 with prev TB)	0	6	0
Number with incident active TB	2/27	2/20	3/37	0/25	10	13	9/380 (5/8 QFT pos, 6/8 T.Spot pos) but tested early
Negative predictive value	100%	98.2%	99.9% (738/739)	100%	QFT 99.58% T.Spot 99.46%	100%	QFT 98%, T.Spot 98.3%
Positive progression rate	7% (2/27)	10% (2/20)	8.1% (3/37)	0% (0/25)	QFT 3.5% (3/88); T.Spot 3.9% (4/95)	12.9% (19/147)	QFT 2.81% (5/178), T.Spot 3.3% (6/181)

years (incidence rate of 0.5 per 1000 person years). [76] Table 1.6.7 summarises studies in HIV-infected subjects from Europe.

1.7 Cost-effectiveness of screening

Despite the caveat that 'All models are wrong, but some are useful' (attributed to George Box, British Statistician in 1976), economic models have been used to influence public health policy over recent years. Cost-effectiveness analysis (CEA), specifically, can aid decisions between alternatives in medical care – especially if one treatment is already routine practice. Methods have been standardised and criteria set: analyses should estimate costs to society, show costs and benefit over a lifetime (if empirical data cannot be calculated during a study period) and statistical significance should be indicated. [177] The cost-effectiveness is expressed as the ratio of cost to benefit, and this is then discounted (usually by around 3% per year) to recognise the decreased value of a delayed expense or benefit. [177]

Benefits can be expressed in clinical outcome units (for example heart attacks prevented or cases of TB averted), or in a metric such as the Quality Adjusted Life Year (QALY), which is then comparable between different health states and treatments. A QALY (or health utility) score is the product of any life years gained and the quality of life in that health year. There are different ways to calculate this, based on validated quality of life scores such as the EQ5D, which is the questionnaire preferred by NICE in England and Wales. The Euro-QOL group derived this as a five-dimension questionnaire with either three (3L) or five (5L) responses. It was designed to be simple to understand and not too laborious,

Table 1.7.1: Hypothetical analysis with examples of dominance and extended dominance

Intervention	Total Cost	QALYs gained (compared to SOC)	Cost/QALY	Incremental cost/ QALY (ICER)	Dominance/ Extended Dominance
Standard of care	£10,000	0 (baseline)	NA		
A	£20,000	1.6	£6,250	£6,250	More cost-effective than SOC
B	£40,000	2.0	£15,000	£5,000	More cost-effective than A
C	£50,0000	2.2	£22,727	£50,000	Extended dominance (still benefit but > £30,000/QALY gained)
D	£55,000	2.1	£21,428	Loses QALYs	Dominated (less benefit for more cost)

making repeated assessments easy. Alternative methods include the standard gamble, comparing years of life gained with risk of death (often used to assess major surgery), or trading off years lived versus higher quality of life. [177]

To compare interventions, and judge if these are cost-effective, cost/outcome (usually QALY) is compared. NICE (England and Wales) use a threshold of £20-30,000 per QALY, which has not changed over the past decade, whilst the US has been noted to use $50,000. [178-180]

If one intervention has less benefit (i.e. fewer QALYs gained) than another but costs the same or more, it is said to be 'dominated'. When it has more QALYs, but these extra QALYs each cost more than the threshold allowed (e.g. £30,000) this is called 'extended dominance'.

Given assumptions are often necessary to construct the model, sensitivity testing is used to assess confidence in the outcomes. Changing one parameter (univariate analysis) gives an idea about which factors influence models the most. Best and worst case (multivariate) scenarios can also be calculated. Uncertainty can be assessed using 'bootstrapping' or a probability sensitivity analysis (PSA) such as the Monte Carlo simulation, which uses a large number of estimates (often 10,000-100,000) based on random numbers and applies them to distributions around each assumption.

1.7.2 Costs of TB care and treatment

Costs of active TB have published and used in health economic models. White et al. suggested £6040 to treat a case of active TB in a London Hospital in 2000, whilst the UK Department of Health, when exempting prescription charges,

Table 1.7.2: Published costs of active and latent TB

Variable	Cost	Author	Year published	Costs from time period	Ref
Latent TB medication (3RH)	£86	NICE	Assumption		[185]
Latent TB case (6H)	£524.59	Pooran	2010	2008	[186]
Active TB case	£5,000	Department of Health	2009	2009	[182]
	£6,040	White	2000	1996-1998	[181]
	£7,619	Pooran	2010	2008	[186]
	£4,742-£7,820 (€5,691-€9,384*)	Diel (Individual Western European range)	2014	2008-2012	[184]
	£8,568 (€10,282*)	Diel (EU15 - European average)	2014	2008-2012	[184]
MDR TB case	£47,677 (€57,213*)	Diel	2012	2008-2012	[184]
	£60,000	White	2000	1996-1998	[181]

* Adjusted to 2012 prices; Exchange rate €1.2=£1
EU-15: First 15 European Union member states; 6H: 6 months isoniazid therapy; 3RH: 3 months rifampicin and isoniazid

estimated £5000 as the cost of a drug sensitive case. [181,182] Pooran et al. suggested £7,619 in 2010, similar to published Western European ranges, collated in 2014 (Table 1.7.2). [183,184]

NICE, in their 2011 guidelines, have used estimates of: £500 for chemoprophylaxis treatment per patient, £5100 for the treatment of active disease, IGRA £22 (updated to £50) and clinic appointments after a positive IGRA result at £250. [185]

1.7.3 Quality of life in TB

One of the most difficult assumptions for TB cost-effectiveness modelling has been an assessment of the quality of life (QoL) in TB. This has been measured using various generic tools, albeit with little consensus on which method is optimal. The EQ5D has been criticised for not being sensitive enough for use in TB, and there is no TB related data set using this yet, but the questionnaire does provide a fast and straightforward assessment, especially when used repeatedly. [187-189]

There are only two QoL data sets from high-income countries in order to calculate the loss of quality of life due to active TB disease. Both of these (one British, the other Canadian) have used the San Francisco-36 questionnaire (SF36). [188,190] There are even fewer data to quantify the quality of life lost due to preventive treatment for LTBI. This utility is often an assumption, and some papers have counted it as one (i.e. no loss of quality of life) unless there is associated hepatotoxicity. [191-193]

All the studies in HIV-uninfected individuals have shown lower QoL in those with active TB compared to LTBI or no TB, although in active disease the QoL

tends to improve at the end of treatment. [188,190,194,195] Two studies, however, show quite significant, prolonged lung impairment and disability after active disease. [195,196] Some QoL loss has also been attributed to the anxiety and stigmatisation around the diagnosis of TB. [197]

HIV/TB coinfection studies have tended to come from low resource settings. A South African and an Ethiopian study both showed lower QoL in those with HIV coinfection compared those without HIV, whereas a Thai and Brazilian study demonstrated little difference between HIV-infected and uninfected TB patients. [109,198-200]

1.8 Rationale for a study in cost-effectiveness of TB testing in HIV

There is no agreed consensus, either nationally or internationally on testing for TB in HIV-infected patients. Most rely on historical studies conducted when fewer patients were taking ART. In the UK clinicians were not consistent in their approach to testing and only a third adhered to national guidelines. [201] We felt it was important to assess how feasible and cost-effective it would be to test patients with HIV for active, latent and subclinical disease.

It still has not been established that IGRA are superior to TST, and although they do not require a return trip for interpretation, they require more technology and therefore cost significantly more, there is variability in their results, and neither test has optimal sensitivity or predictive value. There is still a paucity of data from large studies that treating IGRA positive patients with IPT (especially if TST negative) prevents active TB.

1.8.2 Existing evidence for LTBI testing

The very increased risk of TB reactivation has been known since 1987, initially in studies comparing HIV-infected and non-infected injecting drug users. [32,88,202,203] Isoniazid prophylaxis has been used since then and shown to reduce the risk of active TB. [71] As ART was introduced in the late 1990s, the risk of TB began to fall in all groups. [86] In 2004, the Swiss study showed that treatment for LTBI was effective, but it failed as it was poorly implemented by physicians. [76] UK epidemiological studies showed a higher risk of TB disease predominantly in black Africans, those with low blood CD4 cell counts and individuals just starting ART. [31] However, studies over the past decade in Europe and the US, using IGRAs rather than the TST, have shown that very little active TB develops in people who have a negative IGRA result or have had LTBI preventive treatment. As ART increases, the risk of developing TB (even in those that are IGRA positive) is even lower. [172,174,175] Despite national guidelines, testing in clinics in the UK has been patchy and inconsistent. Many HIV physicians feel there is little risk of active TB or that LTBI testing strategies in HIV clinics have not been justified as cost-effective. [201]

In order to improve this, both NICE and BHIVA released guidelines for the UK in 2011. NICE modelled the cost-effectiveness of targeted testing based on blood CD4 cell count, using assumptions from a school based analysis reviewing BCG. [43]

The British HIV Association (BHIVA) guideline was not assessed for cost-effectiveness but was based on UK epidemiological data and results from the Swiss study in order to prevent active TB disease in those at the highest risk of

reactivation. [31,42,76] IGRA was used as a single test and given the lack of data available at the time, further research in the area encouraged. Since the CHIC and Swiss data sets were published, HIV demographics in the have UK changed, there were fewer immigrants from subSaharan Africa and ART use became more widespread. TB/HIV notifications have also decreased. [46,48]

There has not been a study to assess how feasible and cost-effective testing for TB infection would be, or what may be the most effective strategy, in people living with HIV in a Western European city where there is a high uptake of ART.

As a response to the high incidence of active TB seen in sub-Saharan African ART clinics, studies were conducted screening asymptomatic HIV patients for active tuberculosis. These demonstrated high numbers of patients with microbiological or radiological evidence of active TB, but with no symptoms (described as subclinical tuberculosis). Some of these patients also had a negative IGRA or TST. [62] Subclinical TB had been described in an HIV clinic in London, but only in the context of a TB testing study that cultured sputum from patients with a positive IGRA or TST. [77] The prevalence of subclinical TB in asymptomatic HIV infected individuals in London (irrespective of IGRA status) is unknown.

1.9 Study hypothesis, aims and objectives

The aim of the study was to determine the feasibility of extensive testing for TB infection in a contemporary HIV population with widespread use of ART, and to assess its cost-effectiveness. This could be established by a cross-sectional study to show the prevalence of active TB disease, subclinical and latent TB infection and modelling the effects of various testing strategies to prevent active TB. By performing a comprehensive array of tests, limitations of symptoms, radiology

or immunological tests could be shown. The same patients could then provide a cohort to assess the prognostic value of TST/IGRA against the risk of TB over the next 5-20 years.

1.9.2 Hypotheses

1. There is a significant difference in the prevalence of TB infection between black Africans and those from low TB incidence countries attending a UK HIV clinic.

2. Systematic testing for *M. tuberculosis* infection (with IGRA) is feasible and cost-effective in a UK HIV population.

3. TST provides no further information compared to a single step, blood IGRA in the detection of *M. tuberculosis* infection in a contemporary UK HIV-infected clinic population.

4. Within the Royal Free clinic population, asymptomatic HIV-infected individuals with normal chest radiographs have negative mycobacterial sputum microscopy and culture, despite originating from high TB incidence areas.

1.9.3 Primary objectives

To determine the feasibility, yield and cost-effectiveness of systematic testing for *M. tuberculosis* infection in UK HIV-infected individuals.

1.9.4 Secondary objectives

For all subjects:

1. To determine the prevalence of subclinical and active TB in a UK HIV-infected clinic

2. To determine the sensitivity and specificity of systematic screening questionnaires for detecting cases of active TB outside of high TB prevalence settings

3. To determine concordance between TST and blood TSpot.TB in latent TB infection

4. To identify risk factors for latent TB infection in the clinic population

5. To determine the sensitivity and specificity of Xpert MTB/RIF PCR testing of sputum and induced sputum compared to mycobacterial microscopy and culture for *M. tuberculosis* infection

6. To determine quality of life scores (EQ-5D) for those with HIV infection, with and without latent TB infection and/or undergoing treatment

7. To determine the underlying frequency of airways disease (using spirometry) and of respiratory symptoms

In those with evidence of LTBI:

8. To determine uptake of latent TB therapy (6 months isoniazid treatment)

9. To determine cost of latent TB treatment (including screening costs, clinic time)

10. To determine quality of life, and rate and severity of adverse events on latent TB treatment

11. To determine rate and time until active TB in those with LTBI on or off ART and/or LTBI preventive treatment

In all patients (over a 20-year follow-up):

12. To determine the rate of incident active TB

13. To determine the risk and time until progression to active TB in patients with abnormal radiographic changes consistent with old tuberculosis exposure or disease

1.9.5 Contributions of experimental and analytic procedures

For the analysis and cost-effectiveness calculations of the retrospective data, I performed the: statistical analysis of retrospective data, initial cost-effectiveness calculations giving point estimates, building of the cost-effectiveness model (with Colette Smith and Stephen Morris), calculation of the probabilistic sensitivity analysis including tables and graphs and wrote the critical analysis.

For the prospective study, I designed the study protocol (with Marc Lipman), wrote and submitted the ethics and research and development forms and attended the ethics board meeting. I recruited the subjects (along with Janey Sewell, Research Nurse, UCL Department of Infection and Population Health), administered tuberculin skin tests (with Janey Sewell), performed phlebotomy (with Janey Sewell and staff of the Ian Charleson Centre if other bloods were taken), performed spirometry (with Janey Sewell) and sputum induction (with Janey Sewell). I organised and posted T.Spot tests to an external laboratory, centrifuged and pipetted blood for storage, reviewed the initial chest X rays, collected and analysed results, performed the statistical analysis (with some confirmation from Colette Smith), built the cost-effectiveness model and calculated the probabilistic sensitivity analysis, along with tables and graphs (with some methodological help from Professor Steve Morris from the Department of Applied Health Research).

Colette Smith (from the UCL Department of Infection and Population Health) collected data for the retrospective chapter, along with the Royal Free Database team (Robert Tsintas) and helped build the initial cost-effectiveness model. She also confirmed the power calculation and some other statistical analyses in the thesis, including odds ratios.

Chest X ray reporting was performed by Consultant Radiologists, Royal Free Hospital; sputum mycobacterial culture by the Laboratory staff, Royal Free Hospital, Department of Clinical Microbiology; extra sputum disinfection and freezing by Dr Isobella Honeybourne, UCL Department for Clinical Microbiology and the qPCR analysis by Dr Camus Nimmo and Sarah Thurston, UCL Department for Clinical Microbiology.

CHAPTER 2: METHODS

2.1 Setting

The studies were performed at the Ian Charleson HIV ambulatory care clinic at the Royal Free Hospital, London, which provides care for a large, stable population of HIV infected individuals of over 2,500 people. Approximately a third of patients treated here originate from sub-Saharan Africa. At the time of the analyses, the background prevalence of HIV in London was 525/100,000 adults aged 16-59 and the incidence of active TB local to the hospital was 36.8/100,000. [204,205]

There was no routine testing for latent TB infection (LTBI) in individuals attending the Ian Charleson Centre at this time.

2.2 Modelling LTBI Testing from 2000-2010

We used clinical and demographic data from the Royal Free HIV clinic cohort to model systematic LTBI testing in this group between 2000 and 2005 and then between 2005 and 2010.

2.2.2 Data source

Retrospective data were obtained from the Royal Free HIV database. This is a prospective database containing demographic, clinical, virological and immunological information for all patients receiving care at the Royal Free Hospital and updated yearly.

2.2.3 Ethics

Patients consent either at HIV diagnosis or when transferring care to the Royal Free Hospital. Ethical approval has been granted previously for prospective data extraction.

2.2.4 Model structure

Place of birth, serial blood CD4 cell counts and a diagnosis of active tuberculosis disease was extracted from the database for all patients attending the clinic between 2000-2010. Each blood CD4 cell count was used as a surrogate for an HIV clinic appointment. This was used to calculate how many individuals would be eligible for LTBI testing using BHIVA 2011 or NICE 2011 guidance.

The model structure, assumptions and details of the sensitivity analyses are described further in the methods section of that chapter.

The results of the economic analysis were measured in terms of the incremental cost per case averted (ICCA) and incremental cost per QALY gained. The cost-effectiveness evaluations are described more below.

2.3 Prospective study

2.3.1 Ethics

The study was sponsored by University College London, approved for R&D by Royal Free/UCL Joint Research Office and Ethics approval was granted by the City and East Ethics Committee on the 16th November 2012. REC reference 12/LO/1516; UCL protocol number 12/0212; 'Study of systematic TB testing

for active, sub-clinical and latent tuberculosis infection in a UK HIV-infected cohort'. Clinicaltrials.gov number was NCT02712671. There was no outside funding provided for the study.

The study was performed at the Royal Free Hospital, London.

All patient assessments were conducted on the hospital site.

2.3.2 Storage of information

Patient consent, questionnaires and checklists were filed and kept in a locked office in the Centre for Clinical Microbiology, in the UCL Department for Population Studies or in the Ian Charleston Centre. Subjects were issued with subject numbers at recruitment, which were used to pseudoanonymise data for analysis. All computer files about the study were stored with password protection on encrypted hard drives. Any email correspondence within the centre was sent using an encrypted system.

No personal details were sent by email outside of UCL or the Royal Free Hospital. TSpot.TB tests were ordered and identified using the pseudoanonymised research number only and results received on password protected files using encrypted email.

2.3.3 Recruitment and assessments

2.3.3.1 Selection

All subjects were recruited from the Ian Charleson Centre.

Selection criteria were:

1. All patients with a new diagnosis of HIV

2. Patients attending routine ambulatory HIV care clinics, using stratified selection. We approached the 1st, 4th and 7th patients on each clinic list on Mondays, Tuesdays, Wednesdays and Fridays

Recruitment was not possible on Thursdays as the tuberculin skin test (TST) had to be interpreted at 48-72 hours.

We aimed to enrol 180 patients from subSaharan Africa and 120 from lower TB incidence areas. This was to demonstrate a difference of 10% in the prevalence of TB infection between black Africans (13% prevalence) and those from low TB incidence countries (3% prevalence), based on data by Kall et al. [77] The power calculation suggested these numbers to show a difference with a power of 80% and a 5% chance of a Type I error, allowing for a 20% drop out rate.

Patients were approached in the waiting area and taken to a quiet part of the centre to have the study explained. They were given as long as necessary to consent, but to minimise travel costs and inconvenience to subjects, where possible, TB testing occurred on the same day as a routine clinical appointment. Travel costs were met for subjects to re-attend for clinical investigations, radiology and sputum induction related to the study. There was no financial incentive offered for taking part.

Full written consent was taken. All subjects were asked specifically as part of the consent process if they wanted to be told the results of all their tests plus any action recommended, and the outcome of the entire study if interested. Specific consent was also requested to inform the GPs of the subjects' involvement in the study and results (Appendix 1).

2.3.3.2 Inclusion and exclusion criteria

Inclusion Criteria:

- Able to give informed consent
- Over the age of 18
- HIV infection, with confirmed positive HIV antibody status
- Under the care of the Royal Free Ian Charleson Day Ambulatory Unit

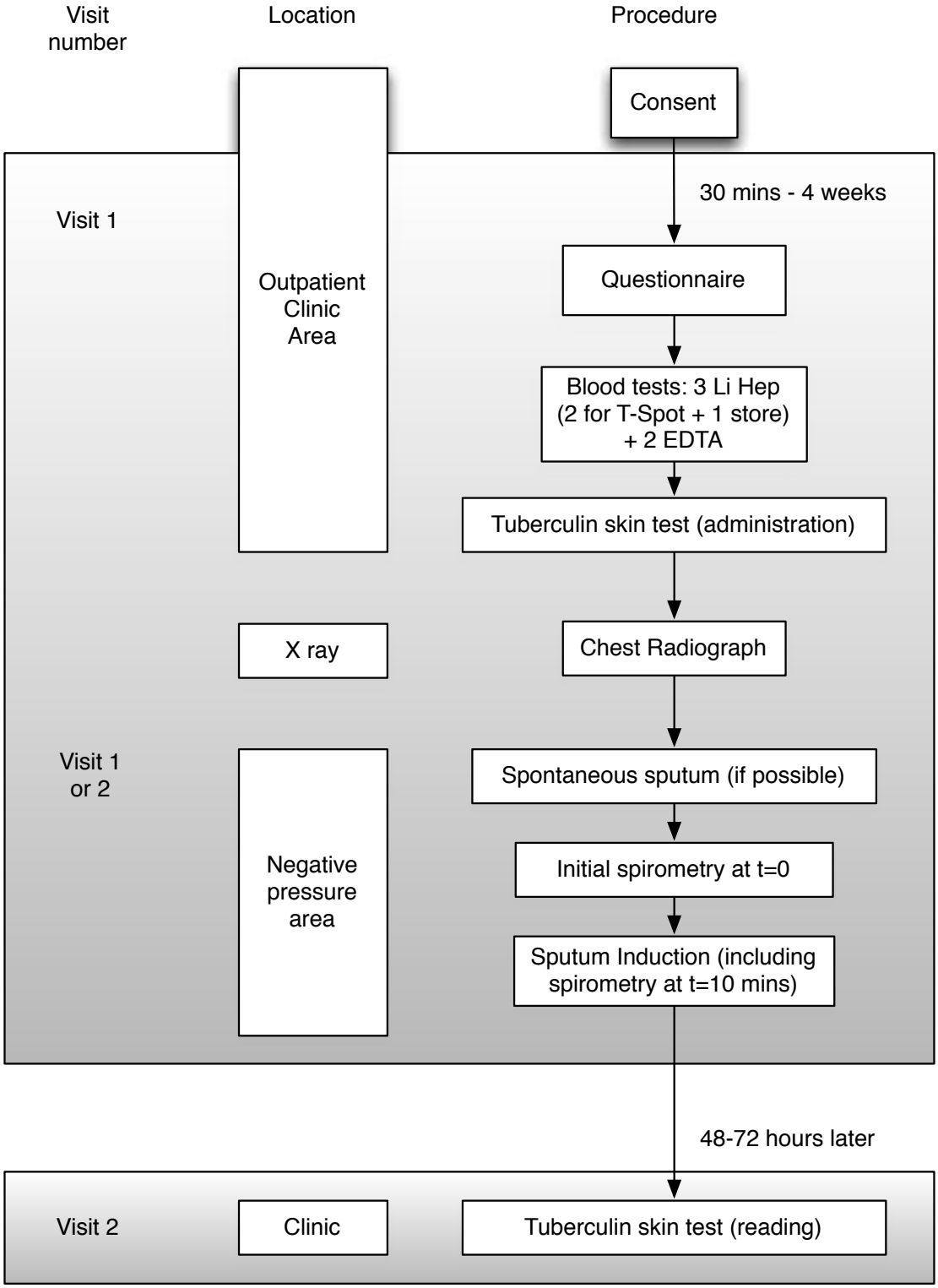
Exclusion Criteria:

- Diagnosis of active TB or undergoing treatment for active or latent TB
- Inability to produce sputum by coughing (e.g. recent rib fracture, chest pain, pneumothorax)
- Pregnancy
- Use of steroids (equivalent to 15mg prednisolone for ≥4 weeks) or any other immunosuppressive drugs (e.g. azathioprine) (relative contraindication)
- Active solid organ or haematological malignancy (excluding Kaposi's sarcoma) or undergoing chemotherapy
- Previous hypersensitivity to purified protein derivative (PPD)
- Extensive eczema

2.3.3.3 Diagnosis

All subjects recruited had a previous positive HIV 1 or 2 serum antibody test and blood HIV viral load confirmed on the Royal Free pathology database.

Figure 2.3.4: Flowchart of Procedures



2.3.3.4 Demographic and symptom questionnaire

Subjects were asked to self-complete a questionnaire including

- Age
- Place of birth
- Previous time living abroad
- History of TB contact or previous TB disease
- History of time in prison or immigration camps
- Respiratory or infective symptoms (including cough, haemoptysis, fever, weight loss, lymphadenopathy) – see appendix
- Smoking history
- History of injecting drug use
- Previous BCG vaccination
- History of respiratory, renal and rheumatological conditions (including history of asthma, COPD and bronchiectasis) plus inhaler or immuno-suppression usage

Recent blood test results were collected from the pathology database including:

- Blood CD4+ lymphocyte cell count and percentage (most recent and six months previously)
- HIV viral load (including most recent and six months previously)
- Serum creatinine
- Blood glucose
- Nadir blood CD4 lymphocyte count and percentage when available

A limited examination for BCG scar and cervical lymphadenopathy was performed.

2.3.3.5 Information extracted from the Royal Free database

Clinical and medication data were taken from subjects' medical records including:

- Suspected route of infection with HIV
- Time of diagnosis with HIV
- Previous antiretroviral treatments
- Most recent and nadir blood cell CD4 counts where available
- HIV viral load and previous chest radiograph reports

2.3.3.6 Quality of life and costs of investigation

Quality of life was measured by EQ5D-5L questionnaire at the time of recruitment. This was used (with UK value sets) to estimate quality of life loss for subjects with latent and subclinical TB. In those with active, subclinical or latent TB infection detected, further quality of life scores and adverse events were recorded at each clinic appointment and also after 1-2 years in those without. Adverse events were recorded systematically using a standardised questionnaire, based on those used in cancer chemotherapy. The number of clinic appointments and time spent with health professionals related to TB care were estimated using the Cerner computer appointments system. Further blood tests or investigations were recorded and costs estimated using NHS or local tariffs.

2.3.4 Study investigations

Subjects were asked to undergo a series of tests for TB infection that included a symptom questionnaire, blood interferon gamma release assay (IGRA, in this study a TSpot.TB), tuberculin skin testing (TST), a frontal chest radiograph (CXR), spontaneous sputum if possible, sputum induction.

2.3.4.1 Symptom questionnaire

TB symptoms were based on WHO and Cain symptom questionnaires. [104,206]

Four respiratory symptoms, based on the symptoms used in the NICE COPD guidelines and screening questions used for the diagnosis of COPD in General Practice were also asked to identify those at risk of airways disease. These were: history of tight chest, history of wheeze, breathlessness walking up one flight of stairs, productive cough most winters. [207-209]

2.3.4.2 TSpot.TB

Two x 6ml lithium heparin tubes of whole blood, drawn at the time of recruitment (preferably at the same time as routine clinic blood testing), were sent to Oxford Diagnostic Laboratories for TSpot.TB testing using the DX same-day courier service. Samples were identified by study number only.

TSpot.TB results were reported as positive, borderline (positive or negative), negative or indeterminate/invalid. The result is interpreted by subtracting the number of spots in the test wells (with mitogens CFP10 or ESAT6) from the

number of spots in the negative control well. A positive result is defined as difference of greater or equal to eight spots. Four spots or fewer is a negative result. Where the difference between the higher of both test wells and the nil control is five, six or seven spots, the result is expressed as borderline. If there are fewer than 20 spots in the positive control or greater than ten spots in a negative control, the test is expressed as indeterminate or invalid. [160] Borderline and indeterminate results were recorded and a blood sample retested at the next available clinic appointment or convenient time.

2.3.4.3 Tuberculin skin tests (TST)

TST was administered using an intradermal injection of 2 tuberculin units (TU)=0.1ml purified protein derivative (Statens Serum Institute, Denmark) with a 28 gauge insulin needle on the volar aspect of the upper third of the forearm to form a wheal 6-10mm in diameter. The time and date of injection, lot number of solution and location of injection site were documented and the subject advised to avoid pressure or bandage at the injection site. The diameter of the lesion was measured at follow-up 48-72 hours later by the investigators, or failing that, by the subject. Instructions to measure the indentation with a pen were given, plus a ruler issued if they felt they would not be able to return. In these cases, subjects were also asked to provide a photograph of the forearm if possible. An induration measuring 5mm or above was considered a positive result.

2.3.4.4 Chest Radiograph

Subjects were asked to have a departmental posterior-anterior frontal chest

radiograph (unless one had been performed in last four weeks). This was reported by a respiratory radiologist at the Royal Free Hospital within 72 hours. If found to be abnormal (e.g. parenchymal lesion or pleural effusion), further testing (including CT scan as appropriate) was conducted as necessary, as part of routine care.

Women aged under 50 had a urinary beta-hCG measured before undertaking a chest radiograph.

2.3.4.5 Spirometry

Spirometry was performed routinely before sputum induction and at five minutes of inhaling 3.5% hypertonic saline. The best of three attempts was recording including peak flow measurement at each time point (detailed further below).

2.3.4.6 Sputum induction

Sputum induction was performed in a negative pressure closed unit within a side room for infection control purposes. This consisted of a transparent polypropylene tent around a 2.2m x 1.5m frame with reinforced Nyplax floor. This used a single HEPA filtered inlet and double HEPA filtered outlet. A motor maintained 15 air exchanges per hour within the chamber. Bacterial/viral filters were used on the spirometer to prevent cross infection.

The procedure was explained to the participants before sputum induction. Spirometric (FEV_1, FVC) and peak flow measurements were performed using a hand held spirometer (MicroPlus, MicroMedical, UK) as a precaution to identify airways disease before starting the procedure and again 5 minutes after commencing the saline nebuliser. Forty millilitres of 3.5% hypertonic saline were

nebulised over 20 minutes using an ultrasonic nebuliser (DeVilbis Ultraneb 3000), with active cycle of breathing and huffing to augment airway clearance. The procedure was stopped if the subject complained of nausea, chest tightness or breathlessness, or if the FEV_1 fell below 15% of the pre-induction value. Salbutamol 100mcg 2 puffs via a spacer was also given if this occurred. Oxygen, inhaled and nebulised salbutamol were available if necessary for treatment of bronchospasm. Sputum was expectorated into three pots in rotation and analysed for mycobacterial microscopy and culture and Xpert MTB/RIF, stored for possible further testing or, if required clinically, for routine sputum culture.

Sputum samples were tested in the Department for Clinical Microbiology, Royal Free Hospital. If sputum volume was low, samples were sent preferentially for acid-fast bacillus (AFB) smear and mycobacterial culture. Any residual sputum was stored at -80ºC in the Department for Clinical Microbiology and identifiable by study number only. Following each procedure, the entire chamber and equipment were cleaned using freshly made Tristel 2% solution (Tristel Solutions Ltd, Cambridgeshire, UK). Filters for the ultrasonic nebuliser, spirometer, plus mouthpiece and tubing were all single use and disposed of in hazardous waste.

2.3.4.7 AFB SMEAR AND MYCOBACTERIAL CULTURE

Induced sputum received was decontaminated and examined using auramine stain for the presence of acid-fast bacilli in a Category III laboratory for respiratory samples. It was then cultured using Bactec-MIGIT liquid culture (Becton, Dickinson, New Jersey, USA) for the presence of mycobacteria for up to 42 days. This was performed by staff at the Royal Free Department of Clinical Microbiology.

2.3.4.8 Xpert MTB.RIF

Induced sputum was routinely tested using Xpert MTB.RIF (Cepheid, Sunnyvale, California, USA) within 48 hours in the Department of Clinical Microbiology, Royal Free Hospital by microbiology staff.

2.3.4.9 Other sputum - use and processing

Any unused sputum was used for further research purposes and collected in a universal container which was identified by date and study number only. This was sealed in the sputum induction tent and frozen at -80^{o}C within four hours with no additives. Samples were stored at the Centre for Clinical Microbiology, UCL Royal Free Hospital Campus.

DNA extraction and multiplex quantitative polymerase chain reaction (qPCR) processing was performed on sputum for airway bacteria (namely *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella pneumophilia*, *Chlamydophila pneumoniae* and *Mycoplasma pneumonia*). This was performed by Dr Camus Nimmo and Sarah Thurston in the research department of the UCL Centre for Clinical Microbiology.

2.3.4.10 Other blood tests

Two EDTA and one Lithium heparin blood samples were drawn at the same time as TSpot.TB testing and stored for other tests of immune function (including for the detection of biomarkers, cytokines or microRNA associated with active and latent TB). Written consent was obtained for these blood samples and only for use in ethically approved future studies. These were centrifuged

at 2500g for 10 minutes at 4ºC, plasma was removed using disposable pipettes and stored in screw-top tubes (Fisher Scientific, UK) at -80ºC in the Centre for Clinical Microbiology, UCL Royal Free Hospital Campus, identified by study number, date and preservative only.

2.3.4.11 Abnormal test results

Those who have abnormal chest radiograph results as a consequence of testing were investigated as per normal clinical care and offered follow up in respiratory clinic as appropriate.

2.4 Economic modelling

Retrospective and prospective data were used to model the uptake, yield and cost-effectiveness of TB testing. This was performed using Excel for Mac 2011 and Excel for Windows 2010.

Cost effectiveness was measured in terms of the incremental cost per case averted (ICCA) and incremental cost per quality associated life year (QALY). Utilities and costs were taken from published sources, and local and national NHS tariffs. [43, 183, 85, 210]

Cost-effectiveness ratios were calculated as the difference in costs divided by the difference in outcomes (active TB cases or QALYs).

2.4.1 Prospective data for cost-effectiveness modelling

A cost-effectiveness model was derived using the results of the prospective study. The study gave real-world variables to be used for uptake and cases of

active, latent and subclinical TB. To calculate the baseline risk of TB (number of new cases of active TB that may arise without testing), a progression rate was estimated using previous prospective studies. [173-5, 211] Numbers of cases prevented was then subtracted from this and cost-effectiveness calculated.

2.4.2 Sensitivity analysis

Univariate and multivariate sensitivity analyses were performed with costs varied for tests, treatment of TB infection (active, subclinical or latent). Uptake, test sensitivity, effectiveness of LTBI chemoprophylaxis were all varied, as were quality of life scores. Multivariate most-costly and least costly scenarios were also estimated.

A probabilistic sensitivity analysis with 10,000 Monte Carlo simulations was used to calculate: 1. uncertainty ranges for each of the point estimates and 2. a cost-effectiveness acceptability curve, showing the probability of cost-effectiveness for each strategy at each threshold.

2.4.3 Costings and utilities

For those with active, subclinical or latent TB, we estimated:

- The monetary cost to the NHS of diagnosis, treatment and ongoing care due to a new diagnosis of TB infection (calculated as the product of blood tests, further investigations, new clinic appointments, plus time with TB nurses, ad hoc attendances to the Emergency Department and Ian Charleson centre and NHS national tariffs)

- Adverse events due to latent and active TB treatment
- Quality of life scores on those with and without LTBI or active/subclinical TB and those on treatment for LTBI and active/subclinical TB (using Euro-QoL/EQ-5D)

2.4.4 Progression rates and efficacy of testing

We estimated the progression rate of those with positive TST and IGRA based on the number who progress to active TB and time after testing.

We also calculated the efficacy of testing by comparing those enrolled in the study with LTBI and who took LTBI preventive treatment, compared to those who did not begin or complete treatment and those who attended the Ian Charleson Centre but did not take part in the study.

2.5 Statistical methods

Data were analysed using SPSS version 20 (IBM SPSS Statistics, USA) for Mac, or Excel 10 for Windows and Excel 2011 for Mac (Microsoft, Seattle, USA). Data were expressed using mean and standard deviation for parametric data and median and interquartile range for non-parametric data. Data were assessed for normality using histograms.

Non-parametric data were compared with the Mann-Whitney U test and proportions compared with the Pearson Chi-Squared test.

Economic modelling was performed in Excel 10 for Windows or Excel 2011 for Mac.

Statistical analyses were reviewed by Dr Colette Smith (Lecturer in Biostatistics,

Department of Infection and Population Health, University College London) and economic analyses by Professor Stephen Morris (Professor of Health Economics, Department of Applied Health Research, University College London).

2.6 Funding

Funding was provided by the Royal Free Department of HIV and Thoracic Medicine.

TSpot.TB tests were paid for by the Royal Free Department of HIV and Thoracic Medicine at a negotiated price. There was no other transfer of funds to external sites.

CHAPTER 3: COST EFFECTIVENESS OF TESTING FOR LATENT TB INFECTION 2000-2010

3.1 Introduction

Testing and treatment for latent TB infection (LTBI) in HIV infected individuals is recommended by national guideline bodies in Europe and North America. In 2011, the National Health Institute for Health and Care Excellence (NICE) and the British HIV Association (BHIVA) published advice, although their strategies differed. [42,43]

In previous retrospective studies, Black African ethnicity and low blood CD4 count (<500 cells/μL) were found to be the greatest risk factors for the development of active TB disease. [31,76] In the UK, BHIVA guidance (2011) advises very targeted testing with an IGRA alone, depending on country of origin, blood CD4 count and duration of ART) (Figure 3.2.3a) [31,42,76] NICE 2011 recommended targeted testing in any HIV infected individuals with a blood CD4 count <500 cells/μL irrespective of ethnicity of place of birth. [43] In 2016, this was updated to include at least an IGRA in all those with HIV plus TST in at least those with blood CD4 <200 cells/μL. Other national guidelines (including European) suggest testing all attendees at HIV clinics with either a tuberculin skin test (TST) or a blood interferon gamma release assays (IGRA). The strategies had not been compared previously for cost-effectiveness.

Sustained anti-retroviral therapy (ART) appears to reduce progression to active TB by up to two-thirds. [59,212] Over the past decade, the demographics of the UK HIV population have changed, with fewer new HIV diagnoses in migrants from high HIV and TB prevalence areas. [213]

We sought to compare the utility and cost-effectiveness of testing: all HIV clinic attendees with a single IGRA, NICE 2011 and BHIVA 2011 latent TB testing strategies using HIV clinic data obtained during two consecutive time periods: 2000-2005 and 2005-2010. Five-year ranges were selected as ART usage became increasingly widespread and national HIV demographics were changing in the UK. We expressed the outcomes in incremental cost per case averted (ICCA - the extra cost required by one strategy compared to another to avert one case of active tuberculosis) and incremental cost per QALY gained. The predictive accuracy of health economic models depend on their ability to model factors that contribute to future need, and these may change over time.

3.2 Methods

3.2.1 Setting and selection

Demographic and clinic data were obtained from the Royal Free HIV Database.

All patients attending the Ian Charleson Centre and the Royal Free HIV inpatient service from 2000 to 2010 were included, other than those who had been given a diagnosis of active TB disease before, or within 3 months of their HIV diagnosis. Three months was used in the model to ensure that all subjects under follow up would have had time to be assessed for LTBI prior to a subsequent diagnosis of active TB.

3.2.2 Data source

The Royal Free Hospital HIV Database contains information prospectively gathered from all patients receiving care. Routine testing for latent TB infection between 2000 and 2010 was not performed in people with HIV infection in this centre. Using clinical and demographic data between 2000 and 2005, and then 2005 to 2010, we modeled: a) no testing, b) NICE 2011, c) BHIVA 2011 strategies and d) testing all patients with a single IGRA to assess the costs and benefits of testing for LTBI. Costs of testing the clinic for LTBI, for preventive treatment and treating active TB cases were calculated. Benefits were measured in terms of active TB cases prevented and quality-adjusted life years (QALYs). The incremental cost per case averted (ICCA) and incremental cost per QALY gained were calculated for each strategy. For the 2000–2005 model, all patients eligible for testing under BHIVA or NICE guidance were tested based on their first CD4 count in 2000. We used each subsequent CD4 count as a surrogate for an HIV clinic appointment – usually every 3-6 months, and those not initially eligible would be tested as soon as they satisfied the requirement for testing using the relevant guideline criteria (Figure 3.2.3a). The CD4 follow up continued until the end of December 2004 and cases of active TB disease recorded. The same analysis was performed using 2005–2010 data.

3.2.3 Model structure and assumptions

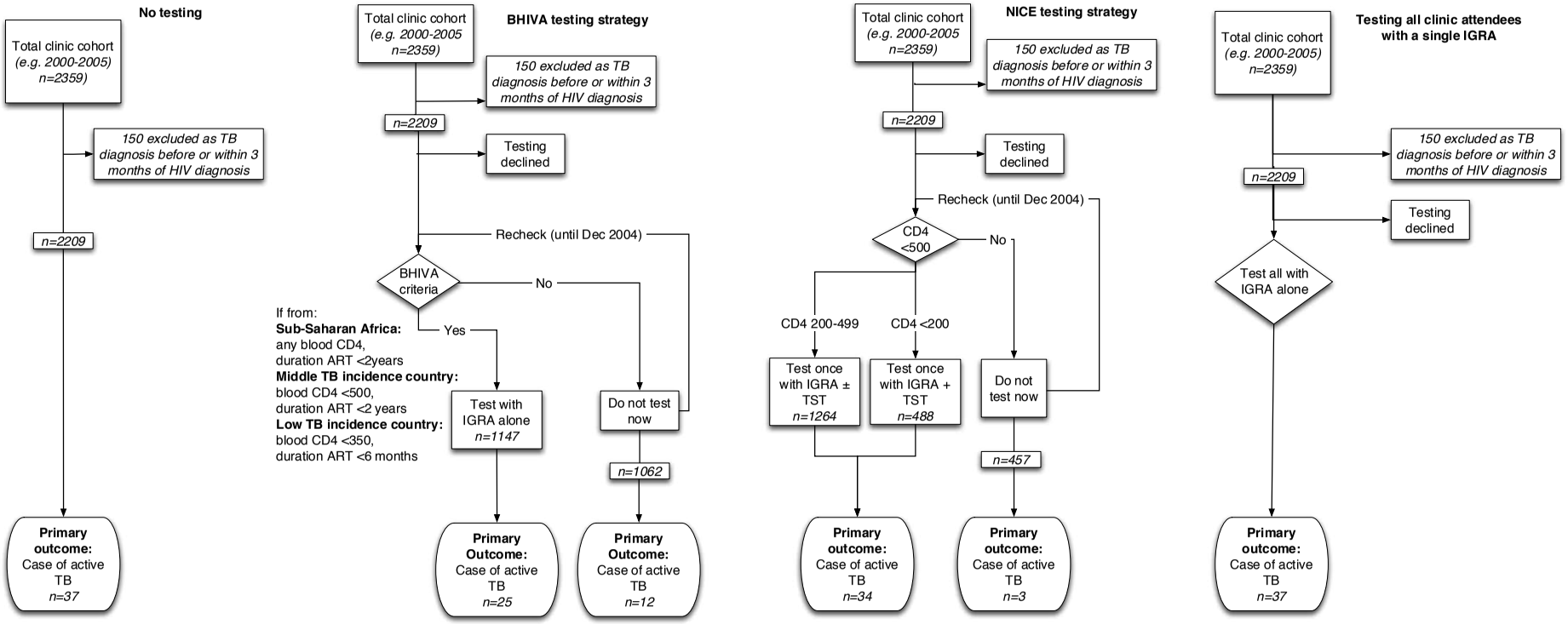
We assumed:

- All HIV infected patients would be eligible except those with an active TB diagnosis in before or within 3 months of their HIV diagnosis
- Initial testing would occur in 87% of those eligible [77]
- Subjects were only tested once, but assuming 3% had an indeterminate IGRA result and would require a repeat test [172]
- 13% of subjects from subSaharan Africa, 10% from middle TB incidence countries and 3% from low TB incidence countries would have a positive IGRA/TST [77]
- Sensitivity of IGRA was 91% [175]
- Uptake of LTBI preventive treatment with 6 months isoniazid was 87% with effectiveness 62% [71]
- QALY reductions for active and latent TB were 0.676 and 0.007 respectively using estimates generated in the NICE guidelines (See table 3.2.3c) [214]

Costs were measured using an English National Health Service perspective in 2011/12 £ sterling. We measured the costs of IGRA, TST, six months treatment with isoniazid, and treatment for active TB using costs from the British National Formulary and published estimates. [43,215] The additional cost of antiretroviral therapy in any in subjects with TB/HIV coinfection who had no other indication for starting ART was not included. Unit costs were based on published sources and local hospital charges (Table 3.2.3c). The time horizon was lifelong, although TB follow up data were available for 5 years. Costs and benefits were discounted at 3.5% per year. [178]

Figure 3.2.3a: Testing algorithms for: No testing, BHIVA strategy, NICE strategy, testing all clinic attendees with data from 2000-2005

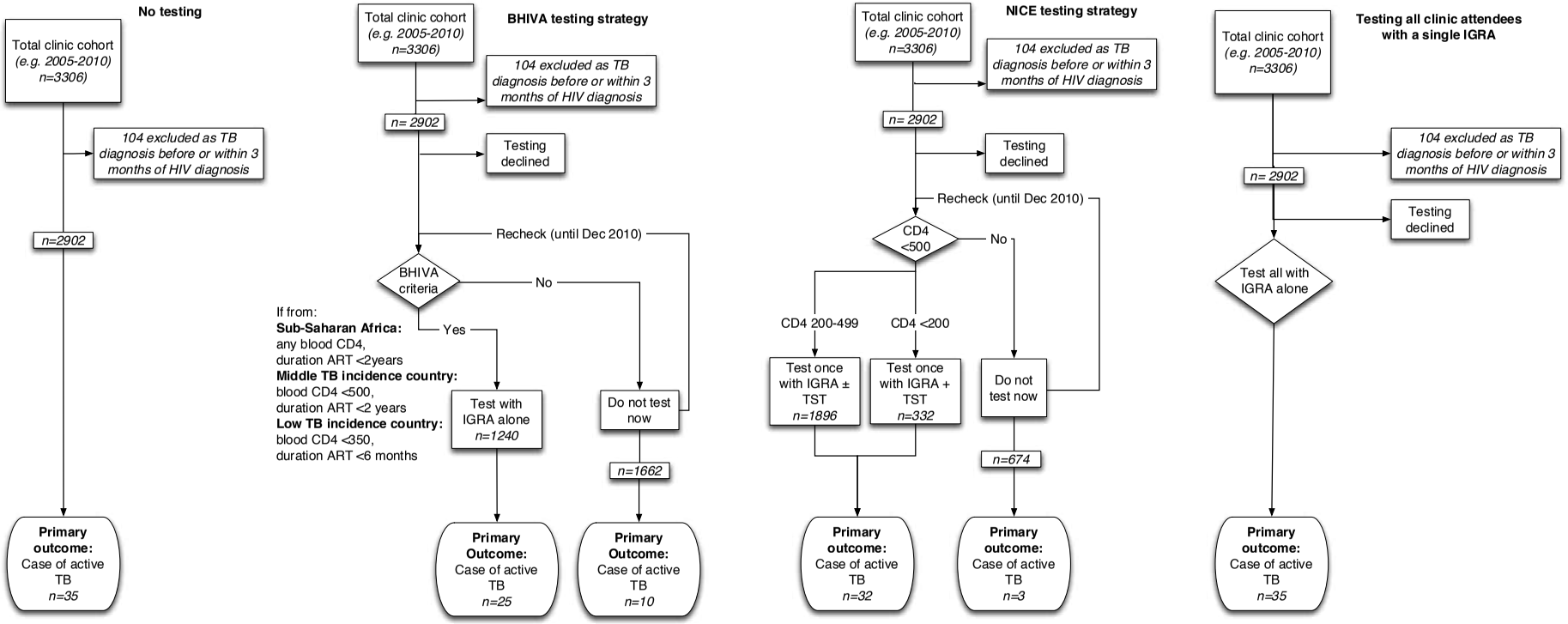
[42,43]



Numbers marked in italics represent the number of subjects at each stage using hospital cohort data between 2000-2005.

Figure 3.2.3b: Testing algorithms for: No testing, BHIVA strategy, NICE strategy, testing all clinic attendees with data from 2005-2010

[42,43]



Numbers marked in italics represent the number of subjects at each stage using hospital cohort data between 2005-2010.

Table 3.2.3c: Variables for univariate and probabilistic sensitivity analyses

Variable	Baseline variable	Range for univariate sensitivity analysis	Distribution for Probabilistic Sensitivity Analysis	Alpha	Beta	Source
Cost IGRA (based on T.Spot.TB test)	£60	£23-£90	Gamma	10.10	5.94	[43], [133] local charges
Cost TST	£16.14	£8.08-£32.28	Gamma	15.35	1.05	[43]
Cost 6 months isoniazid	£786.5	£374.50-£1316.50	Gamma	13.99	56.18	[43],[215], local charges
Cost treatment for active TB	£7619.67	£3809.93-£15239.30	Gamma	15.37	495.86	[183]
QALY reduction for active TB	0.676	0.271 to 6.72	Gamma	16.72	0.0404	[[43][195]
QALY reduction for latent TB	0.007	0.001 to 0.1	Gamma	7.530	0.0009	[43]
Sensitivity of IGRA	91%	70%-100%	Beta	710.8	71.16	[175]
Uptake testing	87%	87%-100%	Beta	519.1	79.87	[77]
Uptake LTBI treatment	87%	60%-100%	Beta	39.13	5.870	[77]
Efficacy LTBI treatment	62%	40%-100%	Beta	1474	903.3	[71]
Indeterminate IGRA rate	3%	0%-10%	Beta	20.03	569.0	[172]
Proportion of black Africans with positive IGRA	13%		Beta	16.9	113.1	[77]
Proportion of subjects from middle TB incidence countries with positive IGRA	10%		Beta	7.8	70.2	[77]
Proportion of subjects from low TB incidence countries with positive IGRA	3%		Beta	7.23	233.8	[77]

3.2.4 Cost-effectiveness

Cost-effectiveness was measured in terms of the ICCA and the incremental cost per QALY gained over each five-year period; and calculated separately for each of the time periods (2000-2005, 2005-2010). Incremental analyses of the BHIVA strategy versus no testing, NICE versus BHIVA strategies, and testing all attendees versus NICE were performed. Cost-effectiveness ratios were calculated as the difference in costs between the two strategies being compared, divided by the difference in outcomes (cases of active TB disease, QALYs).

3.2.5 Sensitivity analysis

3.2.5.1 Univariate and multivariate analyses

Costs for IGRA, TST, treatment of latent and active TB were varied to reflect the additional expense of increased TB-related morbidity, isoniazid-induced hepatotoxicity or TB drug resistance. The uptake of testing, sensitivity of IGRA, uptake and effectiveness of isoniazid preventive therapy (IPT) were varied using published data. The effectiveness varied between 40% (an estimate, given non-optimal adherence) and 100% (a figure approached in a study in East London in 2014). [76,77] Quality of life utility was also varied for LTBI preventive treatment and active TB treatment. Most-costly and least-costly multivariate scenarios were considered (Table 3.2.3c).

A probabilistic sensitivity analysis (PSA) with 10,000 Monte Carlo simulations of the model was also performed and uncertainty ranges for each point estimates

of cost-effectiveness and cost-effectiveness acceptability curves were calculated, showing the probability that each option was cost-effective for different cost-effectiveness thresholds. This analysis accounted simultaneously for uncertainty in uptake, IGRA sensitivity, incidence of TB, detection rate of each strategy, costs and quality of life years lost for TB infection. The distributions and parameter values used are given in Table 3.2.3c.

3.3 Results

The Royal Free HIV clinic cohort consisted of 1136 individuals in 2000, 2025 in 2005 and 2461 in 2010. 689 (61%) were on ART consisting of three drugs in 2000, 1505 (74%) in 2005 and 2119 (86%) in 2010.

3.3.2 Cases of active tuberculosis with HIV infection

Between 2000–2010, there were 256 cases of tuberculosis with HIV co-infection at this centre. Seventy-two (28%) had a TB diagnosis ≥ 3 months after their HIV diagnosis. Of these, 38 (53%) had culture confirmed TB, sensitive to all first line anti-tuberculosis drugs, one of isoniazid resistant TB and one of multidrug resistant TB.

3.3.3 Cases not prevented by testing guidelines

Had either BHIVA or NICE strategies been used, neither would have tested all people that would later develop active tuberculosis. When compared to BHIVA, NICE's broader criteria predicted more cases consistently (Figure 3.2.3a and Table 3.3.4a), although the costs associated with testing were higher. Five of the

six cases that would not have been tested by NICE were already taking ART or had interrupted ART. Two of the six were UK born. Twenty-two of the 31 cases not eligible for testing using BHIVA criteria were born in the UK, whilst 28 were using ART or had interrupted ART when diagnosed with active TB.

3.3.4 Comparative cost effectiveness 2000–2005 and 2005-2010

Between 2000–2005, 37 patients known to be HIV positive and undergoing care at the Royal Free Hospital developed active tuberculosis. Over five years, using BHIVA criteria, 1147 subjects would be tested and 12 of 37 (32.4%, 95% confidence intervals, CI 18.0, 49.8%), who later developed tuberculosis would not have been tested. Using the NICE testing model, 1752 subjects would have been tested, including 34 of the 37 patients with TB disease (8.1% not tested, 95% CI 1.7, 21.9%). Allowing for an uptake of testing of 87%, testing all eligible subjects over five years, plus treating those with latent tuberculosis as well as the active TB cases missed by testing, would cost £315,594, £329,854 and £349,940 using BHIVA and NICE guidance and testing all clinic attendees respectively (Table 3.3.4a). These equate to an extra £143 (BHIVA), £149 (NICE), £158 (all) in costs for each person attending the HIV clinic. Compared to no testing, 6.4 QALYs would be gained with BHIVA guidance, 8.9 with NICE and 9.6 testing all. Comparing BHIVA to no testing, NICE to BHIVA, and all to NICE, the incremental cost-effectiveness ratios were £ 5,225 (95% uncertainty ranges, UR £2,902 to £6,553), £5,832 (£3,442 to £15,678) and £27,894 (£5,746 to £137,099) respectively (Table 3.3.4b).

Using 2005–2010 data, 35 patients developed tuberculosis. Using BHIVA criteria, 1,240 subjects would be tested and 11/35 (31.4%, 95% CI 17.4, 49.4) who later developed TB would not have been tested. Using NICE guidance, 2,228 subjects

would have been tested including 30/35 subjects with subsequent TB (14.3% not tested, 95% CI 5.4, 31.1%). Discounted QALYs gained by testing were 6.4 with BHIVA, 8.2 with NICE and 8.8 testing all and the incremental costs per QALY gained (95% UR) were £7,777 (£4,497 to £9,965), £27,137 (£20,888 to £55,209) and £61,723 (£16,354 to £554,778) (Table 3.3.4b).

3.3.5 Sensitivity analysis

LTBI testing became more cost effective as the cost of an IGRA fell, the uptake or effectiveness of LTBI preventive treatment increased, or the cost of treatment for active tuberculosis rose. The IGRA indeterminate rate made little difference. If an IGRA cost £25, LTBI preventive treatment was 98% effective, or treatment of one case of active TB increased to £11,600, testing for LTBI between 2000–2005 using any strategy became cost-saving compared to no testing (see Tables 3.3.5c and d, Figure 3.3.5e).

The cost effectiveness acceptability curves, derived from the probabilistic sensitivity analysis, are shown in Figures 3.3.5a and b for the time periods 2000-2005 and 2005-2010 respectively. These indicate that if a health service were willing to pay an extra £20,000 for an additional QALY,[178] the NICE strategy would most probably be best value between 2000 and 2005, and the BHIVA strategy between 2005-2010 (Figures 3.3.5a and b).

Table 3.3.4a Cases and costs of no testing, testing using BHIVA and NICE strategies and testing all attendees

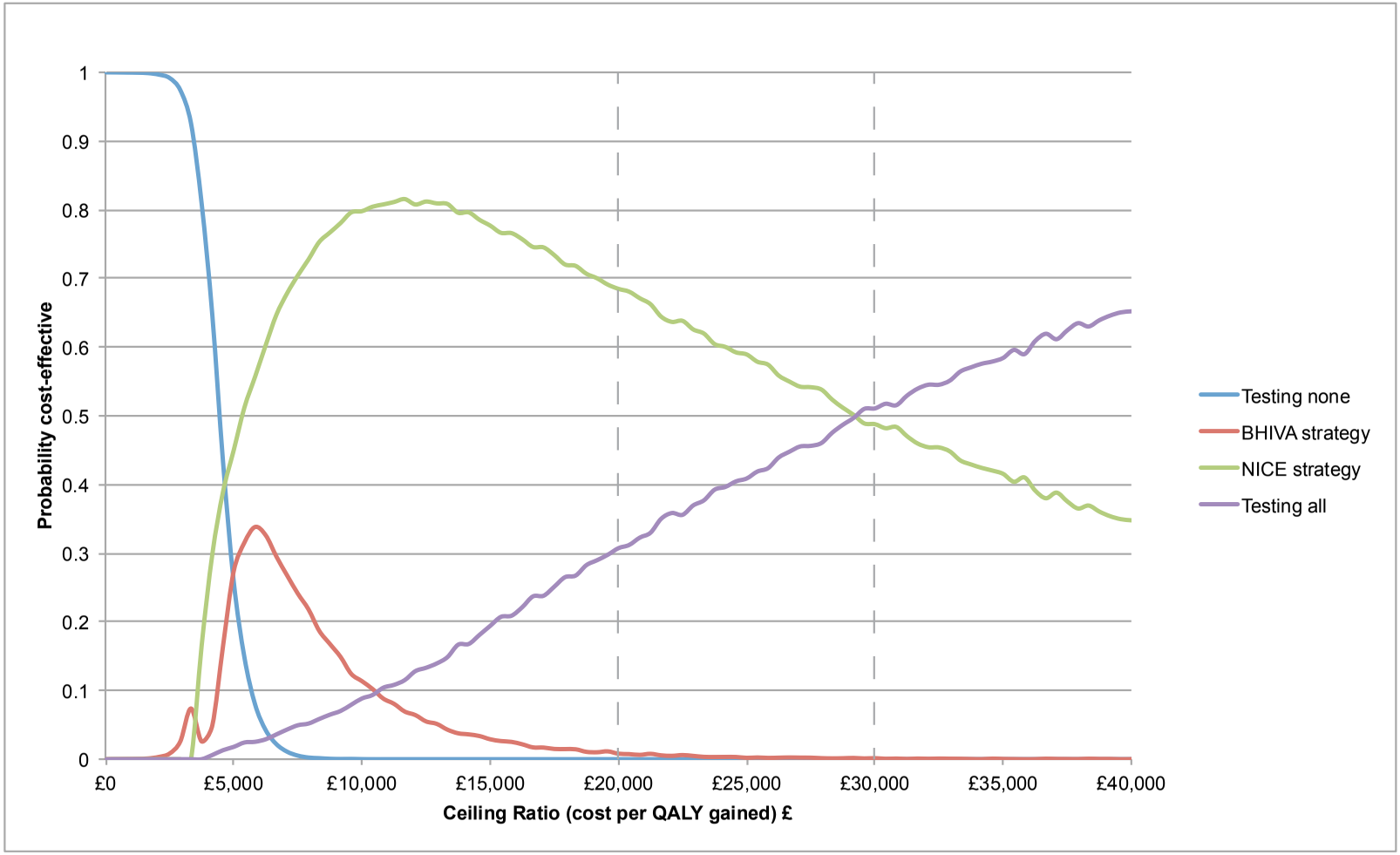
Data from 2000–05 (n=2,209) and 2005–2010 (n=2,902)

	No testing		BHIVA testing		NICE testing		Testing all	
	2000-2005	2005-2010	2000-2005	2005-2010	2000-2005	2005-2010	2000-2005	2005-2010
Total cases of active TB under testing strategy	37	35	26	24	23	21	21	20
Total cost for of testing for LTBI	£0	£0	£61,672	£66,673	£101,028	£124,440	£118,773	£156,035
Average cost/ patient of testing for LTBI	£0	£0	£28	£23	£46	£43	£54	£54
Total cost of preventive treatment	£0	£0	£52,902	£63,726	£56,931	£77,416	£68,982	£96,359
Average cost/ patient of preventive treatment	£0	£0	£24	£22	£26	£27	£31	£33
Total cost of remaining active cases	£281,928	£266,688	£201,021	£185,782	£171,894	£163,128	£162,185	£153,418
Average cost/ patient of remaining active cases	£128	£92	£91	£64	£78	£56	£73	£53
Total cost	£281,928	£266,688	£315,594	£316,180	£329,854	£364,983	£349,940	£405,813
Average cost/ patient of entire strategy	£128	£92	£143	£109	£149	£126	£158	£140

Table 3.3.4b Comparative testing comparing BHIVA strategy to No testing, NICE strategy to BHIVA strategy and testing all attendees to NICE

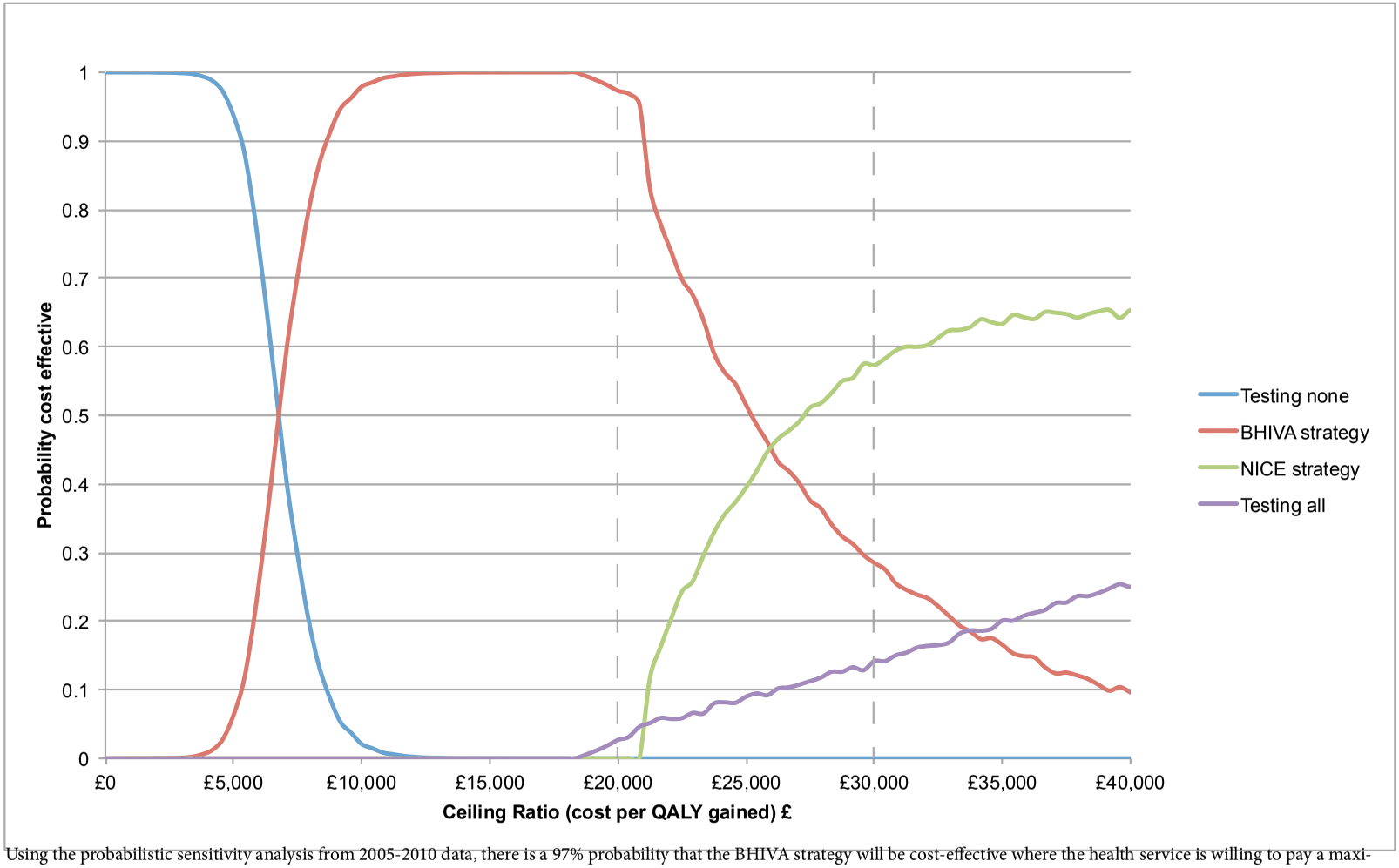
	BHIVA vs No testing		NICE vs BHIVA		All vs NICE	
	2000-2005	2005-2010	2000-2005	2005-2010	2000-2005	2005-2010
Difference in costs						
Cost of testing	£61,672	£66,673	£39,357	£34,863	£17,745	£31,595
Cost of preventive treatment	£52,902	£63,726	£4,030	£13,690	£12,050	£18,943
Cost of treating active TB	-£80,907	-£80,907	-£29,127	-£22,654	-£9,709	-£9,709
Total cost (95% uncertainty ranges)	£33,667 (£8,538 to £88,951)	£49,491 (£13,333 to £130,048)	£14,260 (£4,436 to £53,226)	£48,803 (£18,140 to £127,063)	£20,087 (£3,889 to £54,193)	£40,830 (£11,959 to £98,653)
Extra cost/ patient in clinic	£15.24	£17.06	£6.46	£16.82	£9.09	£14.07
Difference in outcomes, discounted at 3.5%/year (95% uncertainty ranges)						
Cases of active TB prevented	10 (7.5-15)	10 (7.6-14)	4 (3.3-4.3)	3 (2.4-3.4)	1 (0.6-1.8)	1 (0.6-1.8)
QALYs gained	6.44 (1.8-12.5)	6.36 (2.0-12.1)	2.45 (1.3-3.6)	1.80 (1-2.6)	0.72 (0.5-0.8)	0.66 (0.5-0.9)
Cost effectiveness, discounted at 3.5%/year (95% uncertainty ranges)						
Incremental cost per case prevented	£3,331 (£1,108 to £6,163)	£4,896 (£1,708 to £9,151)	£3,792 (£1,467 to £14,746)	£16,573 (£8,298 to £43,955)	£16,503 (£2,183 to £76,265)	£33,534 (£6,498 to £146,982)
Incremental cost/ QALY gained	£5,225 (£2,902 to £6,553)	£7,777 (£4,497 to £9,965)	£5,832 (£3,442 to £15,678)	£27,137 (£20,888 to £55,209)	£27,894 (£5,746 to £137,099)	£61,723 (£16,354 to £554,778)

Figure 3.3.5a Cost effectiveness acceptability curves for No testing, BHIVA and NICE algorithms and testing all clinic attendees, 2000-2005



Using the probabilistic sensitivity analysis from 2000-2005 data, there is a 68% probability that the NICE strategy will be cost-effective where the health service is willing to pay a maximum of £20,000 per QALY gained (vertical dashed line).

Figure 3.3.5b Cost effectiveness acceptability curves for No testing, BHIVA and NICE algorithms and testing all clinic attendees, 2005-2010



Using the probabilistic sensitivity analysis from 2005-2010 data, there is a 97% probability that the BHIVA strategy will be cost-effective where the health service is willing to pay a maximum of £20,000 per QALY gained (vertical dashed line) and 58% probability that the NICE strategy will be cost-effective at maximum £30,000 per QALY gained (vertical dashed line).

Table 3.3.5c Univariate sensitivity analysis (Cost/case averted)

Variable	BHIVA to No testing		NICE to BHIVA		All to NICE	
	2000-2005	2005-2010	2000-2005	2005-2010	2000-2005	2005-2010
Middle inputs	£3,331	£4,896	£3,792	£16,573	£16,503	£33,534
TST £8.06	£3,331	£4,896	£2,884	£15,784	£19,308	£35,442
TST £32.28	£3,331	£4,896	£5,608	£18,151	£10,893	£29,719
IGRA £23	Cost saving	£828	Cost saving	£5,448	£4,053	£15,179
IGRA £90	£6,381	£8,194	£8,118	£25,593	£26,595	£48,416
LTBI £374.50	£589	£1,593	£3,231	£14,138	£11,316	£25,383
LTBI £1316.50	£6,858	£9,144	£4,514	£19,706	£23,173	£44,018
Active £3809.93	£7,333	£8,898	£7,665	£20,420	£20,490	£37,521
Active £15239.33	Cost saving	Cost saving	Cost saving	£8,880	£8,525	£25,560
LTBI efficacy 0·4	£9,564	£11,991	£10,138	£29,920	£29,964	£56,363
LTBI efficacy 1	Cost saving	Cost saving	Cost saving	£7,352	£7,200	£17,761
Uptake of testing 60%	£3,331	£4,896	£3,792	£16,573	£16,503	£33,534
Uptake of testing 100%	£3,331	£4,896	£3,792	£16,573	£16,503	£33,534
Uptake of LTBI treatment 60%	£8,423	£10,692	£2,173	£15,664	£23,052	£45,193
Uptake of LTBI treatment 100%	£1,853	£3,213	£4,262	£16,838	£14,600	£30,149
Sensitivity of IGRA 70%	£6,715	£8,748	£7,237	£23,818	£23,810	£45,927
Sensitivity of IGRA 100%	£2,299	£3,723	£2,742	£14,365	£14,274	£29,757
Indeterminate rate 10%	£3,720	£5,317	£4,344	£17,725	£17,791	£35,434
Indeterminate rate 0%	£3,130	£4,679	£3,508	£15,980	£15,838	£32,556
Least expensive testing, most expensive costs	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving
Most expensive testing, least expensive costs	£49,952	£57,483	£29,302	£72,237	£90,613	£164,726

Table 3.3.5d Univariate sensitivity analysis (Cost/QALY gained)

Variable	BHIVA to No testing		NICE to BHIVA		All to NICE	
	2000-2005	2005-2010	2000-2005	2005-2010	2000-2005	2005-2010
Middle inputs	£5,225	£7,777	£5,832	£27,137	£27,894	£61,723
TST £8.06	£5,225	£7,777	£4,435	£25,845	£32,637	£65,235
TST £32.28	£5,225	£7,777	£8,623	£29,720	£18,413	£54,702
IGRA £23	Cost saving	£1,317	Cost saving	£8,922	£6,852	£27,939
IGRA £90	£10,010	£13,015	£12,483	£41,907	£44,957	£89,114
LTBI £374.50	£924	£2,532	£4,968	£23,149	£19,128	£46,722
LTBI £1316.50	£10,758	£14,525	£6,943	£32,267	£39,171	£81,020
Active £3809.93	£11,503	£14,133	£11,788	£33,436	£34,635	£69,062
Active £15239.33	Cost saving	Cost saving	Cost saving	£14,540	£14,412	£47,046
LTBI efficacy 0·4	£15,521	£19,853	£15,938	£52,051	£55,086	£120,364
LTBI efficacy 1	Cost saving	Cost saving	Cost saving	£11,568	£11,530	£29,843
Uptake of testing 60%	£5,225	£7,777	£5,832	£27,137	£27,894	£61,723
Uptake of testing 100%	£5,225	£7,777	£5,832	£27,137	£27,894	£61,723
Uptake of LTBI treatment 60%	£13,213	£16,983	£3,343	£25,648	£38,966	£83,181
Uptake of LTBI treatment 100%	£2,906	£5,104	£6,554	£27,569	£24,680	£55,493
Sensitivity of IGRA 70%	£10,728	£14,208	£11,263	£40,286	£42,088	£91,383
Sensitivity of IGRA 100%	£3,587	£5,873	£4,202	£23,295	£23,812	£53,547
Indeterminate rate 10%	£5,836	£8,446	£6,681	£29,023	£30,073	£65,219
Indeterminate rate 0%	£4,910	£7,433	£5,394	£26,166	£26,772	£59,922
QALY loss active TB 0.271	£14,328	£21,803	£15,463	£80,561	£88,440	£242,470
QALY loss active TB 6.72	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving
QALY loss latent TB 0.001	£4,968	£7,314	£5,640	£24,860	£24,854	£51,038
QALY loss latent TB 0.1	£26,609	£393,057	£12,312	Strictly dominated	Strictly dominated	Strictly dominated
Least expensive testing, most expensive costs	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving
Most expensive testing, least expensive costs	£83,476	£98,681	£46,947	£132,638	£179,828	£406,588

Figure 3.3.5e Tornado chart of variables affecting the cost/QALY gained (BHIVA compared to no testing, (2000-2005)

3.4 Discussion

3.4.1 Principal findings

At an incremental cost per QALY gained cost-effectiveness threshold of £20,000-£30,000, and using data from 2000-2010, testing and treating latent tuberculosis in people with HIV (using ART in the majority of cases) appeared to be cost-effective with respect to no testing in a low TB incidence, high resource setting. [178] Of the four strategies compared, testing based on NICE criteria was the most cost-effective option using 2000-2005 data at a cost-effectiveness threshold of £20,000/QALY and testing all clinic attendees at £30,000/QALY (Figure 3.3.5a). Between 2005-2010, the BHIVA strategy was most likely cost-effective at a threshold of £20,000 and NICE at £30,000. Testing all clinic attendees became considerably less cost effective in this time period (Figure 3.3.5b). This change could have resulted from altering UK HIV demographics (e.g. as there were proportionally fewer HIV infected individuals in the UK from TB endemic countries) or from an increase in ART usage, which would reduce the risk of progression from LTBI to active TB. [54,213] For example – one third of our clinic population now have a blood CD4 cell count under 500 μL. If these changes are representative of other low TB incidence settings and continue, testing may become less cost effective in future, irrespective of the strategy selected.

Of note, even with optimal implementation, our data indicate that these testing strategies would prevent only around one quarter of recorded cases of active tuberculosis. The majority of patients with HIV co-infection in the UK do not know their HIV status when they initially present with active TB disease and

are diagnosed with HIV subsequently. [54] These patients tend to access HIV care at a later stage in their illness, have a lower blood CD4 count and higher disease associated morbidity and hence treatment costs. [54] A possibly more effective strategy may involve community-based HIV testing, and then if positive, subsequent assessment for TB.

3.4.2 Limitations, criticisms and assumptions

This cost-effectiveness analysis is based on retrospective data and is not a contemporary, prospective study of LTBI preventive therapy versus placebo in people living with HIV with positive TST or IGRA. It did, however, reflect the cost-effectiveness of testing over a decade and showed that external factors may influence this relatively rapidly, and these factors should be acknowledged when modelling to influence guidance. Although a five-year outcome was used in this study to illustrate the changes over time, LTBI preventive therapy is likely to lead to benefit over a longer time period.

A number of assumptions were used. Costings were used for TB cases without HIV coinfection as there is little in the published literature for cases of TB/HIV coinfection. Previous studies have suggested an increased morbidity and mortality, and more drug-interactions associated with TB/HIV coinfection. [68,216] If there were an increase in treatment cost and decrease in the quality of life associated with coinfection, systematic LTBI testing could be justified further. Also, HIV care in the UK already involves regular follow up, and testing and preventive treatment for other opportunistic infections (such as Pneumocystis pneumonia or toxoplasmosis) has become an intrinsic part of this. Similarly,

LTBI preventive treatment may be relatively easy to incorporate, requiring fewer resources than LTBI testing and treatment than other contexts such as amongst TB contacts or new entrants. Finally, the cost-effectiveness of preventing onward transmission using LTBI preventive therapy was not included here.

The costs of hepatotoxicity related to preventive TB treatment and active TB treatment were not specifically determined, but the increased costs associated with this were included within the sensitivity analysis. In this model, an IGRA cost £60, the hospital list price for a TSpot.TB test. The actual costs for this assay may be less and could also fall if using the QuantiFERON Gold In-Tube, which tends to be less expensive. It is not clear if the two tests have equivalent sensitivity or indeterminate result rates in this population. [163,167,217]

Again, due to lack of data in people with HIV, QALY reductions from TB cases without HIV coinfection were used. A recent study has shown a similar loss in quality of life measured by EQ-5D in those with active drug-sensitive TB with or without HIV coinfection in Thailand. [200] Our analysis has been from a clinical perspective and has only used the potential costs and health status in those subjects tested. We have not included potential cases prevented in contacts and the monetary or quality of life costs associated with this. From a public health position, the appropriateness of a £20-30,000/QALY or £12-19,000/case averted ceiling could be questioned.

3.4.3 Implementation

Previous studies have reported difficulties in implementation of systematic LTBI testing in HIV, both at a clinic and patient level. In the Swiss Cohort Study, a programme to treat latent TB resulted in only 37% of HIV patients with a positive

TST receiving a full course of such therapy. In part this was due to physicians' poor adherence to the recommendation. [76] In those that were given preventive treatment, however, there were no subsequent cases of active TB, a finding that has been mirrored in more recent studies from Western Europe. [77,174] Our assumptions of uptake and LTBI treatment completion are based on contemporary studies from London;[77] however, by using results from a meta-analysis on TST positive HIV infected individuals, comparing LTBI treatment against placebo, we may have underestimated the efficacy of LTBI treatment in people with a positive IGRA (as modelled here) and hence the cost-effectiveness of testing. [71,77] As technologies to detect LTBI improve, the potential for a test with a better positive predictive value for the development of active TB would further reduce the costs and morbidity associated with LTBI treatment.

3.5 Conclusion

Retrospective data between 2000-2010 show that testing for tuberculosis infection in those with a known HIV diagnosis seems cost-effective using either NICE 2011 or BHIVA strategies, both of which were published in 2011 and drew on data from 1996-2006. Using our clinic data from 2000-2005, the NICE strategy is simple, less likely to miss cases and cheaper to implement than universal testing. This has reduced the cost effectiveness of testing. Checking for latent TB in known HIV infected persons cannot impact on the majority of cases of TB-HIV co-infection who are diagnosed with both conditions simultaneously. This argues for more population-based HIV testing, with subsequent TB risk assessment and treatment if found to be infected. [54]

CHAPTER 4: STUDY RESULTS

4.1 Introduction

4.1.1 Testing for TB disease and LTBI in HIV infected individuals

HIV is the single greatest risk factor for the development of active TB. Testing for both active and latent TB in people living with HIV has been recommended since this was first realised. [41,218] Guidelines in resource rich, low TB prevalence countries around the world differ, however. The United States Center for Disease Control (CDC) have very comprehensive advice that tests for active disease and latent infection, whereas the British HIV Association (BHIVA) guidance tests for LTBI just in those at the highest risk of reactivation. [41,42] Over the past five years, the number of TB diagnoses in people with HIV has fallen in the UK annually, perhaps as a result of a change in UK HIV demographics and increasingly widespread use of antiretroviral therapy. [59,219]

4.1.2 Use of TST and IGRA

The British HIV Association (BHIVA) guidelines, published in 2011, were based on a large retrospective epidemiological cohort study from various UK HIV centres (UK CHIC) and the results of a national TB testing strategy, using the tuberculin skin test (TST), in HIV clinics in Switzerland. [31,220] Since this study, Interferon-gamma release assays (IGRA) have been adopted more widely due to their relative convenience and increasing evidence base. Many groups have published studies comparing these tests when investigating the prevalence of LTBI.

Some have used preventive therapy, where as some studied the outcomes in this group when left untreated. [146,165,171,174,175,220-222] Medium and long term follow-up data are relatively sparse, and it remains unclear whether IGRA predicts subsequent active TB in a manner to TST. [171,175,221,222] The prevalence of active TB disease and latent TB infection across European centres, however, have been surprisingly similar using either test. LTBI is detected in 13-24% of black Africans and in around 3% of white Western Europeans. [77,172,175,222]

4.1.3 Rationale of testing strategies

Many of these studies start with an immunological test as a first step, then investigate only those with a positive result for active TB. Some individuals with a positive TST or IGRA were found to have active or clinically unapparent (subclinical) TB at the time of testing (so called prevalent TB). Since only those with a positive TST/IGRA were investigated for active disease, the prevalence subclinical TB in those that are TST/IGRA negative is unknown. Frequently these studies have investigated the impact of LTBI preventive therapy, and people with previously treated TB were therefore excluded. [77,175]

Despite the number of studies of TB testing in HIV-infected adults in low TB prevalence areas, none of the guidelines have been compared for cost-effectiveness.

4.1.4 Aim of the study

In this cross-sectional study, we sought to determine the prevalence of LTBI (with both TST and IGRA), subclinical and active TB; the uptake and yield of testing; quality of life data and costings, to determine the feasibility and cost-effectiveness of TB testing in a representative, contemporary UK HIV clinic.

4.1.5 Hypotheses

1. There is a significant difference in the prevalence of TB infection between black Africans and those from low TB incidence countries attending a UK HIV clinic.

2. Tuberculin skin testing provides no further information compared to single step blood Interferon Gamma Release Assay in the detection of *M. tuberculosis* infection in a UK HIV-infected clinic population.

3. Within this clinic population, asymptomatic HIV-infected individuals with normal chest radiographs have negative mycobacterial sputum microscopy and culture despite originating from high TB prevalence areas.

4.1.6 Objectives

1. Determine the feasibility of systematic testing for *M. tuberculosis* infection in a UK HIV-infected population

2. To determine the prevalence of subclinical and active TB in a UK HIV clinic

3. To determine the sensitivity and specificity of systematic screening questionnaires for detecting cases of active TB outside of high TB incidence settings

4. To determine concordance between TST and blood TSpot.TB in latent TB infection

5. To identify risk factors for latent TB infection in the clinic population

6. To determine the sensitivity and specificity of Xpert MTB.RIF polymerase chain reaction (PCR) testing of sputum and induced sputum compared to mycobacterial microscopy and culture

7. To determine uptake of latent TB therapy (6 months isoniazid treatment)

8. To determine cost of latent TB treatment (including screening costs, clinic

time)

9. To determine quality of life and rate and severity of adverse events on latent TB treatment

Airways disease

10. To determine the underlying frequency of airways disease (using spirometry) and of respiratory symptoms

4.2 Methods

4.2.1 Study design

1. Cross-sectional study to assess the prevalence of active, subclinical and latent tuberculosis in people living with HIV undergoing care at the Royal Free Hospital

2. Quality of life and subsequent economic analysis of systematic TB testing and latent tuberculosis treatment in this group

3. Establishment of baseline measures for a cohort that can be followed over time while receiving long-term HIV care

4.2.2 Study population

Selection criteria were:

Ambulatory care patients at the Royal Free Hospital with HIV-1 or 2 positive antibody and over the age of 18, and:

a new diagnosis of HIV during dates of recruitment, or

in care and attending routine ambulatory HIV care clinics, selected by stratified sampling.

Recruitment was carried out at the Ian Charleson Centre for HIV care at the Royal Free Hospital. Subjects were approached either before or after their routine appointments by their clinician or the researchers. Further details plus inclusion and exclusion criteria are listed in Chapter 2 (Methods), section 2.3.3.

All female participants under the age of 50 were asked to have urinary bHCG testing before frontal chest radiograph.

4.2.3 Data sources

Participants were asked to self-complete a questionnaire, including basic demographics, previous countries of residence, previous: education, occupation, history of TB exposure, smoking and drug use, other medical conditions and use of prescription medications other than antiretrovirals. A baseline quality of life score (EQ5D) was also requested.

Antiretroviral use was taken from pharmacy records.

Full blood count; creatinine and glucose measurements; plasma HIV viral load; nadir, previous and most recent blood CD4 cell counts were extracted from the pathology database. Previous CXR reports were taken from the radiology (PACS) system. HIV risk factors, nadir blood CD4 cell counts, viral loads at diagnosis and time from HIV diagnosis were extracted from the Royal Free HIV database.

At the time of enrolment subjects were asked to have:

- A frontal chest radiograph (CXR)
- Blood sampling for blood IGRA (TSpot.TB, Oxford Immunotec, Abingdon, Oxfordshire) with two lithium heparin tubes and other research blood tests for cytokine and RNA analysis (a further lithium heparin and two

3ml EDTA vials)

- Tuberculin skin testing (TST): 0.1ml purified protein derivative (Statens Serum Institute, Copenhagen, Denmark) was injected intradermally and instructions given on how to interpret the result in the case of non-reattendance. Some participants agreed to sputum induction the same morning, some when they returned to have their TST measured 48-72 hours later
- Baseline spirometry, examination for BCG scar and limited cervical lymph node examination
- Sputum induction, using 3.5% hypertonic saline was performed with repeat spirometry at 5 minutes for safety. Further details are in Methods Chapter 2, Section 2.3.4

No routine bronchodilators were used before spirometry. If subjects had a history of bronchospasm, they were asked to pre-medicate with salbutamol.

Participant results could be used in the analysis if they consented, provided a questionnaire and a blood IGRA or TST result was available.

4.2.4 Definitions

Black Africans (BA) were defined as people born and raised in countries in subSaharan Africa (sSA), approximating to a national active TB disease incidence of >300/100,000. Middle incidence (MI) countries were defined as those outside of subSaharan Africa (including South America, South and East Asia and Eastern Europe) approximating to countries with a TB incidence of 30-300/100,000. Low incidence (LI) included Western Europe, North America and Australia, approximating to a TB incidence <30/100,000.

Active TB disease was defined as symptoms consistent with TB, radiographic changes and positive sputum microbiology for *M. tuberculosis* or a positive XpertTB.RIF. Subclinical TB was defined as positive sputum microbiology for *M. tuberculosis* or a positive XpertTB.RIF but without symptoms, with or without radiographic changes. Latent TB infection was defined as a positive tuberculin skin test (≥5mm) and/or positive blood IGRA in those without a prior history of treated TB and with an absence of symptoms or radiographic changes.

4.2.5 Power calculation and statistics

The study was powered to show a difference in the prevalence of TB infection between black African (13% prevalence) and subjects from low TB incidence (LI) areas (3% prevalence), based on data by Kall et al. [77] The power calculation estimated 180 black African subjects and 120 patients from low TB incidence areas would have to be recruited, with a power of 80%, a 5% chance of a Type I error and allowing for a 20% drop out rate. To achieve this, the study pool would have to be enriched by recruiting only black African and subjects from middle TB incidence (MI) areas after enrolling 120 LI participants. This would involve only recruiting BA and MI participants after this point.

Statistics were performed using Excel 11 for Mac, Excel 10 for Windows (Microsoft) and SPSS 20.0 for Mac (IBM Systems). Demographics were compared using the Chi-Square test (proportions) and Mann-Whitney U tests (medians). Confidence intervals were calculated using an exact binomial distribution.

4.2.6 Ethics

The study was sponsored by University College London, approved for R&D by Royal Free/UCL Joint Research Office and Ethics approval was granted by the City and East Ethics Committee on the 16th November 2012. REC reference 12/LO/1516; UCL protocol number 12/0212; 'Study of systematic TB testing for active, sub-clinical and latent tuberculosis infection in a UK HIV-infected cohort'. Clinicaltrials.gov number was NCT02712671. There was no outside funding provided for the study.

The study was performed at the Royal Free Hospital, London.

All patient assessments were conducted on the hospital site.

4.3 Results

4.3.1 Place, time period

The study was performed between 10th June 2013 and 6th September 2014 at the Ian Charleson Centre for HIV ambulatory care, Royal Free Hospital, London. As specified in the protocol, from June to September 2014, only black Africans and those from MI countries were approached.

Local TB incidence was 20 per 100,000 population in Camden (41.8/100,000 London average and 13.9/100,000 in the UK) in 2013 and the HIV prevalence 6.99 per 1000 population (1.5/1000 for the UK as a whole). [2,19,219,223,224]

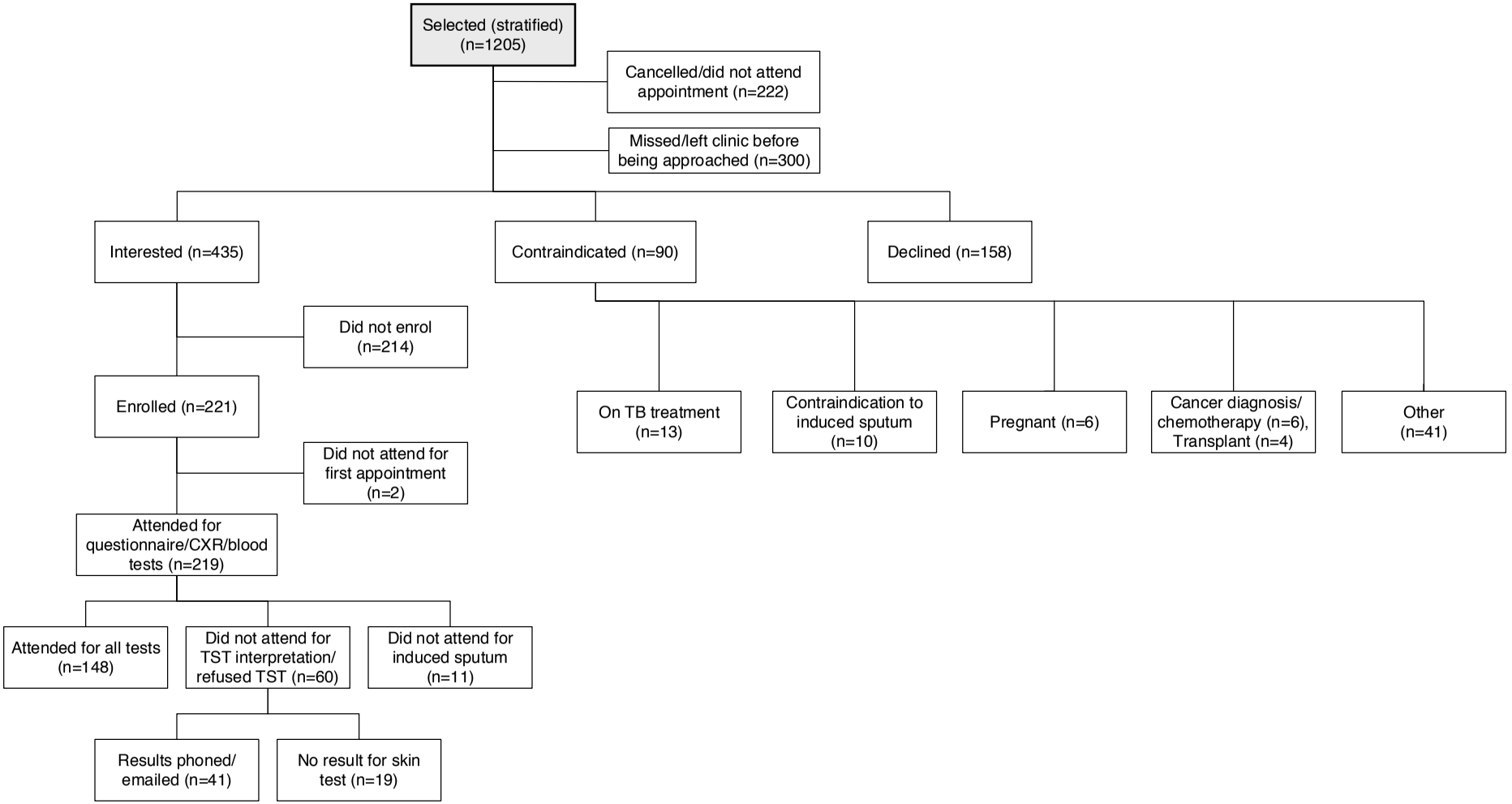
4.3.2 Recruitment

In total, 1205 outpatient attendees were identified from clinic lists to be approached, of which 222 did not attend or cancelled their appointment. A further 300 patients were missed or left the clinic before being approached, and 683 were approached to take part. Of these, 158 declined, 90 had contraindications to inclusion and 435 agreed. In total, 219 participants attended in the 14 months between June 2013 and September 2014.

4.3.3 Demographics

Of those enrolled, 160 (73%) were male, median age was 46 years, 62 (28%) were black African, 31 (14%) from middle TB incidence (MI) countries and 126 (58%) from low TB incidence (LI) countries. Forty percent had a reported heterosexual HIV acquisition route, 2% injecting drug use (IDU) and 55% men who have sex with men (MSM). The demographics of those recruited were similar to all those

Figure 4.3.2 Consort diagram



who were eligible and also to the total Royal Free HIV cohort (Table 4.3.3).

4.3.3.1 ART status

Nine patients (4%) had a new diagnosis of HIV and 210 recruited by stratified selection from patients already attending the HIV clinic in established care.

There were 202 participants (92%) taking antiretroviral treatment (ART), and the HIV viral load was 'undetectable' (<40 copies/ml) in 186 (85%). In those with an undetectable viral load, 51(27%) were black African, 26 (15%) from middle TB incidence (MI) countries and 109 (59%) from low incidence countries. The median age of this group was 46 years (IQR 41-53) and median blood CD4 count was 631 cells/μL (range 534-788).

4.3.3.2 HIV viral load in participants

Thirty three subjects (15%) had a detectable HIV viral load. Apart from the nine patients (27%) with a new HIV diagnosis, a further three (9%) had only recently started antiretroviral therapy (ART) (within 6 months), eight (24%) still had not started ART, seven of whom had not met indications to start ART yet (ART naïve) at the time of the study.

Twelve subjects (36%) either had poor adherence or had elected to take a break from ART (none of these advised by a clinician). One patient (3%) had a break-through viral load due to multi drug resistant HIV. Of these 33, 11 (33%) were black African, five (15%) from MI countries and 17 (51%) from LI countries. The median age of this group was 44 years (Interquartile range, IQR 35-50), median CD4 431 cells/μL (IQR 265-535; range 29-1260) and viral load 4851 copies/ml

Table 4.3.3 Table of demographics

	Study group (n=219)	Subjects eligible, but not recruited (n=761)	p	Total HIV cohort, Royal Free Hospital 2013 (n=2551)
Female	60 (27%)	229 (30%)	0.42	26%
Median age in years (IQR)	46 (41-52)	46 (41-53)	0.859	46 (40-52)
Black African	62 (28%)	213 (28%)	0.78	24.5%
From medium TB incidence country	31 (14%)	122 (16%)		18.2%
From low TB incidence country	126 (57.5%)	426 (56%)		57.3%
HIV transmission Heterosexual	89 (40%)	323 (42%)	0.81	39.7%
Injecting drug user	4 (2%)	12 (2%)		2%
Men who have sex with men	122 (55%)	402 (53%)		56%
Other	5 (2%)	24 (3%)		26 (1%)
On antiretroviral therapy	209 (95%)	698 (92%)	0.1	92.4%
HIV plasma load <50 copies/ml	183 (84%)	667 (88%)	0.05	84.8%
Median blood CD4 cells/μL (IQR)	643 (449-780)	617 (447-718)	0.567	626 (458-819)
Number with blood CD4 <200 cells/μL	5 (2%)	34 (5%)	0.14	4.6%
Number with blood CD4 <500 cells/μL	63 (29%)	249 (33%)	0.22	30.6%
BCG vaccinated	179 (85%)	Not measured		Not measured
Previous TB	18 (8.4%)	Unknown		8.8%
Self reported TB contact	48 (22%)	Unknown		Unknown

(IQR 501–48,183; range 41-7.5 million).

4.3.4 Uptake of testing

4.3.4.1 IGRA

Results were available for IGRA in 217/219 participants (99%). Two participants (1%) had an indeterminate first IGRA result. One (0.5%) result remained indeterminate on repeat testing. Two participants had no TSpot results, both of these failed to be processed in the time period required due to a failure of delivery on the courier's part. One participant declined a repeat, whilst another agreed but this sample was delivered to the wrong place again.

4.3.4.2 TST

One hundred and sixty-two participants (74%) returned to the hospital to have their TST interpreted, 40 (18%) had been given a small plastic ruler and instructions on how to interpret their TST result and emailed or telephoned their result (read at 48-72 hours). Five (2%) refused to have TST testing and twelve participants (5%) did not return to have their TST measured. In all, 202 (92%) had TST results.

4.3.4.3 CXR

Chest radiographs were available on 214 (98%). Five participants did not return for CXR.

4.3.4.4 Sputum induction

Two hundred and eight participants attended for sputum induction (11 did not re-attend), and samples were produced from 178 (85%; 27 subjects were unproductive). One participant's sample leaked in transit.

One hundred and sixty-one participants (90%) had a XpertTB.RIF result. One sample was inhibited and one PCR failed.

4.3.5 Yield of testing

4.3.5.1 IGRA

Of the 216 definitive IGRA results, 12 (6%) were positive. Four of the participants with positive results had been treated previously for active TB. Of the remaining eight, six were black African and two from middle incidence countries. All but one of the 12 subjects also had a positive TST result (≥5mm). Three IGRA results (1.4%) were borderline and two (1%) indeterminate (see 4.3.7.6 and 4.3.7.7).

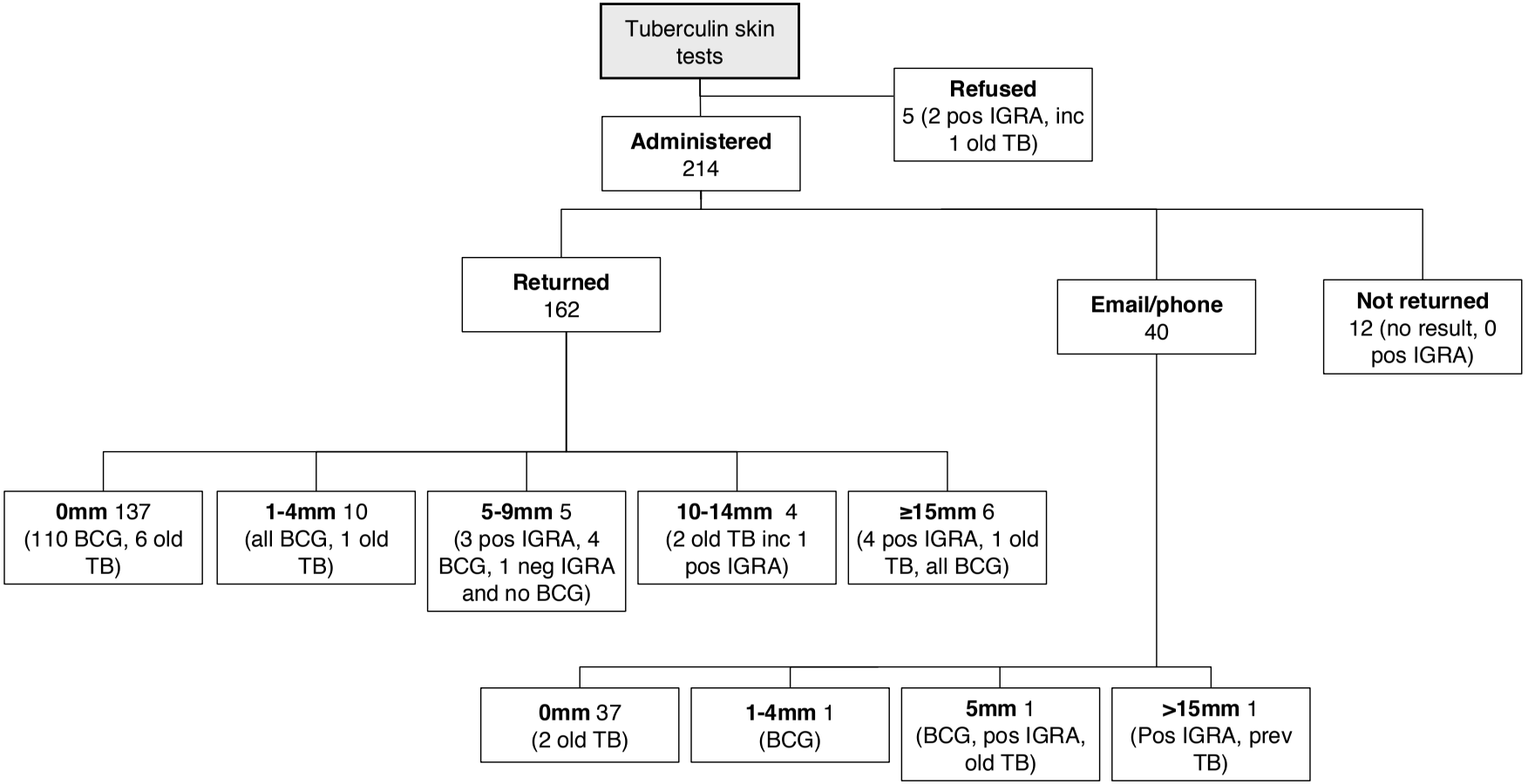
4.3.5.2 TST

Of the 202 TST results, 17 (8%) were positive (≥5mm) of which five (29%) had a self-reported history of previous active TB. In those with negative results, 174 (86%) measured 0mm and 11 (5%) between 1 and 4mm.

Two hundred and eleven had data relating to BCG status, of which 172 (82%) had either a BCG scar or self-reported previous BCG vaccination or both. Of these, 137 (80%) had a TST of 0mm, 11 (6%) were 1-4mm, 4 (2%) 5-9mm, 4 (2%) 10-14mm and 5 (3%) participants had ≥15mm results.

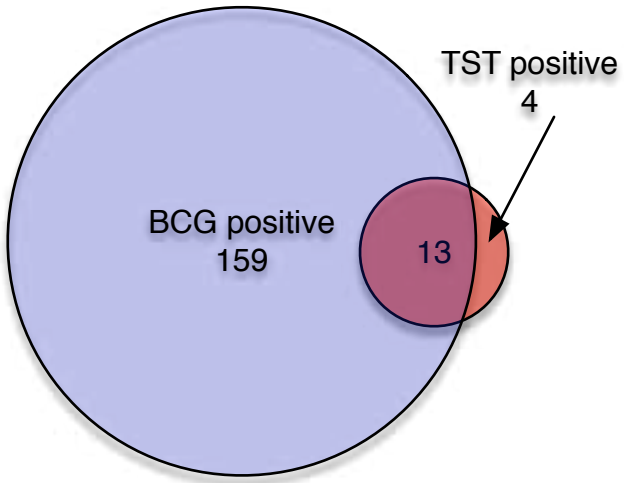
Thirty-nine subjects (18%) had no history of BCG nor a scar, only one had a

Figure 4.3.5.2a TST results



positive TST (7mm result). Five subjects (2%) had TST results but there was no BCG information available.

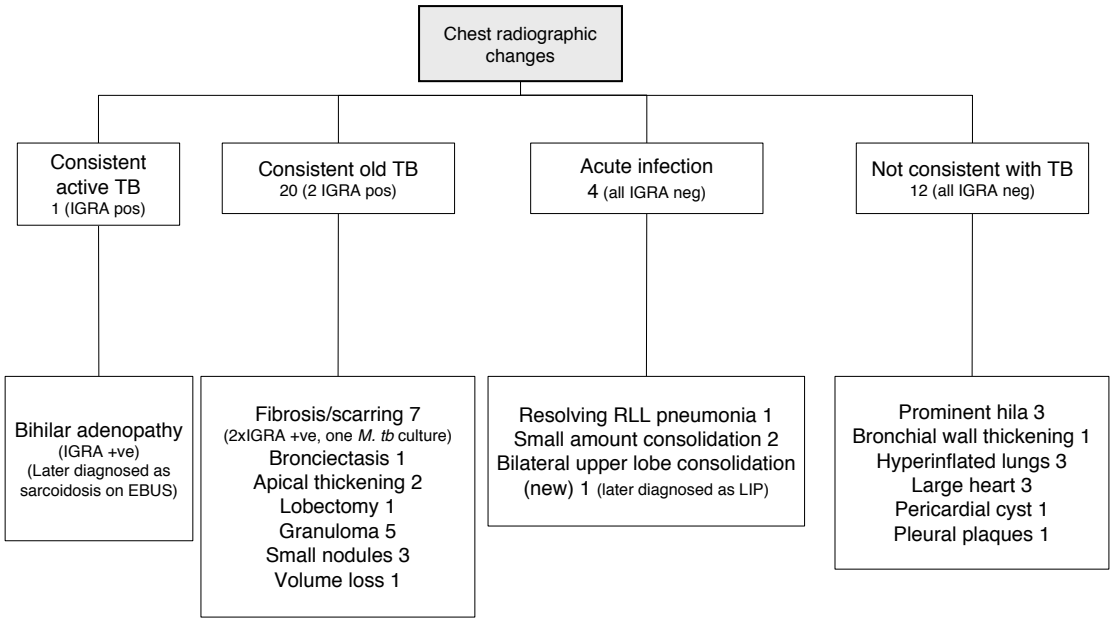
Figure 4.3.5.2b Venn diagram of TST and BCG status



4.3.5.3 CXR

One CXR was consistent with active TB (bihilar adenopathy), but on further investigation using endobronchial ultrasound and cytology, this was diagnosed as sarcoidosis. Mycobacterial culture was negative after 42 days. Another CXR was reported as possible active TB disease, but a CT scan of the chest was performed and reported as having changes consistent with old TB infection. Seventeen radiographs (8%) were consistent with possible previous TB (in which four had a self-reported history of previous TB), fifteen (7%) with other diagnoses and 181 (85%) reported as normal.

Figure 4.3.5.3 Abnormal CXR results



4.3.5.4 Sputum induction

Of the 178 induced sputum samples produced, two (1%) subjects' samples were culture positive for *M. tuberculosis* (neither with symptoms or signs of active TB and both culture positive at around 40 days). A third participant's sputum cultured *M. peregrinum* (the patient had previously treated active TB, no history of chronic airway disease nor systemic symptoms; CXR showed a granuloma only). All XpertTB.RIF results were negative for all three patients' samples.

4.3.6 Diagnoses of active and subclinical tuberculosis

Based on diagnostic criteria, there were no cases of incident active TB (0%; 95% confidence intervals, CI 0%-1.67%), two cases of subclinical TB (0.9%; 95% CI 0.1-3.3%) and 14 cases of LTBI (6.4%; 95% CI 3.2-9.6%). There was a difference of 14.4% (CI 4-28%) between the incidence of total TB infection between high and low TB incidence countries (p=0.001).

Table 4.3.6 Results

	Prevalence n=219	Percentage	95% Confidence intervals
Active TB	0	0%	0% – 1.67%
Subclinical TB (total)	2/219	0.9%	0.11% – 3.26%
Black African	1/62	1.6%	0.04% – 8.66%
from Middle Incidence country	1/31	3.2%	0.08% – 16.7%
from Low Incidence country	0/126	0%	0% – 2.89%
Latent TB (total)	14/219	6.4%	3.16% – 9.64%
Black African	8/62	13%	4.63% – 21.37%
from Middle Incidence country	2/31	6.5%	0.8% – 21.4%
from Low Incidence country	4/126	3.2%	0.9% – 7.9%
Previous TB (total)	17/219	7.8%	4.25% – 11.35%
Black African	12/62	19.4%	9.56% – 29.24%
from Middle Incidence country	3/31	9.7%	2.0% – 25.8%
from Low Incidence country	2/126	1.6%	0.2% – 5.6%

4.3.6.2 Descriptions of participants with subclinical tuberculosis

Two participants were found to have subclinical TB.

The first was a 45-year-old man, born in Ethiopia and diagnosed with HIV ten years previously, not yet treated with ART. His blood CD4 count was 359 cells/μL. He worked, was a never-smoker, but had visited Ethiopian/Eritrean cafes socially in the UK, although denied doing so in the past six months. He had no symptoms of TB disease. His baseline CXR was normal. His TST result was 0mm and TSpot negative (plate A 2 spots, B 0). Sputum was smear negative and XpertTB.RIF negative. Blood C-reactive protein (CRP) was <1 mmol/mL. At 40 days' incubation his induced sputum grew *M. tuberculosis* and Variable Nucleotide Tandem Repeat (VNTR) testing revealed this to be a unique strain, making laboratory contamination extremely unlikely.

Two subsequent sputum inductions, at six and 12 weeks after detection of the first organism, were both smear and culture negative after 42 days incubation. A CT scan of his chest/abdomen/pelvis to look for a site of disease was completely normal. Two further TSpot tests at three and six months were also negative.

He was offered treatment for subclinical tuberculosis (with four drugs), but declined and preferred to stay under observation as he had just started ART as part of a clinical trial and would have required a medication switch in order to take a rifampicin. He has had no subsequent symptoms of active TB disease in the 36 months following this.

The second case was in a 28 year old Filipino man who had previously been treated for active TB ten years previously in the Philippines. A few weeks before enrolment he had a self-limiting cough. Both his TST and TSpot were positive (TST 18mm induration, TSpot A3, B24). His CXR showed established upper lobe

fibrosis consistent with old TB infection with some possible new subtle nodules. Blood CRP was <1 mmol/mL.

At HIV diagnosis a year previously, he had had a CT scan that had shown chronic upper lobe TB changes. A bronchioalveolar lavage for mycobacterial culture at that time was negative after 42 days incubation.

At the time of recruitment, he had been taking ART for 11 months. His most recent blood CD4 count was 331 cells/μl and HIV viral load <40 copies/mL. Both spontaneous and induced sputum were smear and XpertTB.RIF negative but both were mycobacterial culture positive at 41 days, with fully drug sensitive *M. tuberculosis*. This had a unique strain type. He was treated for subclinical TB with four drugs, which were fairly well tolerated (see Quality of life, Section 4.3.11.1), and he made an uneventful recovery.

4.3.6.3 Sensitivity and specificity of symptoms for active and subclinical tuberculosis

Of the two cases of subclinical disease, one patient had no symptoms, the other had some recent self-limiting cough and sputum plus insomnia.

Due to the lack of no active cases, sensitivity and specificity of symptoms could not be calculated.

4.3.6.4 Prevalence of subclinical tuberculosis by place of birth

The prevalence of subclinical TB (positive sputum culture of *M. tuberculosis*) was 1.6% (CI 0.04%-8.66%) in black Africans, 3.2% (0.08%-16.7%) in those from middle TB incidence countries and 0% (CI 0%-2.89%) in those from low TB incidence countries.

4.3.6.5 Risk factors for active and subclinical tuberculosis

Due to the small numbers of cases of subclinical TB, no risk factors were statistically significant.

4.3.6.6 Use of XpertTB.RIF and time to sputum positivity

All 161 XpertTB.RIF results, including those from patients with subclinical disease were negative. The sputum from both individuals with subclinical disease had time to positive culture of >40 days.

4.3.7 Diagnoses of LTBI

4.3.7.1 TSpot and TST outcomes

Fourteen patients (7%) without a history of previous active TB infection had evidence of latent TB on TSpot or TST testing. Eight (57%) were black African, one Chinese, one white Eastern European, three white British (21%) and one black British. One subject had previously worked in healthcare.

4.3.7.2 Prevalence of LTBI by place of birth

This gave a prevalence of latent TB (by positive TST or IGRA) of 13% (CI 5.7%-23.9%) in black Africans, 6.5% (0.8%-21.4%) in those from middle TB incidence countries and 3.2% (CI 0.9%-7.9%) in those from low TB incidence countries. Consequently, the number needed to test for a single positive IGRA was 7.7 in black Africans, 15 in those from middle TB incidence countries and 31 for those from low TB incidence countries.

4.3.7.3 Description of cases of LTBI

There were eight black African participants with LTBI. One had CXR changes consistent with old TB, was not on ART (blood CD4 712 cells/μL), and had negative mycobacterial culture from bronchoscopic lavage and induced sputum. All of the other black African participants had normal CXR and were taking ART with blood CD4 cell counts of >350 (80% over 500) cells/μL. Four (50%) had reported TB contact. One participant had already taken a course of LTBI preventive treatment after TB contact in Zambia.

Of the eight Africans with LTBI, one was lost to follow up (history of severe depression, obesity, likely returned to his country of origin), three declined LTBI treatment, one stopped LTBI treatment due to side effects and three completed treatment.

One patient, male, born in China, had a positive TSpot and TST of 7mm. His sister had recently been diagnosed with TB. He had a normal CXR and completed LTBI preventive treatment without averse events. Another, a Polish man, was taking methotrexate for rheumatoid arthritis. His CXR showed hilar adenopathy that spontaneously regressed and was negative on lymph node culture from EBUS. His case is discussed in the chest radiographic changes section.

The four patients from low incidence countries with LTBI were all from the UK. All had negative TSpots and three of four were BCG vaccinated at school age, the fourth unknown (although no BCG scar was seen). Two subjects had 7mm TST responses (one BCG vaccinated, the other unknown), no TB risk factors, were taking ART and were adherent (CD4 cell counts were 1501 and 609 cells/μL), and normal CXRs. Two other subjects (both BCG vaccinated) had larger reactions (14mm and 15mm) and both had worked in healthcare at some

Table 4.3.7.3 Details of those with LTBI

Study ID	Sex	Age	Ethnicity	TB contact	HIV VL	Recent CD4	CXR	Nadir CD4	TSpotResult	Result TST mm	BCG (history or scar)	Sputum culture	Treatment started	Treatment outcome
133	M	44	African	Y	<40	585	N	Missing	Pos	20	Y	Neg	Started previously	Completed previously
127	F	52	African	N	<40	377	N	377	Borderline Pos	20	M	Unproductive	Yes	Stopped due to adverse effects
174	F	36	Mixed Black African/ White	N	1,01,108	712	Fibrosis	686	Pos	17	Y	Neg	Yes	Completed, rifampicin reaction
145	F	42	African	Y	<40	1197	N	296	Pos	9	Y	Neg	No	Declined
211	F	46	African	N	<40	653	N	653	Pos	6	M	Neg	Yes	Completed
202	F	44	African	Y	<40	559	N	150	Pos		Y	Neg	No	Declined
155	M	36	African	Y	<40	736	N	227	Neg	18	Y	Neg	Yes	Lost to follow up
93	F	43	African	N	<40	728	N	Missing	Neg	11	Y	Neg	No	Declined
85	M	38	Chinese	N	<40	532	N	Missing	Pos	7	Y	Neg	Yes	Completed
189	M	38	White Eastern European	N	<40	740	Bilateral hilar adenopathy	67	Pos	0	Y	Neg	Yes	Completed
70	M	56	White British	N	<40	574	N	Missing	Neg	15	Y	Neg	Yes	Completed
194	M	45	White British	N	<40	643	N	204	Neg	14	Y	Neg	Yes	Completed (abroad)
75	M	45	Black British	N	<40	1501	N	275	Neg	7	Y	Neg	No	Declined
111	M	50	White British	N	<40	609	N	310	Neg	7	M	Neg	No	Declined

point. Both were adherent with ART and blood CD4 counts were 574 and 643 cells/μL respectively and their CXRs normal. One had diabetes; both started and completed LTBI treatment.

4.3.7.4 Risk factors for LTBI

Univariate analysis revealed that only TB incidence associated with the country of origin was associated with latent TB status. Those with a reported TB contact had a higher chance of latent TB infection (OR 1.51, CIs 0.452-5.101) but this was not significant (p=0.504).

4.3.7.5 Concordance between TST and TSpot

Excluding those with self-reported previous TB, seven subjects had positive and two had borderline positive TSpot tests. Of those with positive results, five had positive TST and one had no result. Six patients had a positive TST (≥5mm) and negative TSpot. All had previously had a BCG vaccination apart from one participant who was unsure (and had no visible scar).

Excluding borderline or indeterminate results, a kappa statistic of 0.569 (Standard Error 0.145), n= 178, p<0.0005, was calculated comparing those with both a TSpot result and a TST result (see Table 4.3.7.5b).

4.3.7.6 Change in diagnoses with differing TST cut off values

Were a positive TST redefined as ≥10mm, the number of subjects with latent TB infection fell to nine from 14. Three of those with positive IGRA and risk factors for TB infection (two with close TB contact, all three from medium or high

Table 4.3.7.4 Univariate analysis of risk factors for LTBI

Factor	LTBI	No LTBI	Odds Ratio	95% confidence interval	p
Age <40	4	39	2.3	0.48 – 10.61	0.56
Age 40 – 50	7	82	1.9	0.47 – 7.55	
Age >50	3	66	1		
Female	6	47	2.2	0.74 – 6.77	0.15
On ART	13	164	1.8	0.23 – 14.6	0.57
HIV load undetectable	13	161	2.1	0.26 – 16.7	0.47
Low TB**	4	120	1		0.02
Medium TB**	2	26	2.3	0.40 – 13.3	
Black African	8	41	5.9	1.78 – 20.5	
History of smoking	6	100	0.7	0.22 – 1.95	0.44
BCG	13	149	3.3	0.42 – 26.14	0.23

Age (years); ART - antiretroviral therapy; BCG - self-reported history or scar associated with Bacille Calmette-Guerin vaccination; *HIV load undetectable signifies <50 copies/ml; **Low TB - originates from low TB incidence country, Medium TB - orginates from medium TB incidence country.

Figure 4.3.7.5a Venn diagram of TST and TSpot

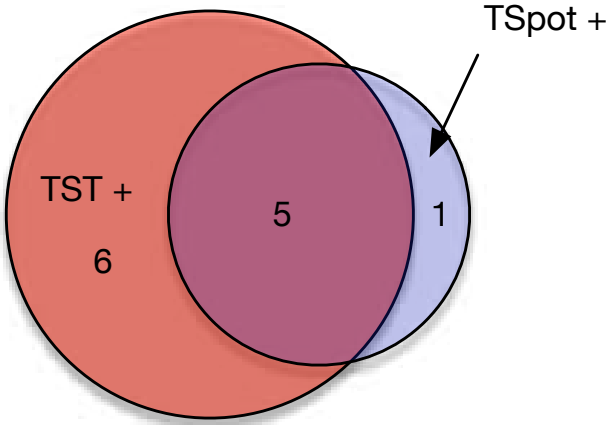


Table 4.3.7.5b 2x2 table TST vs TSpot for those with latent TB infection

		TST		
		Positive	Negative	Total
TSpot	Positive	5	1	6
	Negative	6	166	172
	Total	11	167	178

Kappa 0.569 (Standard Error 0.145), p<0.0005

TB-incidence countries) would then be TST negative, whilst two of those with negative IGRA would become TST negative (neither with any TB risk factors, one of whom was BCG vaccinated and the other not).

The TST/TSpot kappa value would then drop to 0.310 (Standard error 0.179), p=0.013.

4.3.7.7 Indeterminate IGRA and results of repeat tests

Two participants had indeterminate TSpot results, both due to spot formation in the negative control. The repeat TSpot for Subject 88 was negative (ESAT-6 and CFP-10 both zero spots, positive control >20). He had: no TB risk factors, a blood CD4 count of 1147 cells/μL (45%), undetectable HIV viral load, was a non-smoker, had a negative TST (no history of BCG) and normal chest X ray. Subject 125 had a repeat TSpot which was also indeterminate. He had no TB risk factors, a blood CD4 count of 541 cells/μL (24%), undetectable HIV viral load, nadir blood CD4 count of 239 cells/μL, negative TST, had been BCG vaccinated, was an ex-smoker and had previous PCP.

4.3.7.8 Borderline IGRA results

Three participants had borderline results. The first had a borderline negative result (5 spots on plate B) that on repeat six weeks later was negative; another had a borderline positive (7 spots on plate B) but was offered treatment for LTBI anyway as she had a positive TST (20mm) and came from a high TB incidence country. A third participant had a borderline positive result (6 spots on plate B) but a repeat showed a borderline negative result (5 spots on plate B). This subject had had a BCG in adolescence, had never smoked, previously worked as a physiotherapist, his blood CD4 count was 1028 cells/μL (nadir unavailable), his TST was 2mm and he was not started on LTBI preventive treatment.

4.3.8 Previous TB disease

4.3.8.1 Self reported previous TB disease

Seventeen subjects (7.8%) had a self-reported history of previous active TB. Of these, seven (41%) had TB treated in London – only three cases (18%) had been treated in the last ten years. Radiology was consistent with previous TB in eight cases (47%) (see Table 4.3.8.1).

Five of the 17 (39%) with self reported previous TB had positive TSpots results. Four of these five also had positive TST (≥5mm) and one had declined a TST.

4.3.8.2 Case descriptions

One individual had subclinical (possibly recurrent) TB with radiographic changes. The other four participants with positive TSpots had normal CXRs. Of

Table 4.3.8.1: Details of participants with self-reported previous TB disease

Age	Sex	Ethnicity	Country of Birth	Time in UK (years)	Organ involved *	Place TB treated*	Year TB treated*	CXR report	HIV risk factor	Recent CD4 (cells/ μL)	Recent HIV VL (copies/ ml)	Date/year started ART	Nadir CD4 (cells/μL)	Result T.Spot	Result TST mm	Sputum Mycobacterial culture
28	M	Fillipino	Philippines	3	Pulm	Manilla	2004	Bilateral fibrosis and nodules	MSM	331	<40	2013	243	+	18	*M. tb*
45	M	White British	UK	45	Pulm	London	2000	Normal	MSM	1029	<40	2005	79	+	30	Unproductive
50	M	African	DRC	12		DRC	1981	Normal	Heter	625	<40	2009	461	+	10	–
66	M	Carribean	Jamaica	42		Not stated	Not stated	Normal	MSM	427	1010	2001	11	+	5	–
55	F	South American	Ecuador	18		London	2001	Normal	Heter	802	<40	2002	56	+	Did not attend	Did not attend
54	M	White British	Wales	54	Pulm	Wales	1980	Left apical scarring and volume loss	MSM	250	109	2007	171	–	11	–
45	F	African	Uganda	10	Pulm	London	2004	LUL nodule on CT 2013	Heter	569	<40	2006	191	–	4	–
45	M	African	Uganda	15		London	1995	RUL linear fibrosis and pleural thickening	MSM	190	140	NA	0	–	0	Declined
48	M	African	Ivory Coast	25		Ivory Coast	1960s	Left upper lobe fibrosis	Heter	29	19000	NA	NA	Not delivered	0	–

Age	Sex	Ethnicity	Country of Birth	Time in UK (years)	Organ involved *	Place TB treated*	Year TB treated*	CXR report	HIV risk factor	Recent CD4 (cells/ μL)	Recent HIV VL (copies/ ml)	Date/year started ART	Nadir CD4 (cells/μL)	Result T.Spot	Result TST mm	Sputum Mycobacterial culture
60	F	African	South Africa	32		London	1997	Left apical granuloma	Heter	918	<40	1997	208	–	0	*M. peregrinum*
45	M	African	Zimbabwe	12		Zimbabwe	1977	Left lower lobe bronchiectasis	Heter	302	<40	2005	7	–	0	–
46	M	African	South Africa	10	Pulm	Not stated	2008	Previous right lobectomy	Heter	403	<40	2005	97	–	0	–
54	M	African	Congo	23		London	1998	Large heart	Heter	371	<40	NA	371	–	0	–
59	F	African	Ivory Coast	20		Not stated	2000	Large heart	Heter	824	<40	2000	143	–	0	–
23	F	African	Kigali	10		Rwanda, UK	Not stated	Normal	Vert	244	<40	2003	4	–	Did not attend	–
47	M	African	Zambia	23	Pulm	London	2003	Normal	Heter	523	515	1996	3	–	0	–
48	M	African	Zimbabwe	2		Harare	1996	Normal	Heter	610	96	2002	528	–	0	–

*: self reported; DRC: Democratic Republic of Congo; F: Female; Heter: Heterosexual; M; Male; MSM: Men who have sex with men; M. tb: *Mycobacterium tuberculosis* Pulm: Pulmonary; Vert: Vertical transmission

these, one had TB treated at the Royal Free London 10 years previously and his TST ulcerated with an induration of 30mm; one had been in the treated for TB and also imprisoned in the Democratic Republic of the Congo.

Of the 11 with negative TSpots, six (54%) had radiographic changes consistent with old TB (as did one who had a negative TST, and no TSpot result). Only one of the patients with radiographic changes had a positive TST.

Twelve (71%) subjects were from high TB incidence countries, of which ten had negative TSpots (one missing); nine had TST indurations of <5mm, one subject declined TST and one had a positive TST (10mm).

One patient of the 17 isolated *M. tuberculosis* on sputum culture (and was treated for subclinical disease), whilst one other isolated *M. peregrinum* from induced sputum (with no nodules, cavities nor bronchiectasis on CXR, and the organism was not isolated again on subsequent sputum cultures).

In cases of previous TB where both the TST and TSpot results were present (n=14), the kappa coefficient of agreement was 0.837 (Standard Error 0.155, p=0.005).

4.3.9 Uptake and completion of LTBI preventive treatment

In those with a diagnosis of LTBI, 50% (7/14) completed LTBI treatment. Four participants (29%) did not start treatment.

4.3.9.2 Descriptions of patients offered LTBI preventive treatment

Two participants, who were British, both male and with no TB risk factors, had marginally positive (7mm) TST results only and negative IGRA. One had had a history and evidence of a BCG vaccination, the second was unsure and no scar was seen. The other two participants were both female and from Nigeria. One lady was told the result but did not attend TB clinic or HIV appointments (even after follow up telephone calls). She had a positive IGRA and her TST measured 7mm, blood CD4 cell count was 1197/μL and she had previous self-reported TB exposure. The second lady had a positive IGRA, 11mm TST, blood CD4 count of 728 cells/μL and despite a discussion, was not interested in taking LTBI preventive treatment.

4.3.9.3 Adverse events on LTBI preventive treatment

Three of the participants who started LTBI preventive treatment had adverse events that impacted on their quality of life and that required a change or cessation of treatment. Two had peripheral neuropathy on isoniazid, a third had a rash and low platelets on rifampicin.

Of the seven that completed LTBI treatment, one patient had a short admission for a fever and malaise after 5 months isoniazid that may have been unrelated to LTBI treatment. Another developed peripheral neuropathy (despite the use of pyridoxine). He had been taking ART for many years. Also see Section 4.3.11.3.

4.3.10 Chest radiographic changes

4.3.10.1 CXRs consistent with active or previous TB

Thirty six subjects (16%) had an abnormal CXR. Three patients with CXR

consistent with active or previous TB disease also had positive IGRA or TST (patients 189, 174 and 107).

4.3.10.2 Details of subjects with abnormal CXR

One participant had bihilar adenopathy (patient 189). He was a Polish man with no previous TB contact, although his wife was African. His mother had sarcoidosis. He had a blood CD4 count of 740 cells/μL and an undetectable HIV viral load. His IGRA was positive and TST 0mm. A subsequent CT showed bihilar adenopathy with no parenchymal changes. Cytopathology from a lymph node aspirate via endobronchial ultrasound showed granulomata. Mycobacterial culture of this node was negative at 42 days. The adenopathy reduced spontaneously without antituberculous medications, but he was subsequently treated with LTBI preventive therapy.

The second case was a 36 year old Angolan lady, diagnosed with HIV at prenatal testing and treated with ART only whilst pregnant. She had never had chest radiographs previously because she was diagnosed with HIV during pregnancy. Her blood CD4 count at the time of the study was 712 cells/μL.

Her CXR at testing showed upper lobe fibrosis with opacification. Her CT chest suggested old TB changes. Both induced sputum and then a bronchioalveolar lavage were negative for mycobacterial culture at 42 days. She was treated initially with 3 months rifampicin/isoniazid but developed a rash and low platelets on rifampicin, and switched to isoniazid alone. She then started ART.

Subject 107 was found to have subclinical TB and his clinical case was described earlier.

Two other participants, (210 and 218) both had previous treated TB and radiographic changes consistent with old TB but with negative TSTs (IGRA samples were lost by the courier).

Three subjects had a history of previous TB and scarring, bronchiectasis and a previous lung lobectomy – presumed for active TB or subsequent bronchiectasis (Subjects 33, 76, 9 respectively).

Three other subjects had CXR reported as prominent hila. On review, these were thought to be vascular but in one case a thoracic CT scan showed fatty adenopathy. None of these participants had a history of TB exposure and all three had negative IGRA, TST and sputum culture.

Fourteen other subjects had other abnormal CXR consistent with old TB or TB exposure. These ranged from fibrosis and pleural thickening to multiple small nodules or small calcified granulomata (see Table 4.3.10.2).

4.3.10.3 CXR CONSISTENT WITH ACUTE INFECTION

Four subjects had CXRs consistent with acute infective changes. One subject had pneumonia as a first presentation of HIV (HIV viral load of 7.5 million copies/ml) which was also the time of recruitment to the study. This had already improved radiographically with antibiotics. Another had basal consolidation with a history of cough (already on co-amoxiclav) and another a small amount of consolidation with some back pain but no other symptoms. A fourth (a Ugandan lady, on cotrimoxazole prophylaxis for PCP) had recently started ART and had bilateral upper lobe consolidation. Her sputum culture was negative for mycobacteria and she was diagnosed with lipoid interstitial pneumonia (LIP)

Table 4.3.10.2 Details of participants with changes consistent with TB on CXR

Study no	Country of origin	CXR report	Symptoms	TB history	TSpot	TST (mm)	Sputum culture	Recent CD4	HIV VL	Time on ART	S mo ker
189	Poland	Bilateral enlarged hila	Cough, weight loss	No	Pos	0	Neg	740	<40	6 years	N
174	Angola	Left upper lobe volume loss, linear atalectasis, right upper lobe fibrosis, widened mediastinum	Fatigue, back pain	No, no known contact	Pos	17	Neg	712	101,108	Naïve	N
107	Philippines	Bilateral fibrosis and nodules	Cough and fever (stopped)	Yes	Pos	18	*M. tb*	331	<40	1 year	N
210	Uganda	RUL linear fibrosis and pleural thickening	None	Prev TB (treated)	Neg	0	Declined	190 (6%)	140	Not adherent	N
218	Ivory Coast	Left upper lobe fibrosis consistent with old TB	Weight loss and loss of appetite	Yes, treated 1960s	Did not arrive	0	Neg	29	19,000	Non adherent	N
33	Wales	Left apical scarring and volume loss	Fatigue	Yes	Neg	11	Neg	250	109	6 years	Y
76	Zimbabwe	Left lower lobe bronchiectasis	Cough, fever for a week	Yes	Neg	0	Neg	302	<40	1.5 years	M
9	South Africa	Previous right lobectomy	Back and muscle pain past day only	Yes	Neg	0	Neg	403	<40	10 years	Y
55	UK	Bulky hila	Sputum, fatigue, back pain	No	Neg	0	Neg	675	<40	12 years	N
90	Colombia	Bulky hila	Diarrhoea	No, no known contact	Neg	0	Neg	246	106	Not adherent	Y
12	UK	Prominant hila	Fatigue and insomnia	No, no known contact	Neg	0	Neg	1000	1123	Not adherent	Y
32	Portugal	Apical thickening	Lymphadenopathy 1 week previously	No	Borderline negative	0	Neg	397	1433	6 months	N

Study no	Country of origin	CXR report	Symptoms	TB history	TSpot	TST (mm)	Sputum culture	Recent CD4	HIV VL	Time on ART	S mo ker
198	Scotland	Bilateral apical thickening, pos right lower zone fibrotic band, consistent with prev TB	None	No	Neg	0	Neg	776	<40	10 years	Y
24	UK	Apical thickening, otherwise normal lung fields	Cough and sputum 2 weeks ago	No	Neg	0	Neg	1283	<40	17 years	Y
27	UK	Apical thickening consistent with old TB	Sputum and fatigue past day	No	Neg	0	Neg	708	<40	16 years	Y
184	South Africa	Left apical granuloma	Cough and sputum 1 month ago	Yes	Neg	0	*M. pereg-rinum*	918	<40	17 years	N
3	Tanzania	Multiple small nodules and calcified opacity left midzone	None	No, prev contact	Neg	0	Neg	698	<40	7 months	Y
34	Hong Kong	Multiple small nodules and calcified opacity left mid zone	None	No	Neg	0	Neg	593	<40	5 years	Y
57	Lebanon	Right upper lobe granuloma	Muscle pain	No	Neg	0	Neg	731	<40	19 years	N
203	Uganda	Left basal granuloma	None	No, prev contact	Neg		Neg	567	<40	1.5 years	N
172	UK	Right apical granuloma	None	No	Neg	0	Unprodu ctive	840	<40	Missing	Y
165	UK	3mm dense calcified granuloma at right base	Sputum past week only	No	Neg	0	Neg	989	<40	Missing	Y
46	France	Multiple small nodules	Night sweats, diarrhoea, muscle pain 1 day	No, prev contact	Neg	0	Neg	1092	<40	14 years	N
204	South Africa (BA)	Left lower lobe volume loss	Cough and sputum 1 day	No, prev contact	Neg	0	Neg	811	<40	1.5 years	N
113	England	Pleural plaques	None	No	Neg	0	Neg	445	<40	6 years	Y

on CT scan that improved with antiretrovirals.

4.3.10.4 CXRs consistent with airways disease

Four subjects (1.8%) had CXR changes consistent with airways disease. One had possible bronchial wall thickening, three with hyper inflated lungs. Of the four, only one had an established asthma/COPD history and only one other had symptoms suggestive of airways disease. Symptoms and CXR changes are further discussed in the Airways Chapter 6, Section 6.3.7.

4.3.10.5 CXR changes felt unrelated to previous TB

Three subjects (1.4%) had an increased cardiothoracic ratio (cardiomegaly) and one (0.5%) had a pericardial cyst. Two of the subjects with cardiomegaly were black African and had a history of previous TB.

4.3.11 Quality of life changes and adverse events

4.3.11.1 Quality of life on active/subclinical TB treatment

There was relatively little loss in quality of life in the one patient treated for subclinical disease (Health utility of - 0.941 (CI 0.867-1), QALY loss of 0.06. Mostly this was in pain/discomfort and loss usual activities (likely not secondary to treatment).

In the second patient with subclinical disease (not on preventive treatment), there was no net change in quality of life utility values through the time being monitored.

4.3.11.2 Quality of life on LTBI preventive treatment

Of the 8 participants that took LTBI preventive treatment, five had three serial quality of life scores to use to calculate utilities.

The median quality of life scores were 0.8286 (SD 0.11) when starting preventive treatment, 0.7496 (SD 0.073) at 2 months and 0.7686 (SD 0.154) at 4-6 months. This equated to a QALY loss of 0.0576.

4.3.11.3 Adverse events on LTBI treatment

The participant taking four drugs for subclinical TB did not report any grade 3 or 4 adverse events.

Of those taking latent TB preventive treatment, there were reports of grade 3 events: in 2 cases joint pain, one case diarrhoea and feeling tired, one of tingling in the hand and feet. One participant reported new, grade 3 weakness, confusion and itch.

4.3.11.4 Adverse events after tuberculin skin testing

One patient with a known history of anxiety developed chest pain and breathlessness six hours after TST. There was no rash, wheeze, stridor or tongue swelling. He attended the emergency department at the Royal Free Hospital and his electrocardiogram (ECG) and troponin tests were normal. The symptoms settled and thought to be due to hyperventilation. Follow up ECGs and cardiac enzymes were normal.

One patient with previous tuberculosis developed a large ulcerated lesion on his forearm at the side of tuberculin skin testing. His IGRA was also strongly positive. He was unproductive at induced sputum and chest radiology was normal. He was treated with a steroid cream but has been left with a scar.

4.3.11.5 Adverse events during sputum induction

Sputum induction seemed well tolerated, although formal satisfaction with the procedure was neither qualitatively or quantitatively assessed. One patient developed post-tussive vomiting during the procedure but elected to continue. Another patient complained of nausea and had to stop early. Eight subjects had a drop in FEV_1 by 15% or greater, although in three of these, this was felt due to poor spirometry technique (corresponding also with a fall in FVC and rise in peak flow). Of the remaining five, three had a history of asthma and one had asthma symptoms and a history of smoking but no formal diagnosis. The fifth was a smoker with normal lung function, but with an FEV_1 drop of 15%. These are further reviewed in the Airways Chapter 6 (Section 6.3.6.3).

4.3.12 Costs associated with testing and treatment

4.3.12.1 Subclinical TB treatment and support

Including clinic appointments, two months pyrazinamide and ethambutol, six months of rifampicin and isoniazid and the blood tests required to monitor this, the treatment cost of the one participant with subclinical TB was £992.98 and the cost of clinic appointments, a further CT chest and sputum inductions was £1,170.

4.3.12.2 LTBI preventive treatment

Including the costs of fixed clinic appointments, *ad hoc* time with a doctor and nurse to discuss adverse events, drug costs for isonazid ± rifampicin and the blood tests required to monitor these, the total for the eight patients starting latent TB infection preventive treatment came to £16,927, or £2,116 per person.

4.3.13 Subsequent cases of active TB/HIV coinfection at the Royal Free Hospital

None of the patients that had taken part in the study has developed active TB since the study ended in September 2014. There have been four cases of active TB at the HIV clinic at the Royal Free Hospital, all in non-participants. One patient had miliary tuberculosis and the other three had extra-pulmonary disease.

4.4 Discussion

4.4.1 Summary

In this real-world cross-sectional study, we tested a group of patients consisting of those with newly diagnosed HIV and also those sustained in care. This study was novel in a low incidence TB area, in that it tested all selected HIV infected individuals for TB infection using chest radiographs and sputum culture irrespective of TST or IGRA result.

We found fewer than one in three subjects approached were willing to undergo all tests. In those that consented to all tests, three quarters returned for TST interpretation.

The prevalence of subclinical TB was 0.9% in all, and LTBI was 13% in black Africans, 6.5% and 3% in those from middle and low TB incidence countries respectively. This is similar to findings in other studies in Western Europe. [77,221] Neither of the two patients with subclinical TB in this study would have been detected in those using IGRA/TST as a first diagnostic step.

The uptake for LTBI treatment was lower than expected. In those that completed treatment, this resulted in adverse events and fall in quality of life utility.

4.4.2 Recruitment and demographics

Stratified sampling led to a cohort that were representative of the Royal Free cohort with similar proportions of black Africans, and people from middle and low TB incidence countries, and with similar results to that reported nationally. [219]Towards the end of the study, recruitment became more difficult as many

patients selected by stratified sampling had already being approached. It was not possible to recruit 300 patients in the time available but the numbers gained did demonstrate a significant difference between levels of TB infection in individuals from low and high TB incidence countries (p=0.001). Median CD4 cell count and proportion of patients on ART were higher than that seen in any other comparable European study so far published. [77,80,166, 171-175]

4.4.3 Uptake of testing

One third of subjects approached went on to take part in the study. Another third did not clearly decline taking part, but did not attend during the recruitment period. Comprehensive TB testing was perceived as time-consuming (involving up to three hours of patient time, over two visits) and uptake may have improved if only blood samples and CXRs been required. Some, predominantly black African, patients seemed unkeen to know about their TB infection status and were quick to decline testing when they were told about the study, perhaps a result of stigma associated with TB. Unfortunately the reason for refusal was not systematically recorded.

4.4.3.2 TST return rate

Three quarters of participants returned to have their TST result interpreted and a further fifth phoned or emailed the results. Many participants lived a distance from the clinic and with transport logistics and costs, an inability to complete the study in one morning was perhaps the biggest disincentive to reattend. In a study with similar methodology, 79/304 patients (26%) in a Norwegian setting

did not return for TST interpretation, whilst 43% did not attend in an Irish study. [80,166] Data from elsewhere are similar, with TST return rates of between 19-40%. [146,164,202,225] In one study in an HIV clinic in the United States that investigated the use of incentives, the 35% return rate only improved to 61% at best with voucher incentives and education. [226]

4.4.4 Results of investigations

4.4.4.1 TST results

The majority of TST results were unreactive (0mm), even in those with high CD4 counts and previous BCG vaccination. Very few subjects had blood CD4 counts below 200 cells/μL and TSpot tests (which are reported to be more sensitive than the QFT at low CD4 counts) were also negative,[174] inferring that these subjects are more likely to have true negative results rather than anergy, although testing for anergy was not performed specifically.

4.4.4.2 Indeterminate IGRA results

There were a low number (1%) of indeterminate TSpots. Other studies have shown higher rates than ours – 14% in a study in the USA and 7% in an Irish study, with the majority due to low CD4 cell count. [163,166] The higher median blood CD4 cell count in our study and drawing two LiHep bottles in order to increase the lymphocytes available for testing may have led to fewer indeterminate results.

4.4.4.3 Yield of induced sputum

In those that attended for sputum induction, samples were produced in 85%. This compares to a 60% yield with induced sputum in those that couldn't cough in another study in London [77] We did not use quality control methods, such as microscopy for non-squamous cells or for pulmonary macrophages.

4.4.5 Prevalence and diagnoses of subclinical and latent TB

4.4.5.1 Subclinical TB

We found two cases of subclinical TB in our cohort - one was in a black African. In his case, strain typing by VNTR showed that there was no laboratory contamination or related strains. The subject had not travelled abroad for 2 years, but had mixed with Somali and Ethiopian people in the UK. His IGRA, TST and CXR were all negative for active or previous TB. If using an IGRA or TST based testing strategy, he would not have had a sputum induction performed. He elected not to have treatment for TB and has had no evidence of progression to active TB since. It is difficult to say if he would have progressed to TB disease had he not started ART. His two repeat IGRA were also negative, and so it is conceivable that he could have been recently exposed (despite no history) and was asymptomatically excreting the bacteria, as has been described in children. [117] There are no published cases of HIV/TB infection in the UK in asymptomatic patients with negative CXR and immunological investigations. Positive sputum cultures in asymptomatic individuals with HIV with normal CXRs have been documented in low and high TB incidence areas, but in the European studies,

either TST or IGRA were positive in all individuals tested. [77,222,227]

The second case was in a young Filipino gentleman with had very subtle radiographic changes on a background of old TB changes. His TST and IGRA were both positive, but given he had previous TB, he would not have been screened using either immunological method if they were used alone. He had a short history of cough that had resolved, but was still able to produce sputum spontaneously, which was mycobacterial culture positive for *M. tuberculosis* at 42 days. Induced sputum was also culture positive at 42 days, both presumably had a low mycobacillary burden.

The prevalence of subclinical TB was 2/219 (0.9%) for the cohort as a whole, or in 1/60 (1.7%) black Africans and 1/31 (3%) subjects from middle incidence countries.

Since recruitment stopped 36 months ago, there have been no other cases of pulmonary TB in the Royal Free HIV clinic that would have been detected using CXR or sputum induction. Were there to be active or subclinical TB in 0.9% of those in clinic, we would have expected 23 cases of active TB in the entire clinic in the subsequent 9 months. Were there to have been other cases of subclinical TB in the 2331 patients that were not tested, assuming that most cases of subclinical TB will progress to active disease, we would have expected some of them to have presented with symptoms at this point. [61] The prevalence may, therefore, be closer to two cases of subclinical disease (one detectable by CXR, one detectable by induced sputum but not CXR) in a cohort of 2550 cases. The prevalence of subclinical disease in our cohort could be approximately 1/2551 (0.04%).

Kall et al. tested their entire HIV clinic cohort and describe three cases of subclinical TB in 50 IGRA positive subjects, 242 black Africans or 502 HIV infected clinic attendees in total. One subject had CXR abnormalities (a nodule) and another had a normal CXR, but both had induced sputum that was positive at culture and both patients had a positive IGRA. [77] They had no subsequent cases of active TB in IGRA negative patients over the year following testing. Cases of 'prevalent active TB' (active disease found when screening in HIV clinics) were present in an Austrian study in eight of 830 patients (0.96%). [175] Seven had a positive IGRA, one a negative IGRA. In a Norwegian setting there were seven cases of 'prevalent TB' in 298 (2.3%), of which five were microbiologically confirmed. [222]

4.4.5.2 Latent TB

The prevalence of LTBI, as measured by either a positive TSpot or TST, was 13% in black Africans, 6.5% in people from medium TB incidence countries (3% by TST or TSpot alone) and 3% in those from low TB incidence countries. These results are very similar to 13%, 10% and 3% respectively in the Danish and Homerton studies, although these were both measured by QFT only. [77,221] The Swiss study, using TST, found similar results with 15%, 8% and 3% respectively. [76] These studies of HIV-infected individuals from high TB incidence countries show a lower prevalence of LTBI compared studies of immigrants in primary care in the UK. [228,229]

There were four individuals from low TB incidence countries diagnosed with LTBI. They were all from the UK and all had negative TSpots. Two subjects had

7mm TST responses (one BCG vaccinated, the other unknown), with no TB risk factors, were taking ART with CD4 cell counts of over 600. It could be that at least one of these was a false positive TST due to a BCG response.

4.4.5.3 Concordance between tests for LTBI

TST were all positive in those who had positive TSpots apart from one patient, (with bihilar adenopathy, taking methotrexate and had a family history of sarcoidosis). Follow up has shown no subsequent TB or increase in adenopathy. His lack of TST response may be due to either sarcoid or use of methotrexate. [230,231]

In this study, there were more subjects with positive TST and negative TSpot than positive TSpot and negative TST. This is similar to a recent study in Norway (median blood CD4 cell count of 471 cells/μL) with more positive TST than IGRA. They demonstrated 80% agreement, kappa 0.52 between TSpot and TST, which was similar to that between TST and Quantiferon. Clark et al. in the UK had a similar numbers of discordant TST positive and TSpot results. [174]

Other European and US studies, however, have demonstrated higher numbers of positive IGRA than TST. A German study (with median blood CD4 408 cells/μL) had twice as many positive TSpots in subjects as positive TST. [167] In a Spanish setting there were three times more positive IGRA. [164] A US study (median CD4 335), reported more positive TSpots and negative TSTs with poor concordance (kappa = 0.16). Those with positive TST and negative TSpot were more likely to have been BCG vaccinated (OR 17.7). [163] This was not demonstrated in the Norwegian study however. [80] More TSpots were also positive in

an Italian study (median blood CD4 461 cells/μL) and in a Spanish study (mean blood CD4 536 cells/μL). [232,233]

In an African cohort, 5/9 TSpot positive subjects had positive TST (kappa 0.69). [234] This has been reviewed in a meta-analysis, were agreement was higher between the tests (89%) in high income countries than in lower (77%). There were higher numbers of TSpot positive, TST negative subjects, in direct comparison to this study. [162] with agreement of 80% (kappa=0.52) between the two tests.

4.4.5.4 Previous TB

Sixty five percent of subjects with previously reported TB disease had negative TSpot results in this study. The majority of these were people from high TB prevalence countries.

This has been seen frequently in other studies where between QTF is negative in 62-90% and TSpot in 43-72% despite previous TB. [80,165,172,175,233]

4.4.6 LTBI preventive treatment

4.4.6.1 Uptake of LTBI preventive treatment

Fifty percent of subjects managed to complete LTBI preventive treatment. In those that did, there were notable number of adverse events (ranging from peripheral neuropathy at the most minor, to rash and low platelets). Two patients were unable to complete therapy because of these. There was, however, little hepatotoxicity.

The completion rates were similar to other studies in people with or without HIV. Amongst studies in individuals with HIV, only 48% started treatment and

75% of those completed in a Swiss study and 61% in Norway. [76,80] In older LTBI treatment studies, despite 86% starting, only 57% completed in a study in Spain and 56% stared and only 28% (16% total) completed in an Italian study. [78,202] In comparison, a study in Homerton, London had a 90% and 95% adherence rate with LTBI treatment. [77]

Results may be even lower in the HIV-uninfected general population – a London study of TB contacts showed 54% completion rates [235] and around 40% in the USA. [236] In one Canadian study, fewer than 10% completed preventive treatment. [237]

4.4.6.2 Quality of life during LTBI treatment

LTBI treatment seemed to be poorly tolerated in this group. The QALY deduction for LTBI (including treatment) from NICE is only 0.007 QALY. [43] Many other cost-effectiveness analyses have assumed this was zero, but do deduct for the low risk of hepatic toxicity due to isoniazid. [193] There are very few data on the quality of life associated with latent TB treatment in high income countries. It was hoped that this study may generate more data on quality of life and adverse events associated with latent TB treatment. To this end, quality of life data were recorded at each follow up appointment and adverse events were asked about systematically and proactively using standard chemotherapy adverse events forms (see Appendix). This may have led to a higher prevalence of adverse events than would have been expected.

There are otherwise very few published studies for health utility scores for latent TB infection. [188,238,239] In a large study of South African gold-miners, isoniazid preventive therapy was very well tolerated, with adverse events in

only 1 in 200. [240]

A systematic review of health related quality of life did find poorer quality of life in those treated for active TB compared to those with latent infection on treatment (although this was not quantified). [238] In our study, the numbers were small, and some of the patients that stopped preventive treatment were lost to follow up, or failed to submit quality of life data, but the one patient treated for subclinical disease had a lower reduction in quality of life than those that were treated for latent infection.

4.4.7 Limitations of the study

Despite a pragmatic approach, we were unable to recruit as many participants as we would have wished, especially amongst those from high TB incidence countries. A small number were too unwell, or missed appointments. Patients undergoing chemotherapy for solid organ or haematological malignancy, or those who had received solid organ transplants, who may have been at higher TB risk, but were either not well enough to be tested or were excluded (as the immunological results may have not have been reliable). Selection bias may have been introduced as individuals with HIV and chaotic lifestyles, who may be less adherent to ART may also have not attended clinic and therefore not been approached. These individuals may have a higher risk of TB exposure. Conversely, those with symptoms such as cough or chest pain, or who were concerned about TB contact in the past, may have been more willing to take part in the study. Despite this, the demographics of those enrolled were similar to those of the Royal Free cohort; as were the demographics of those who were eligible and those who had not taken part. The symptoms or specific reasons not

to enrol in the study were not systematically recorded in those that declined, so we cannot disprove selection bias due to this.

This cross-sectional study looked at new HIV diagnoses as well as those in established care. This approach was useful if we consider the cost-effectiveness of testing an entire clinic. There were low numbers of patients with new HIV diagnoses during the recruitment period, however, so establishing the cost-effectiveness of TB testing in individuals with new HIV diagnoses alone would have taken far longer, and a large study of treatment naïve individuals may give different results. In those with new HIV diagnoses, the blood CD4 cell counts may be lower, immunological and radiological tests may be less sensitive and the risk of developing TB higher. The very low numbers in this study make post-hoc analysis difficult. Given most individuals with a new diagnosis of HIV will now start ART soon after, this risk may not be as significant.

There were no cases of symptomatic active TB at recruitment. This made the sensitivity of symptoms or radiology as a marker for active TB immeasurable. A reason for this could be the relatively short (16 month) recruitment period.

The recruited cohort had a high median CD4 count – certainly higher than in other Western European and American studies. Although this reflects the immune status of a contemporary population with good uptake and adherence to ART. This may explain the higher numbers of patients with positive TSTs with discordant IGRA results. The use of TSpot rather than Quantiferon in this study may also have led to an increased discrepancy between tests, and use of Quantiferon (which has a higher rate of concordance with TST) cannot be directly compared.

Three participants (21%) were lost to follow up during LTBI preventive

treatment and this led to a lack of data surrounding quality of life results. As the subjects attended clinics at different times, the results are also not directly comparable. There were also fewer cases of active and subclinical TB than expected, and fewer participants with LTBI on treatment than expected and the small numbers make the results not significant enough to use in cost-effectiveness studies.

4.4.8 Conclusion

This cross-sectional study showed that extensive testing for TB in HIV subjects was achievable but time consuming, and that uptake was relatively low for all tests amongst clinic attendees when presented as part of a research study. Similar to other studies, many patients did not return for TST interpretation, despite fully consenting to the study. We found very similar numbers of patients with subclinical and latent TB infection compared to other European studies. Notably, we found that *M. tuberculosis* may be cultured from the sputum of asymptomatic HIV infected individuals with negative immunological tests and normal chest radiographs. In this case, the patient declined treatment and subsequent active TB disease did not develop.

The uptake for LTBI preventive treatment was also similar to other studies, but there were adverse events than expected in those that did take treatment, but none related to hepatotoxicity. In contrast to studies in high TB-incidence areas, XpertTB.RIF added nothing to mycobacterial smear and culture when testing patients attending HIV clinics. The uptake and results of this study will be used to model different testing strategies in Chapter 5.

CHAPTER 5: COST EFFECTIVENESS OF TESTING FROM PROSPECTIVE STUDY

5.1 Introduction

International guidelines advise testing in HIV infected individuals to reduce the morbidity, mortality and transmission associated with active TB disease. [43,44,71,75,134,241] Each guideline recommends a different TB testing strategy – for example the most comprehensive, the US Centre for Communicable Disease Control (CDC) test for active disease and latent infection with a frontal chest radiograph (CXR) and an immunological test (TST or interferon gamma release assay - IGRA) in everyone at HIV diagnosis, plus sputum culture or yearly TST screening in some higher risk groups (see also Chapter 1, Section 1.5.6). [241] By comparison, the British HIV Association (BHIVA) target only those at the highest risk of reactivation of LTBI (based on place of birth, blood CD4 count and time on antiretroviral therapy, ART) and recommend testing using IGRA alone. [75]

These guidelines have often been based on historical studies which contained populations with less ART uptake than is current practice. [19,52] This is important as ART decreases the risk of TB reactivation by at least 65%. [59,89] Also, although these investigated the prevalence of LTBI and active TB in low TB incidence areas such as the USA and Western Europe, none were specifically based on cost-effectiveness in an HIV infected cohort. [31,76]

Using extensive assessments for active, subclinical and latent TB infection, we sought to determine the uptake and yield of TB testing in an adult UK HIV ambulatory care clinic. From this we calculated the most cost-effective management

strategy, based on the England and Wales National Institute for Health and Care Excellence (NICE) threshold of £20-30,000/QALY gained. [178]

5.2 Method

5.2.1 Study population and patient selection

Subjects were selected from those attending routine appointments at the Royal Free Hospital, London by stratified selection between June 2013 and September 2014, unless they had a new diagnosis of HIV in the past four weeks, when all were approached. This and the study procedures are outlined in Chapters 2 (Methods) and Chapter 4 (Prospective Study Results).

5.2.2 Study procedures

Symptom and medical questionnaires, quality of life scores, CXR, blood IGRA (T-Spot.TB), TST, and a single induced sputum were offered to all subjects and were usually performed over two visits 48-72 hours apart. HIV viral load and blood CD4 cell count were recorded from the pathology database. The procedures are further outlined in Chapter 2, Section 2.3.4.

Subjects were reimbursed for any travel costs to return for sputum induction and TST interpretation, but no other financial incentives were offered.

The study was approved by the London - City and East Ethics Committee - number 12/LO/1516, Clinicaltrials.gov number NCT02712671. There was no outside funding provided for the study.

5.2.3 Case definitions

LTBI was defined as a TST result at 48-72 hours of ≥5mm (irrespective of BCG vaccination status), and/or a positive T-Spot.TB. [160,241,242] Active TB disease was defined as symptoms and radiographic changes consistent with tuberculosis and positive sputum microscopy and culture for *Mycobacterium tuberculosis*. Subclinical TB was defined as positive sputum culture for *M. tuberculosis* with or without radiographic changes and in the absence of symptoms. Medium and low TB incidence countries were defined as those with a TB incidence of 30-300 and <30/100,000 population respectively. [75,243]

5.2.4 Economic analysis – Model structure and assumptions

5.2.4.1 TB testing strategies

Participants were assessed using a symptom questionnaire, CXR, blood IGRA, TST, induced sputum for AFB smear, mycobacterial culture and Xpert MTB/RIF testing. This information, along with participant characteristics (including place of birth, history of previous TB, time on ART, blood CD4 cell count) and uptake in the study, was used to undertake an economic analysis based on no testing and 29 predefined testing strategies (Table 5.2.4c). These reflected national guidelines or incremental combinations of readily available tests to increase the detection of TB infection. [43,44,75,134,241]

It was assumed:

- subjects would only be tested once
- those willing to attend HIV clinic for routine care would also agree to a

chest radiograph and blood IGRA

- the return rate for TST interpretation reflected that seen in the observational study
- LTBI preventive treatment would only be given to those who returned to have their TST measured
- those with a previous history of TB disease would not be retested for LTBI with TST or IGRA
- LTBI preventive treatment uptake would reflect that seen in the study and have an efficacy of 62% [71]

5.2.4.2 Baseline risk of TB

The probability of developing TB in a lifetime was considered to be 10% in those with a positive IGRA (irrespective of TST result), [173-175,211] 2% in those with a positive TST but negative IGRA, [211] and 0.02% in those with a negative TST and IGRA. [76] Using these, we estimated the expected total number of cases of active TB that would prospectively develop, had no LTBI testing and treatment occurred (see Figure 5.2.4.1b). The number of cases of TB prevented using various testing strategies were then compared against this. Proportions of patients from high, middle and lower TB incidence countries reflected UK HIV demographics. [19]

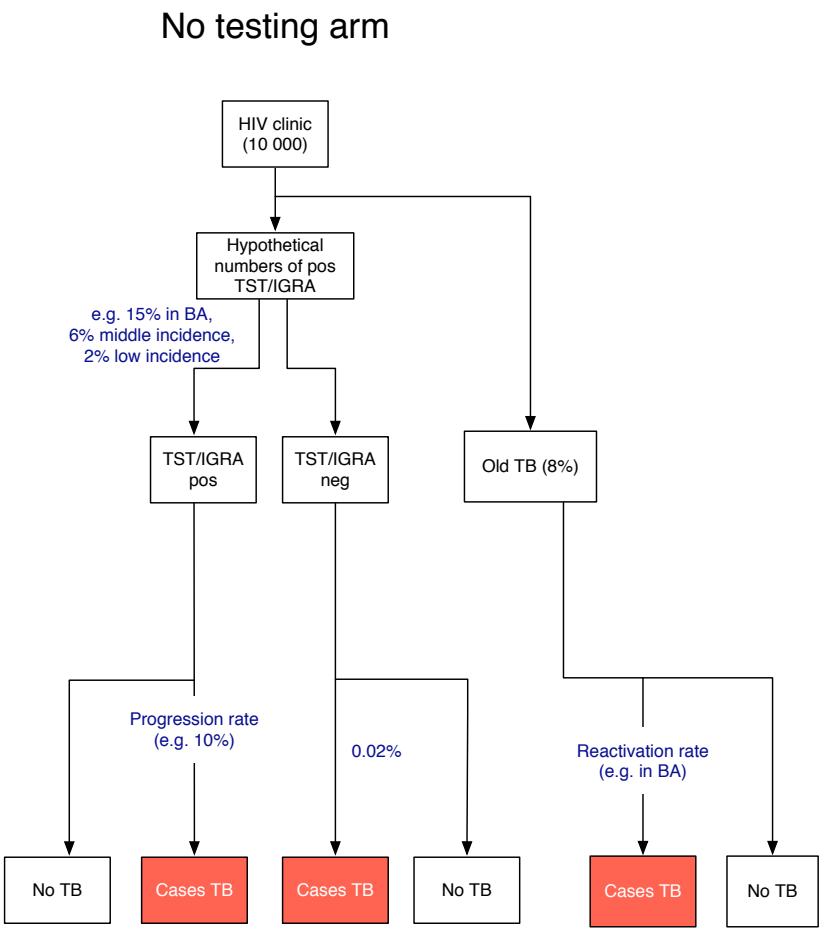
5.2.4.3 Utilities

Health utility due to latent, subclinical and active TB were 0.007, 0.2 and 0.676 respectively. [134,185]

Table 5.2.4.1a Assumptions used for relevant variables within the cost-effectiveness analysis

Variable	Mean/ baseline	Sensitivity analysis lower	Sensitivity analysis upper	Std Dev	Alpha	Beta	Distribution	Source
TST	£16.14	£8.07	£32.28	4.12	15.37	1.05	Gamma	[43]
IGRA	£40.00	£23.00	£90.00	8.67	21.27	1.88	Gamma	Local charges, [43]
CXR	£50.00	£25.00	£100.00	12.76	15.37	3.25	Gamma	Local costs
Sputum induction	£100.00	£67.00	£150.00	16.84	35.28	2.83	Gamma	Estimate, local costs
Sputum induction and TB PCR	£160.00	£116.87	£200.00	22.01	52.86	3.03	Gamma	Estimate, local costs
LTBI	£786.50	£374.50	£1,316.50	210.2	14	56.18	Gamma	Local charges, [43,215]
Active TB	£7,619.67	£3,809.84	£15,239.34	1943.79	15.37	495.86	Gamma	[183]
Cost of subclinical disease	£1655.32	£1234.92	£2075.72	210.2	62.01	26.69	Gamma	Estimate, [183]
Proportion black African	25%	20%	30%	0.002	14938.78	45060.22	Beta	[219]
Proportion middle incidence	13.9%	4%	24%	0.049	6.69	41.3	Beta	Study
Subclinical disease in BA	0.17%	0%	0.41%	0.0012	2.09	1201.91	Beta	Study, [77]
Subclinical disease in MI	0.09%	0%	0.18%	0.00087	1.11	1202.89	Beta	Study, [77]
Subclinical disease in LI	0.04%	0%	0.1%	0.00057	0.48	1203.52	Beta	Study, [77]
Uptake LTBI	50%	35%	65%	0.05	49.5	49.5	Beta	Study
Efficacy LTBI	62%	59%	65%	0.05	1473.74	903.26	Beta	[71]
QALY loss LTBI	0.01	0	0.05	0.01	7.53	0	Gamma	[43]
QALY loss active TB	0.68	0.35	1	0	16.72	0.04	Gamma	[43]
QALY loss subclinical TB	0.2	0.01	0.3	0.17	7.31	0.03	Gamma	Estimate
Progression rate with pos TST alone	2%	1%	4%	0.07	7.68	0	Gamma	[144]
Progression rate with pos IGRA and TST	10%	3%	17%	0.01	7.84	0.01	Gamma	[173-175]
Progression rate with neg TST	0.2%	0%	0.5%	0.04	3.84	0	Gamma	[175,220]
Proportion old TB	7%	2.1%	12.6%	0.02	15.93	200.07	Beta	Study
TST return rate for those having TSTs as well as IGRAs	53%	30%	90%	0.03	116.07	102.93	Beta	Study

Figure 5.2.4.1b Model for cost effectiveness analysis (no testing and intervention arms)



Intervention arms

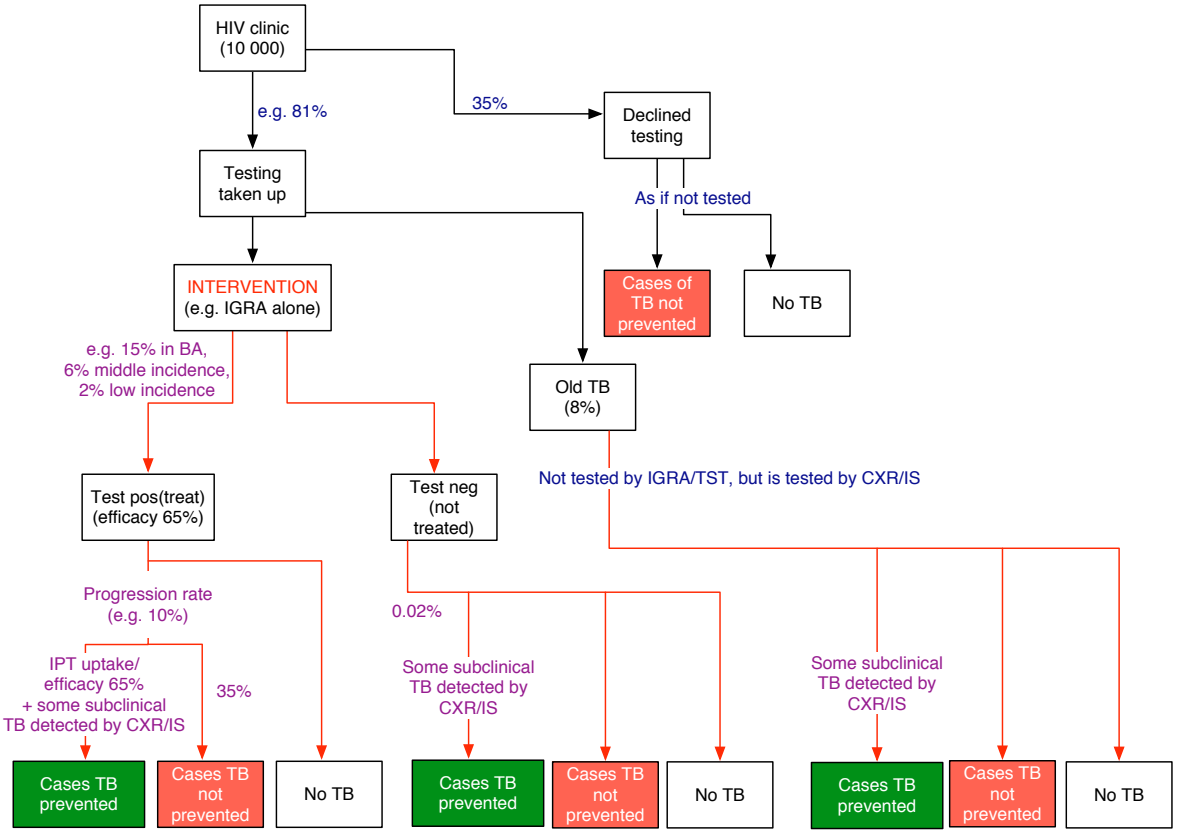


Table 5.2.4.1c Twenty nine strategies tested using the model, in increasing complexity

Abbreviation	Explanation of strategy
BHIVA 2011	BHIVA 2011 - IGRA alone in: black Africans with any CD4, not on ART, or on ART <2 years; from middle TB incidence countries with CD4 <500, on ART <2 years; from low TB incidence countries with CD4 <350 and if on ART <6 months.
BHIVA strategy with CXR	IGRA and CXR in those meeting BHIVA criteria above
BA TST	TST alone, just in black Africans
NICE 2011	NICE 2011 - TST and IGRA if CD4 <200, IGRA alone if CD4 201-500.
BA IGRA	IGRA alone, just in black Africans
BA IGRA&TST	TST and IGRA, just in black Africans
BA TST&CXR	TST and CXR, just in black Africans
BA IGRA&CXR	IGRA and CXR, just in black Africans
BA TST&CXR&IS	TST, CXR and induced sputum just in black Africans (TST in those with no history of previous active TB)
BA IGRA&CXR&IS	IGRA, CXR and induced sputum just in black Africans (IGRA in those with no history of previous active TB)
BA MI TST	TST alone, in black Africans and people from middle TB incidence countries
BA MI IGRA	IGRA alone, in black Africans and people from middle TB incidence countries
BA MI IGRA&TST	TST and IGRA in black Africans and people from middle TB incidence countries
BA MI TST&CXR	TST and CXR in black Africans and people from middle TB incidence countries
BA MI IGRA&CXR	IGRA and CXR in black Africans and people from middle TB incidence countries
BA MI TST&CXR&IS	TST, CXR and induced sputum in black Africans and people from middle TB incidence countries
BA MI IGRA&CXR&IS	IGRA, CXR and induced sputum in black Africans and people from middle TB incidence countries

All TST	TST in all clinic attendees
All IGRA	IGRA alone in all clinic attendees
NICE 2016	NICE 2016 - IGRA in all, plus TST in those with CD4 <200
All CXR	CXR in all clinic attendees
All IGRA&TST	IGRA and TST in all clinic attendees
All TST&CXR	TST and CXR in all clinic attendees
All IGRA&CXR	IGRA and CXR in all clinic attendees
All IGRA&TST&CXR	TST, IGRA and CXR in all clinic attendees
All TST&CXR&IS	TST, CXR and induced sputum in all clinic attendees
All IGRA&CXR&IS	IGRA, CXR and induced sputum in all clinic attendees
All IGRA&TST&CXR&IS	TST, IGRA, CXR and induced sputum in all clinic attendees
All IGRA&TST&CXR&IS inc PCR	TST, IGRA, CXR and induced sputum with GeneXpert TB PCR in all clinic attendees

TST and IGRA only in those with no history of previous active TB; CXR and induced sputum in those that meet criteria irrespective of previous history of TB.

ART - antiretroviral therapy, BA - Black African, BHIVA - British HIV Association, CD4 - blood CD4 cell count in cells/μL, CXR - chest X ray, IGRA - Interferon-gamma release assay, IS - induced sputum, LI - low [TB] incidence countries, MI - middle [TB] incidence countries, NICE - National Institute of Health and Care Excellence, PCR - Xpert MTB/RIF *M. tuberculosis* polymerase chain reaction, TST - tuberculin skin test.

5.2.4.4 Costs

Costs of testing using TST and IGRA, latent TB treatment, and active TB treatment were taken from local charges or published studies. [43,134,183]

Costs were measured from an English NHS perspective in £ Sterling. The time horizon was lifelong and costs and benefits discounted at 3.5% per year. [178]

A full list of assumptions and sources are presented in Table 5.2.4.1a.

5.2.5 Statistics

Sample group proportions were compared using the Chi-square and medians with the Mann-Whitney U test.

5.2.6 Cost effectiveness

Cost effectiveness was measured in terms of incremental cost/case detected and incremental cost/QALY gained. Each testing strategy was compared against no testing and against the last cost-effective (non-dominated) strategy ranked according to local cost. Cost effectiveness ratios were calculated as the difference in cost between the two strategies divided by the difference in outcome (either cases averted or QALYs gained).

5.2.6.2 Sensitivity analysis

Univariate and multivariate (best and worst case) deterministic sensitivity analyses were performed. We varied costs for TST, IGRA, CXR, sputum induction, latent, subclinical and active TB treatment. The rate of uptake of testing was varied to reflect patient acceptance for a second visit within 48 hours for

TST results, and uptake and efficacy of isoniazid prophylaxis. The quality of life parameters used were also varied (Table 5.2.4.1a).

A probabilistic sensitivity analysis using 10,000 Monte Carlo simulations was performed. From this, we calculated uncertainty ranges (UR) for each point estimate and also cost effectiveness acceptability curves, showing which strategy was the most likely cost effective at different cost-effectiveness thresholds.

5.3 Results

5.3.1 Uptake, and cases of active and subclinical TB

Between June 2013 and September 2014, 219 adult outpatients took part within the 14 months recruitment period (See Chapter 4, Figure 4.3.2). These patients were demographically similar to those approached; and were also representative of the total clinic population (Chapter 4, Table 4.3.3). Seventy-three percent (159/219) were male, 28% from subSaharan Africa and 57% from low TB incidence countries, 95% were taking ART, of which 88% had an undetectable HIV load. Median CD4 cell count was 643 cells/μL.

The results of the study are described in Chapter 4. In all, 74% participants returned to have their TST result read whilst 19% telephoned or emailed their result after 48-72 hours. IGRA results were available for 99% and 98% had chest radiographs. Sputum induction was performed on 208 subjects and productive in 178 (86%). Of these, two were positive for *M. tuberculosis* on sputum culture. No samples had *M. tuberculosis* detected by Xpert MTB/RIF.

There were no incidental cases of symptomatic, active tuberculosis disease. Two patients (0.7%) were found to have subclinical TB, but only one had an abnormal CXR and positive IGRA and TST.

Fourteen patients were diagnosed with LTBI – 13% in subSaharan Africans (8/62), and 6.5% (2/31) and 3% (4/126) respectively in those from middle and low TB incidence countries. Seven percent had a history of previous TB.

Uptake of LTBI preventive treatment was 64% (9/14), 50 % (seven) fully completed treatment. Two stopped due to adverse effects and one lost to follow up despite multiple attempts to maintain contact. These data were used to model the cost-effectiveness of the testing strategies.

5.3.2 Cost effectiveness

It was estimated that over their lifetime, 92 of 10,000 people living with HIV (PLHIV) in care in England and Wales would develop active tuberculosis due to reactivation of latent infection in the absence of preventive treatment (Figure 5.3.2). Thirty different testing strategies were then applied using the results obtained from the observational study. In the most targeted strategy (BHIVA), with an uptake rate for LTBI testing of 82%, TST return rate of 53%, completion and efficacy of chemoprophylaxis of 50% and 62% respectively, 2.28 cases of active TB would be prevented, costing an extra £48,658 compared to no testing, with a discounted cost/QALY of £37,952. The estimated costs, cases prevented and QALYs gained for each strategy in order of increasing expense are given in Table 5.3.2. Compared with no testing, only three strategies met the cost-effectiveness criteria by NICE. A single TST in black Africans was the best value at

£23,429/QALY. Testing black Africans and those from MI countries with a TST cost £25,218/QALY and the strategy that prevented the most cases was testing all black Africans with a single IGRA (cost/QALY £28,971). All of these values had wide uncertainty ranges. Testing all BA and those from MI countries with a single IGRA cost just over the threshold at £32,410/QALY gained. Neither of the current UK HIV testing guidelines' strategies were cost-effective from a health services perspective (Table 5.3.2). [75,134] Compared to the previous most costly (non-dominated) intervention, only testing with a TST in black Africans had an incremental cost-effectiveness ratio of less than £30,000/QALY gained.

5.3.3 Sensitivity analysis

Univariate cost effectiveness analysis showed that: TST alone in all became most cost effective if TST cost below £4.98 (from £16.14), IGRA in BA and MI became cost-effective if the price of IGRA fell to £23 (from £40), or if the number completing LTBI preventive therapy increased to over 60%. If the average cost of an active case of TB rose to £15,239, then an IGRA and CXR in BA and MI, or a TST in all became most cost effective. If active TB cost ≤£3,810 to treat then none of the strategies were cost effective. As the uptake and efficacy of preventive therapy for LTBI increased, all strategies became more cost effective, though even with 100% uptake and completion, testing all attendees with IGRA alone never cost <£30,000/QALY. This strategy only became cost-effective if the positive IGRA progression rate was ≥ 16.5%.

Using a Monte Carlo analysis, a cost-effectiveness acceptability curve was calculated for 0-£100,000/QALY. Most regimens were not cost effective at all in

Table 5.3.2 Costs for strategies, discounted cost/case prevented and cost/QALY gained to no testing and last (non-dominated) strategy.

Strategy	Total cost of strategy per 10,000 PLHIV (95% UR)	Cases TB prevented (discounted) (95% UR)	QALYs gained compared to no testing (95% UR)	Cost/case averted (95% UR)	Cost/QALY compared to no testing (95% UR)	Incremental cost/QALY compared to last strategy
No testing	£700,616 (£122,058–£2,573,008)	0	0	£0	£0	
BHIVA 2011	£749,274 (£138,332–£2,682,212)	2.28 (0.18–11)	1.28 (0.06–9.06)	£21,371 (£9,924–£90,557)	£37,952 (£12,059–£254,374)	EXTENDED DOMINANCE
BA TST	£749,660 (£142,610–£2,658,553)	3.9 (1.14–10.58)	2.09 (0.37–8.44)	£12,566 (£8,088–£18,020)	£23,429 (£10,131–£54,996)	£23,429
BA MI TST	£761,797 (£145,305–£2,695,906)	4.49 (1.15–15.19)	2.43 (0.38–12.24)	£13,614 (£8,090–£20,224)	£25,218 (£10,038–£61,681)	EXTENDED DOMINANCE
NICE 2011	£788,037 (£166,361–£2,729,442)	1.11 (0.03–6.19)	0.63 (0.01–5.1)	£78,429 (£25,259–£1,477,123)	£139,281 (£30,693–£4,149,234)	DOMINATED
BA IGRA	£812,048 (£183,630–£2,738,121)	6.83 (2–18.22)	3.85 (0.71–15)	£16,314 (£9,061–£30,779)	£28,971 (£11,010–£86,458)	EXTENDED DOMINANCE
BHIVA strategy with CXR	£829,835 (£190,935–£2,624,585)	5.64 (0.78–18.59)	2.88 (0.26–13.56)	£22,896 (£9,860–£94,773)	£44,794 (£13,518–£282,673)	DOMINATED
BA TST&CXR	£830,223 (£201,436 - £2,734,194)	7.27 (1.78–19.06)	3.7 (0.59–13.82)	£17,828 (£8,455–£44,497)	£35,067 (£11,665–£134,883)	DOMINATED
All TST	£831,181 (£179,898–£2,809,957)	5.63 (1.34–18.81)	2.86 (0.4–14.7)	£23,204 (£12,596–£43,212)	£45,635 (£16,121–£145,855)	DOMINATED
BA IGRA&TST	£856,179 (£203,576–£2,839,172)	7.11 (2.03–19.47)	3.9 (0.71–15.49)	£21,872 (£13,670–£40,228)	£39,884 (£17,179–£114,166)	EXTENDED DOMINANCE

Strategy	Total cost of strategy per 10,000 PLHIV (95% UR)	Cases TB prevented (discounted) (95% UR)	QALYs gained compared to no testing (95% UR)	Cost/case averted (95% UR)	Cost/QALY compared to no testing (95% UR)	Incremental cost/QALY compared to last strategy
BA MI IGRA	£865,959 (£198,166–£2,876,442)	9.06 (2.13–31.39)	5.1 (0.76–25.83)	£18,250 (£9,665–£35,772)	£32,410 (£11,745–£100,483)	EXTENDED DOMINANCE
BA IGRA&CXR	£892,611 (£242,456–£2,813,762)	10.2 (2.64–26.71)	5.45 (0.93–20.37)	£18,827 (£9,014–£45,539)	£35,235 (£11,819–£129,886)	EXTENDED DOMINANCE
BA MI TST&CXR	£892,940 (£220,769–£2,864,008)	8.86 (1.83–28.72)	4.51 (0.6–20.81)	£21,702 (£10,133–£54,062)	£42,690 (£13,986–£163,780)	DOMINATED
BA TST&CXR&IS	£926,775 (£274,953–£2,840,476)	9.06 (2.11–23.7)	4.55 (0.7–16.76)	£24,976 (£11,283–£72,321)	£49,753 (£15,963–£218,816)	EXTENDED DOMINANCE
BA MI IGRA&TST	£927,080 (£223,264–£3,017,376)	9.34 (2.15–32.64)	5.16 (0.76–26.33)	£24,242 (£13,613–£46,996)	£43,924 (£16,875–£133,292)	EXTENDED DOMINANCE
BA IGRA&CXR&IS	£989,163 (£315,973–£2,920,044)	11.98 (2.97–31.35)	6.3 (1.04–23.31)	£24,080 (£11,069–£65,203)	£45,811 (£14,889–£186,961)	EXTENDED DOMINANCE
BA MI IGRA&CXR	£997,103 (£273,630–£3,044,543)	13.43 (2.8–44.92)	7.18 (0.98–34.4)	£22,080 (£10,497–£54,056)	£41,289 (£13,708–£154,157)	EXTENDED DOMINANCE
BA MI TST&CXR&IS	£1,046,430 (£314,718–£3,079,648)	11.18 (2.17–36.11)	5.61 (0.72–25.49)	£30,938 (£14,029–£88,660)	£61,671 (£19,877–£268,104)	DOMINATED
All IGRA	£1,056,702 (£338,840–£3,105,326)	10.17 (2.17–35.76)	5.72 (0.77–29.43)	£35,030 (£14,887–£99,928)	£62,209 (£18,090–£280,697)	EXTENDED DOMINANCE
NICE 2016	£1,058,522 (£339,907–£3,132,635)	10.17 (2.09-35.21)	5.72 (0.77-29.71)	£35,234 (£15,203–£102,528)	£62,571 (£18,562–£291,119)	DOMINATED
All CXR	£1,069,462 (£359,550–£2,865,632)	6.26 (0.65–19.26)	2.98 (0.21–12.06)	£58,903 (£22,038–£373,454)	£123,745 (£35,192–£1,129,118)	DOMINATED
BA MI IGRA&CXR&IS	£1,150,593 (£367,579–£3,260,183)	15.74 (3.15–52.32)	8.28 (1.1–39.08)	£28,582 (£13,135–£77,916)	£54,325 (£17,583–£223,378)	EXTENDED DOMINANCE
All TST&CXR	£1,200,028 (£425,519–£3,232,263)	11.89 (2.02–39.02)	5.84 (0.62–27.49)	£42,007 (£16,896–£150,095)	£85,490 (£23,981–£485,790)	DOMINATED

Table 5.3.2 cont.

Strategy	Total cost of strategy per 10,000 PLHIV (95% UR)	Cases TB prevented (discounted) (95% UR)	QALYs gained compared to no testing (95% UR)	Cost/case averted (95% UR)	Cost/QALY compared to no testing (95% UR)	Incremental cost/QALY compared to last strategy
All IGRA&TST	£1,219,154 (£421,284–£3,413,448)	10.99 (2.31–38.68)	5.88 (0.78–30.59)	£47,166 (£21,730–£129,791)	£88,139 (£27,475–£382,611)	EXTENDED DOMINANCE
All IGRA&CXR	£1,425,548 (£584,461–£3,527,632)	16.43 (2.85–55.96)	8.7 (1–42.22)	£44,130 (£17,058–£162,095)	£83,280 (£22,611–£462,211)	EXTENDED DOMINANCE
All IGRA&TST&CXR	£1,588,001 (£666,905–£3,835,753)	17.26 (2.99–58.88)	8.86 (1.01–43.38)	£51,425 (£21,445–£182,301)	£100,112 (£29,107–£539,356)	EXTENDED DOMINANCE
All TST&CXR&IS	£1,611,816 (£727,630–£3,720,928)	15.21 (2.37–50.07)	7.42 (0.74–34.49)	£59,913 (£22,927–£255,246)	£122,770 (£33,286–£816,397)	DOMINATED
All IGRA&CXR&IS	£1,837,336 (£886,572–£4,016,297)	19.75 (3.2–67.01)	10.28 (1.12–49.21)	£57,564 (£21,537–£238,659)	£110,523 (£29,326–£684,128)	EXTENDED DOMINANCE
All IGRA&TST&CXR&IS	£1,999,789 (£969,016–£4,324,419)	20.58 (3.34–69.93)	10.44 (1.13–50.38)	£63,142 (£25,044–£253,623)	£124,393 (£34,765–£751,337)	EXTENDED DOMINANCE
All IGRA&TST&CXR&IS inc PCR	£2,259,282 (£1,180,302–£4,637,180)	20.58 (3.34–69.93)	10.44 (1.13–50.38)	£75,753 (£29,516–£316,893)	£149,239 (£40,973–£938,769)	EXTENDED DOMINANCE

ART - antiretroviral therapy, BA - Black African, BHIVA - British HIV Association, CD4 - blood CD4 cell count in cells/μL,
CXR - chest X ray, IGRA - Interferon-gamma release assay, IS - induced sputum, LI - low [TB] incidence countries,
MI - middle [TB] incidence countries, NICE - National Institute of Health and Care Excellence,
PCR - Xpert MTB/RIF *M. tuberculosis* polymerase chain reaction, PLHIV - People living with HIV,
QALY - Quality adjusted life year, TB - tuberculosis (includes active disease and subclinical tuberculosis cases),
TST - tuberculin skin test, UR - uncertainty ranges
Strategies are either named (e.g. BHIVA 2011), or consist of the group tested, followed by the test(s)
(e.g. BA TST is Testing black Africans with a tuberculin skin test only).

this range. Of the twelve that were, no testing was most likely cost effective up to £30,000; above which level testing using TST in BA became the strategy most likely to be cost effective. At £50,000/QALY, testing BA and middle incidence groups with IGRA and CXR was the most likely cost-effective (Figure 5.3.4a).

Figure 5.3.4a Cost effectiveness acceptability curve for TB testing strategies

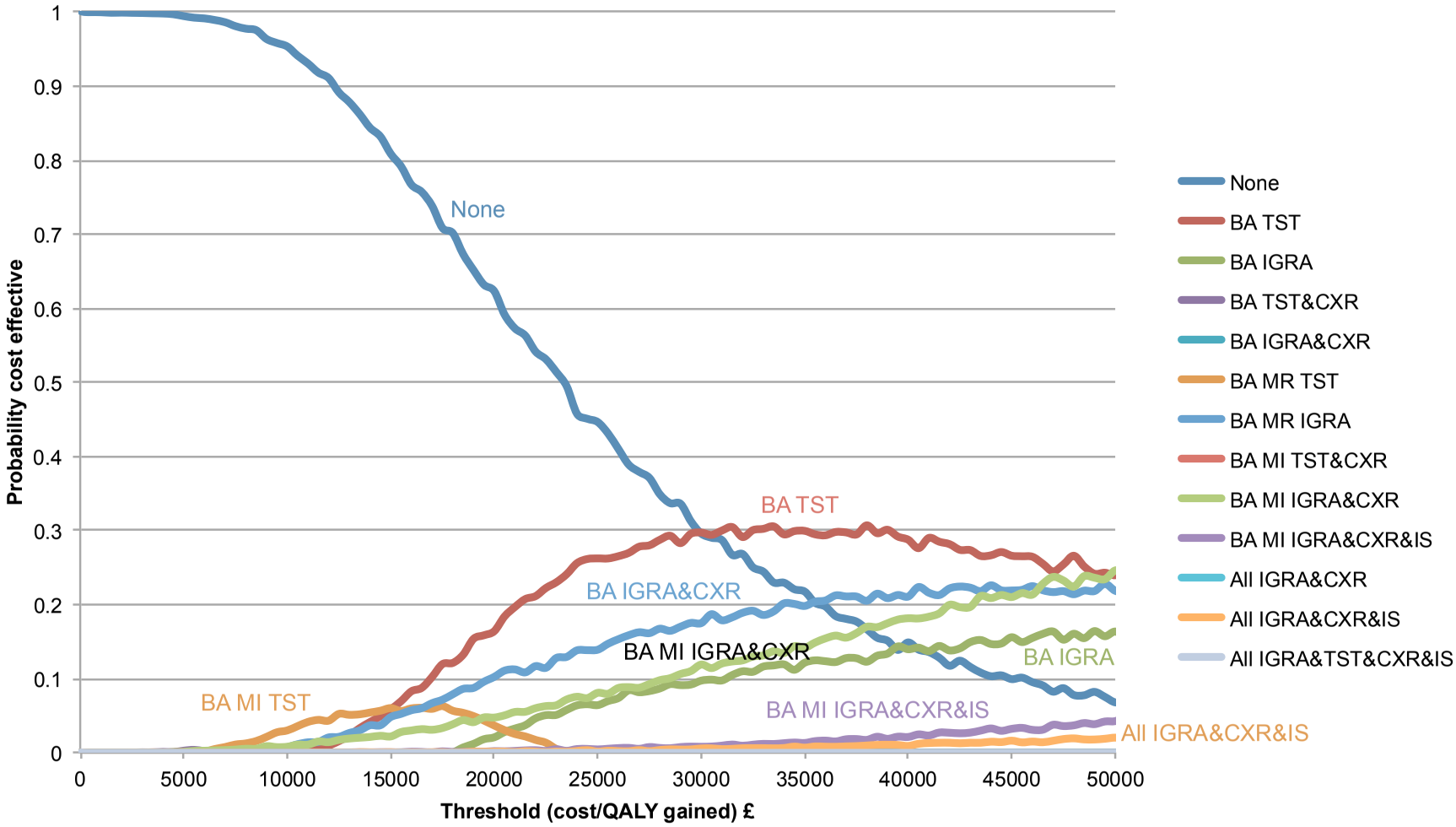


Table 5.3.4b Univariate sensitivity analyses Cost/case prevented (in £'000)

Variable and baseline		Cost TST (£16.14)		Cost IGRA (£40)		Cost CXR (£50)		Cost Sputum induction (£100)		Cost LTBI (£786)		Cost Subclinical TB (£1655)		Cost Active TB (£7620)		Proportion BA (24%)		Proportion MI (14%)		Uptake LTBI (50%)	
Min/Max variable	Base	8.07	32.2	23	90	25	100	67	150	374.	1316	1234	2075	3809	1523	20%	30%	4%	24%	35%	65%
BHIVA 2011	21.4	21.4	21.4	14.5	41.5	21.4	21.4	21.4	21.4	14.4	30.3	21.4	21.4	25.4	13.4	23.1	20.2	21.4	21.4	28.3	17.7
BA TST	12.6	10.5	16.7	12.6	12.6	12.6	12.6	12.6	12.6	4	23.6	12.6	12.6	16.5	4.6	12.6	12.6	12.6	12.6	14.3	11.6
BA MI TST	13.6	10.8	19.2	13.6	13.6	13.6	13.6	13.6	13.6	5.2	24.4	13.6	13.6	17.6	5.6	13.8	13.5	12.9	14.2	16	12.3
NICE 2011	78.4	77.6	80.1	48	167.8	78.4	78.4	78.4	78.4	71.5	87.4	78.4	78.4	82.4	70.5	78.4	78.4	78.4	78.4	109.8	61.6
BA IGRA	16.3	16.3	16.3	11.6	30.1	16.3	16.3	16.3	16.3	9.4	25.3	16.3	16.3	20.3	8.3	16.3	16.3	16.3	16.3	21	13.8
BHIVA strategy with CXR	22.9	22.9	22.9	20.1	31	13.9	40.9	22.9	22.9	20.1	26.5	22.6	23.2	26.9	14.9	21.9	23.7	22.9	22.9	25.3	21
BA TST&CXR	17.8	16.7	20	17.8	17.8	10.8	31.8	17.8	17.8	13.2	23.8	17.6	18	21.8	9.9	17.8	17.8	17.8	17.8	19.6	16.5
All TST	23.2	17.5	34.7	23.2	23.2	23.2	23.2	23.2	23.2	12.9	36.5	23.2	23.2	27.2	15.2	25.6	21.3	24.7	21.8	28.1	20.6
BA IGRA&TST	21.9	19.7	26.1	17.4	35.1	21.9	21.9	21.9	21.9	14	32	21.9	21.9	25.9	13.9	21.9	21.9	21.9	21.9	28.2	18.4
BA MI IGRA	18.2	18.2	18.2	12.7	34.4	18.2	18.2	18.2	18.2	11.3	27.2	18.2	18.2	22.2	10.3	18.6	18	17	19.1	23.8	15.3
BA IGRA&CXR	18.8	18.8	18.8	15.7	28.1	13.8	28.8	18.8	18.8	14.2	24.8	18.7	19	22.8	10.9	18.8	18.8	18.8	18.8	22.2	16.6
BA MI TST&CXR	21.7	20.3	24.5	21.7	21.7	12.8	39.6	21.7	21.7	17.5	27.2	21.5	21.9	25.7	13.7	22.4	21.1	19.1	23.7	24.2	19.9
BA TST&CXR&IS	25	24.1	26.8	25	25	19.4	36.2	21.1	30.9	21.3	29.7	24.7	25.2	29	17	25	25	25	25	27.4	23.1
BA MI IGRA&TST	24.2	21.7	29.3	18.9	39.9	24.2	24.2	24.2	24.2	16.6	34.1	24.2	24.2	28.2	16.3	24.7	23.9	22.7	25.4	31.8	20.2
BA IGRA&CXR&IS	24.1	24.1	24.1	21.4	31.9	19.8	32.6	21.1	28.6	20.1	29.2	23.9	24.3	28.1	16.1	24.1	24.1	24.1	24.1	28	21.3
BA MI IGRA&CXR	22.1	22.1	22.1	18.4	33	16.2	33.9	22.1	22.1	17.4	28.1	21.9	22.2	26.1	14.1	22.7	21.6	20	23.6	26.3	19.3
BA MI TST&CXR&IS	30.9	29.8	33.2	30.9	30.9	23.9	45.1	26	38.5	27.6	35.3	30.7	31.2	34.9	23	32.1	30.1	27	34	34.1	28.5
All IGRA	35	35	35	22.4	72.2	35	35	35	35	28.1	44	35	35	39	27.1	39.2	31.6	39.8	31.4	47.8	28.2
NICE 2016	35.2	35.1	35.4	22.6	72.4	35.2	35.2	35.2	35.2	28.3	44.1	35.2	35.2	39.2	27.2	39.4	31.8	40	31.5	48	28.3
All CXR	58.9	58.9	58.9	58.9	58.9	26.3	124	58.9	58.9	58.9	58.9	58.5	59.3	62.9	50.9	64.7	53.8	63.4	54.9	58.9	58.9
BA MI IGRA&CXR&IS	28.6	28.6	28.6	25.4	37.9	23.6	38.6	25.1	33.9	24.6	33.7	28.4	28.8	32.6	20.6	29.4	28	25.6	30.7	33.4	25.2
All TST&CXR	42	39.3	47.4	42	42	24.9	76.3	42	42	37.1	48.3	41.8	42.2	46	34	46.6	38.1	44.9	39.4	47	38.2
All IGRA&TST	47.2	41.6	58.3	35.5	81.5	47.2	47.2	47.2	47.2	38.5	58.3	47.2	47.2	51.1	39.2	52.6	42.7	53.3	42.3	63.7	38.3
All IGRA&CXR	44.1	44.1	44.1	36.3	67.1	31.7	69	44.1	44.1	39.8	49.7	44	44.3	48.1	36.2	49.2	39.9	49.3	40	53	38
All IGRA&TST&CXR	51.4	47.9	58.5	44	73.3	39.6	75.1	51.4	51.4	45.9	58.5	51.3	51.6	55.4	43.5	57.1	46.7	57.1	46.7	61.5	44.6
All TST&CXR&IS	59.9	57.8	64.2	59.9	59.9	46.5	86.7	50.5	74.1	56.1	64.8	59.6	60.2	63.9	51.9	66.3	54.4	64	56.3	65.9	55.1
All IGRA&CXR&IS	57.6	57.6	57.6	51.1	76.7	47.2	78.2	50.3	68.5	54	62.2	57.4	57.8	61.5	49.6	64.1	52.1	64	52.3	67.1	50.6
All IGRA&TST&CXR&IS	63.1	60.2	69.1	56.9	81.5	53.2	83	56.2	73.7	58.5	69.1	62.9	63.3	67.1	55.2	70	57.3	69.8	57.6	73.6	55.6
All IGRA&TST&CXR & IS&PCR	75.8	72.8	81.7	69.5	94.1	65.8	95.6	66.7	84.2	71.1	81.7	75.5	76	79.7	67.8	84	68.7	83.7	69.1	88.6	66.5

Table 5.3.4b Univariate sensitivity analyses Cost/case prevented (in £'000)

Variable and baseline		Uptake LTBI (50%)		Efficacy LTBI 62%)		Efficacy &Uptake	Progression rate TST + IGRA - (2%)		Progression rate IGRA + (10%)		TST return rate (53%)		Proportion subclinical disease BA (0.17%)		Proportion subclinical disease MI (0.09%)		Proportion subclinical disease LI (0.04%)		Worst case	Best case
Min/Max variable	Base	80%	100%	40%	100%	100%	1%	4%	3%	17%	30%	90%	0%	0.4%	0%	0.2%	0%	0.1%		
BHIVA 2011	21.4	15.3	13.3	37.5	10.2	5.2	21.4	21.4	89.8	9.3	21.4	21.4	21.4	21.4	21.4	21.4	21.4	21.4	110.5	CS
BA TST	12.6	11	10.5	23.9	4.8	3.5	13.2	12	50.6	4.5	12.6	12.6	12.6	12.6	12.6	12.6	12.6	12.6	56.9	CS
BA MI TST	13.6	11.5	10.8	25.5	5.4	3.7	14.2	13.1	54.8	5.1	13.6	13.6	13.6	13.6	13.6	13.6	13.6	13.6	62.3	CS
NICE 2011	78.4	51	41.9	125.9	45.6	23	78.4	78.4	280	42.9	78.4	78.4	78.4	78.4	78.4	78.4	78.4	78.4	393.9	8
BA IGRA	16.3	12.2	10.8	29.7	7.1	3.7	16.3	16.3	73	6.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	16.3	85.3	CS
BHIVA strategy with CXR	22.9	19.5	17.8	28.1	16.8	11.1	22.9	22.9	35	16.1	22.9	22.9	60.3	10.1	22.9	22.9	22.9	22.9	70.7	CS
BA TST&CXR	17.8	15.5	14.6	23.9	11.4	7.8	18.3	17.4	31.6	11.2	17.8	17.8	36.5	8.7	17.8	17.8	17.8	17.8	57.9	CS
All TST	23.2	18.9	17.5	40.3	11.4	7.8	25.3	21.4	69.4	11.6	23.2	23.2	23.2	23.2	23.2	23.2	23.2	23.2	98	CS
BA IGRA&TST	21.9	16.3	14.5	38.3	10.5	5.9	22.4	21.4	83.1	9.9	21.4	22.6	21.9	21.9	21.9	21.9	21.9	21.9	106.5	CS
BA MI IGRA	18.2	13.4	11.8	32.7	8.3	4.3	18.2	18.2	79.4	7.5	18.2	18.2	18.2	18.2	18.2	18.2	18.2	18.2	95	CS
BA IGRA&CXR	18.8	14.9	13.4	27.2	11	6.4	18.8	18.8	42.5	10.3	18.8	18.8	30.1	11.3	18.8	18.8	18.8	18.8	71.3	CS
BA MI TST&CXR	21.7	18.5	17.1	28.2	14.7	9.8	22.1	21.3	36.5	14.3	21.7	21.7	37.3	12.4	25.2	18.4	21.7	21.7	68	CS
BA TST&CXR&IS	25	21.6	20	30.9	18.1	12.5	25.4	24.6	37.8	17.8	25	25	61.1	11.7	25	25	25	25	65.9	CS
BA MI IGRA&TST	24.2	17.6	15.4	42	12	6.5	24.7	23.8	92.3	11.2	23.9	24.7	24.2	24.2	24.2	24.2	24.2	24.2	118.9	CS
BA IGRA&CXR&IS	24.1	19.3	17.3	32.2	15.8	9.5	24.1	24.1	45.4	14.9	24.1	24.1	44.7	13.2	24.1	24.1	24.1	24.1	75.1	CS
BA MI IGRA&CXR	22.1	17.2	15.3	31.5	13.3	7.6	22.1	22.1	49	12.4	22.1	22.1	30.8	15.1	24.3	19.8	22.1	22.1	82.4	CS
BA MI TST&CXR&IS	30.9	26.5	24.4	37.4	23.2	16	31.4	30.5	44.9	22.8	30.9	30.9	59.5	17	36.8	25.8	30.9	30.9	78.4	0
All IGRA	35	23.9	20.2	58.7	18.7	9.5	35	35	135.4	17.3	35	35	35	35	35	35	35	35	178.6	CS
NICE 2016	35.2	24	20.3	59	18.8	9.5	35.2	35.2	136	17.4	35.2	35.2	35.2	35.2	35.2	35.2	35.2	35.2	179.4	CS
All CXR	58.9	58.9	58.9	58.9	58.9	58.9	58.9	58.9	58.9	58.9	58.9	58.9	125.8	32	71.1	48.6	87.1	38.4	128.5	17.9
BA MI IGRA&CXR&IS	28.6	22.6	20.1	38	19.1	11.4	28.6	28.6	53.2	18.1	28.6	28.6	44.1	18.1	32.3	25	28.6	28.6	87.7	CS
All TST&CXR	42	35.3	32.3	52.1	30.8	20.9	43.6	40.6	61.7	31	42	42	59.6	29	46.4	37.7	51.1	32.6	119.7	1.4
All IGRA&TST	47.2	32.7	27.9	77.5	26.2	14.3	49	45.5	148.3	25.5	47.1	47.3	47.2	47.2	47.2	47.2	47.2	47.2	225	CS
All IGRA&CXR	44.1	33.6	29.3	58.8	29.8	17.4	44.1	44.1	83.9	28.4	44.1	44.1	56.2	33.5	47.4	40.8	50.7	36.6	149.7	1.1
All IGRA&TST&CXR	51.4	39.6	34.8	68.8	34.7	21	52.7	50.3	93.1	34.1	51.5	51.3	64.4	39.7	54.9	47.8	58.5	43.2	171.2	3.2
All TST&CXR&IS	59.9	51.2	46.9	70.2	47.4	33.3	61.5	58.4	79.2	47.6	59.9	59.9	90.9	39.6	67.2	52.9	75.5	45.1	139.9	12.5
All IGRA&CXR&IS	57.6	45.2	39.8	72.2	41.9	25.8	57.6	57.6	94.5	40.2	57.6	57.6	78.4	41.3	62.9	52.2	68.5	45.9	159.9	8.8
All IGRA&TST&CXR&IS	63.1	49.9	44.2	79.8	45.6	28.6	64.4	62	100.7	44.9	63.4	62.8	84.6	46	68.7	57.6	74.5	50.9	176.3	10.2
All IGRA&TST&CXR & IS&PCR	75.8	59.4	52.4	95.3	55.1	34.3	77.2	74.4	120	54.2	76.2	75	101.1	55.5	82.3	69.2	89.2	61.3	191.2	16.8

Table 5.3.4c Univariate sensitivity analyses Cost/QALY gained (in £'000)

Variable and baseline		Cost TST (£16.14)		Cost IGRA (£40)		Cost CXR (£50)		Cost Sputum induction (£100)		Cost LTBI (£786)		Cost Subclinical TB (£1655)		Cost Active TB (£7620)		Proportion BA (24%)		Proportion MI (14%)	
Min/Max variable	Base	8.07	32.28	23	90	25	100	67	150	374.5	1316.	1234.	2075.	3809.	15239.	20%	30%	4%	24%
BHIVA 2011	38	38	38	25.8	73.6	38	38	38	38	25.6	53.8	38	38	45	23.8	41	35.8	38	38
BA TST	23.4	19.6	31.1	23.4	23.4	23.4	23.4	23.4	23.4	7.4	44	23.4	23.4	30.9	8.6	23.4	23.4	23.4	23.4
BA MI TST	25.2	20	35.6	25.2	25.2	25.2	25.2	25.2	25.2	9.7	45.2	25.2	25.2	32.6	10.5	25.6	24.9	24	26.2
NICE 2011	139.3	137.8	142.2	85.3	298	139.3	139.3	139.3	139.3	126.9	155.2	139.3	139.3	146.4	125.1	139.3	139.3	139.3	139.3
BA IGRA	29	29	29	20.7	53.4	29	29	29	29	16.6	44.8	29	29	36	14.8	29	29	29	29
BHIVA strategy with CXR	44.8	44.8	44.8	39.4	60.7	27.2	80	44.8	44.8	39.3	51.8	44.3	45.3	52.6	29.2	42.5	46.7	44.8	44.8
BA TST&CXR	35.1	32.9	39.4	35.1	35.1	21.3	62.5	35.1	35.1	26	46.7	34.7	35.5	42.9	19.4	35.1	35.1	35.1	35.1
All TST	45.6	34.3	68.2	45.6	45.6	45.6	45.6	45.6	45.6	25.4	71.7	45.6	45.6	53.5	30	50.9	41.4	49.4	42.2
BA IGRA&TST	39.9	36	47.7	31.7	64	39.9	39.9	39.9	39.9	25.6	58.3	39.9	39.9	47.1	25.4	39.9	39.9	39.9	39.9
BA MI IGRA	32.4	32.4	32.4	22.6	61.2	32.4	32.4	32.4	32.4	20.1	48.3	32.4	32.4	39.5	18.3	33	31.9	30.2	34
BA IGRA&CXR	35.2	35.2	35.2	29.4	52.5	25.9	53.9	35.2	35.2	26.5	46.4	35	35.5	42.7	20.3	35.2	35.2	35.2	35.2
BA MI TST&CXR	42.7	39.9	48.3	42.7	42.7	25.1	77.8	42.7	42.7	34.3	53.4	42.3	43.1	50.5	27	44.2	41.6	37.6	46.7
BA TST&CXR&IS	49.8	48	53.3	49.8	49.8	38.6	72.1	41.9	61.6	42.4	59.2	49.3	50.3	57.7	33.9	49.8	49.8	49.8	49.8
BA MI IGRA&TST	43.9	39.3	53.1	34.3	72.4	43.9	43.9	43.9	43.9	30.1	61.7	43.9	43.9	51.1	29.5	44.6	43.4	41.3	45.8
BA IGRA&CXR&IS	45.8	45.8	45.8	40.7	60.7	37.7	61.9	40.2	54.4	38.3	55.5	45.5	46.2	53.4	30.7	45.8	45.8	45.8	45.8
BA MI IGRA&CXR	41.3	41.3	41.3	34.3	61.7	30.3	63.3	41.3	41.3	32.5	52.6	41	41.6	48.7	26.4	42.4	40.5	37.3	44.1
BA MI TST&CXR&IS	61.7	59.4	66.1	61.7	61.7	47.5	89.9	51.8	76.6	55	70.3	61.1	62.2	69.6	45.8	63.9	60	53.7	67.8
All IGRA	62.2	62.2	62.2	39.8	128.2	62.2	62.2	62.2	62.2	49.9	78.1	62.2	62.2	69.3	48.1	69.6	56.2	70.7	55.7
NICE 2016	62.5	62.4	62.8	40.1	128.5	62.5	62.5	62.5	62.5	50.2	78.4	62.5	62.5	69.6	48.4	70	56.5	71.1	56
All CXR	123.7	123.7	123.7	123.7	123.7	55.3	260.6	123.7	123.7	123.7	123.7	122.8	124.7	132.1	107	135.9	113	133.2	115.3
BA MI IGRA&CXR&IS	54.3	54.3	54.3	48.3	72	44.8	73.4	47.6	64.5	46.7	64.1	54	54.7	61.9	39.2	55.8	53.2	48.8	58.3
All TST&CXR	85.5	80	96.6	85.5	85.5	50.6	155.3	85.5	85.5	75.6	98.3	85	86	93.6	69.3	95.5	77.1	92	79.6
All IGRA&TST	88.1	77.8	108.9	66.3	152.4	88.1	88.1	88.1	88.1	71.9	109	88.1	88.1	95.6	73.3	98.8	79.4	100.9	78.2
All IGRA&CXR	83.3	83.3	83.3	68.5	126.7	59.9	130.1	83.3	83.3	75.2	93.7	83	83.6	90.8	68.2	93	75.2	93.3	75.2
All IGRA&TST&CXR	100.1	93.2	113.9	85.6	142.7	77.1	146.1	100.1	100.1	89.4	113.9	99.8	100.4	107.9	84.6	111.7	90.5	112.3	90.2
All TST&CXR&IS	122.8	118.4	131.5	122.8	122.8	95.3	177.7	103.5	151.9	115	132.8	122.2	123.3	130.9	106.4	136.7	111	131.9	114.6
All IGRA&CXR&IS	110.5	110.5	110.5	98	147.3	90.7	150.2	96.6	131.5	103.7	119.4	110.1	110.9	118.2	95.2	123.3	99.8	123.2	100.1
All IGRA&TST&CXR&IS	124.4	118.6	136.1	112.1	160.6	104.9	163.4	110.7	145.1	115.3	136.1	124	124.8	132.2	108.7	138.5	112.5	138.7	112.6
All IGRA&TST&CXR & IS&PCR	149.2	143.4	160.9	136.9	185.4	129.7	188.3	131.4	165.8	140.1	161	148.8	149.6	157.1	133.5	166.2	134.9	166.4	135.1

Table 5.3.4c Univariate sensitivity analyses Cost/QALY gained (in £'000) continued

Variable and baseline		Uptake LTBI (50%)				Efficacy LTBI 62%)		Effi cac y &Up	Progressio n rate TST + IGRA - (2%)		Progressio n rate IGRA + (10%)		TST return rate (53%)		Proportion subclinical disease BA (0.17%)		Proportion subclinical disease MI (0.09%)		Proportion subclinical disease LI (0.04%)	
Min/Max variable	Base	35%	65%	80%	100%	40%	100%	100%	1%	4%	3%	17%	30%	90%	0%	0.4	0%	0.2	0%	0.1
BHIVA 2011	38	50.2	31.4	27.2	23.7	74.9	16.9	8.7	38	38	299.8	15.2	38	38	38	38	38	38	38	38
BA TST	23.4	26.7	21.7	20.5	19.6	51.9	8.1	5.9	24.9	22.2	182.4	7.6	23.4	23.4	23.4	23.4	23.4	23.4	23.4	23.4
BA MI TST	25.2	29.7	22.8	21.3	20	54.8	9.2	6.2	26.5	24.1	195.6	8.5	25.2	25.2	25.2	25.2	25.2	25.2	25.2	25.2
NICE 2011	139.3	194.9	109.3	90.6	74.4	251.4	75.3	37.9	139.3	139.3	934.5	70.3	139.3	139.3	139.3	139.3	139.3	139.3	139.3	139.3
BA IGRA	29	37.4	24.5	21.6	19.2	59.2	11.7	6.1	29	29	243.5	10.4	29	29	29	29	29	29	29	29
BHIVA strategy with CXR	44.8	50.2	40.6	37.3	33.9	58	30.9	19.7	44.8	44.8	78.5	29.4	44.8	44.8	108.4	20.4	44.8	44.8	44.8	44.8
BA TST&CXR	35.1	39	32.3	30.2	28.1	51	20.8	13.8	36.1	34.1	75.6	20.2	35.1	35.1	68.3	17.6	35.1	35.1	35.1	35.1
All TST	45.6	55.3	40.4	37.2	34.3	96.9	19.9	13.6	50.9	41.3	266.4	20.2	45.6	45.6	45.6	45.6	45.6	45.6	45.6	45.6
BA IGRA&TST	39.9	51.5	33.6	29.7	26.4	80.1	17.7	9.9	41	38.9	289.8	16.5	38.6	41.9	39.9	39.9	39.9	39.9	39.9	39.9
BA MI IGRA	32.4	42.3	27.1	23.8	20.9	65.2	13.7	7.1	32.4	32.4	265	12.2	32.4	32.4	32.4	32.4	32.4	32.4	32.4	32.4
BA IGRA&CXR	35.2	42.2	30.7	27.6	24.6	55.5	19.2	10.8	35.2	35.2	103.8	17.7	35.2	35.2	53.8	21.8	35.2	35.2	35.2	35.2
BA MI TST&CXR	42.7	48	38.8	35.9	33	59.8	26.8	17.3	43.7	41.8	85.9	26	42.7	42.7	70.8	25	49.2	36.5	42.7	42.7
BA TST&CXR&IS	49.8	55.2	45.6	42.4	39	65.7	33.6	22.4	50.9	48.7	87	32.9	49.8	49.8	114.7	23.7	49.8	49.8	49.8	49.8
BA MI IGRA&TST	43.9	57.6	36.6	31.9	28	86.7	20	10.9	44.8	43.1	318.9	18.6	43	45.5	43.9	43.9	43.9	43.9	43.9	43.9
BA IGRA&CXR&IS	45.8	54	40.2	36	32	66.1	28	16.3	45.8	45.8	106.5	26.3	45.8	45.8	79.9	25.9	45.8	45.8	45.8	45.8
BA MI IGRA&CXR	41.3	49.9	35.7	31.8	28.1	64.3	23.1	12.9	41.3	41.3	119.9	21.4	41.3	41.3	55.8	29	45.1	37.4	41.3	41.3
BA MI TST&CXR&IS	61.7	68.7	56.3	52	47.6	79.2	43.4	28.8	62.8	60.7	102.2	42.4	61.7	61.7	114.1	34.5	72.7	51.8	61.7	61.7
All IGRA	62.2	84.8	50	42.4	35.8	117.1	30.8	15.7	62.2	62.2	451.7	28.4	62.2	62.2	62.2	62.2	62.2	62.2	62.2	62.2
NICE 2016	62.5	85.3	50.3	42.6	36	117.7	31	15.7	62.5	62.5	453.7	28.6	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
All CXR	123.7	123.7	123.7	123.7	123.7	123.7	123.7	123.7	123.7	123.7	123.7	123.7	123.7	123.7	264.3	67.2	149.4	102.2	183.1	80.6
BA MI IGRA&CXR&IS	54.3	64.5	47.3	42.2	37.2	77.8	33.7	19.6	54.3	54.3	125.3	31.8	54.3	54.3	80.4	35.5	60.8	48	54.3	54.3
All TST&CXR	85.5	96.2	77.5	71.3	65	114.7	57.7	38.2	89.7	81.8	147.3	58.3	85.5	85.5	119.9	59.5	94.1	76.9	103.5	66.8
All IGRA&TST	88.1	119	71.5	61.1	52.1	169.3	44.5	24.2	92.4	84.3	536.1	43.2	86.2	91.2	88.1	88.1	88.1	88.1	88.1	88.1
All IGRA&CXR	83.3	101.4	71.1	62.4	54	120.3	52.3	29.8	83.3	83.3	200.7	49.4	83.3	83.3	103.5	64.6	88.8	77.5	94.4	70.2
All IGRA&TST&CXR	100.1	121	86.2	76.2	66.6	147.5	62.1	36.7	103.2	97.3	232.9	60.7	98.9	102	123.4	78.5	106.5	93.4	112.9	85
All TST&CXR&IS	122.8	135.8	112.4	104	95.1	152.7	90.6	61.7	127.3	118.7	182.1	91.2	122.8	122.8	184.2	81.8	137.4	108.7	153.8	92.8
All IGRA&CXR&IS	110.5	130.8	96.1	85.2	74.4	148.5	75	44.7	110.5	110.5	218	71.5	110.5	110.5	146.3	81.1	119.8	101	129.7	89.6
All IGRA&TST&CXR&IS	124.4	146.4	108.7	97	85.4	170.4	83	50.6	127.6	121.4	240.7	81.5	123.5	125.8	163.5	92.1	134.6	114	145.3	101.4
All IGRA&TST&CXR & IS&PCR	149.2	176.3	130	115.6	101.3	203.6	100.3	60.8	153	145.7	286.7	98.5	148.5	150.3	195.4	111.1	161.3	137	173.9	122.1

Table 5.3.4c Univariate sensitivity analyses Cost/QALY gained (in £'000) continued

Variable and baseline		QALY loss LTBI (0.007)		QALY loss active (0.676)		QALY loss subclinical (0.2)		Worst case	Best case
Min/Max variable	Base	0	0.05	0.352	1	0.01	0.3		
BHIVA 2011	38	31.6	D	89.4	24.1	38	38	1083.4	CS
BA TST	23.4	18.6	D	59.2	14.6	23.4	23.4	1330.8	CS
BA MI TST	25.2	20.1	D	63.1	15.8	25.2	25.2	1232.3	CS
NICE 2011	139.3	116	D	328	88.4	139.3	139.3	3861.6	8
BA IGRA	29	24.1	D	68.2	18.4	29	29	836.4	CS
BHIVA strategy with CXR	44.8	41.1	99	122.3	27.4	36.7	50.7	1109.6	CS
BA TST&CXR	35.1	30.6	373.3	96.7	21.4	29.9	38.6	1187.1	CS
All TST	45.6	34.3	D	125.8	27.9	45.6	45.6	D	CS
BA IGRA&TST	39.9	32.4	D	97.5	25.1	39.9	39.9	1533.4	CS
BA MI IGRA	32.4	27	D	76.3	20.6	32.4	32.4	931	CS
BA IGRA&CXR	35.2	30.9	269.8	89.5	21.9	31.5	37.6	939.7	CS
BA MI TST&CXR	42.7	37.6	257.6	117.7	26.1	36	47.3	1320.1	CS
BA TST&CXR&IS	49.8	44.4	189	140.3	30.2	40.9	56.1	1327.2	CS
BA MI IGRA&TST	43.9	35.9	D	106.4	27.7	43.9	43.9	1539.2	CS
BA IGRA&CXR&IS	45.8	40.8	184.8	119.4	28.3	39.6	49.9	1061.7	CS
BA MI IGRA&CXR	41.3	36.1	330.4	104.8	25.7	37	44	1082.1	CS
BA MI TST&CXR&IS	61.7	55.6	187.1	174.1	37.5	50.3	70	1517.3	0.1
All IGRA	62.2	51.8	D	146.5	39.5	62.2	62.2	1750.6	CS
NICE 2016	62.5	52.1	D	147.3	39.7	62.5	62.5	1758.4	CS
All CXR	123.7	123.7	123.7	387.5	73.6	88.4	156.7	2470.5	25.6
BA MI IGRA&CXR&IS	54.3	48.4	225	141.4	33.6	47.1	59.1	1235.6	CS
All TST&CXR	85.5	73.6	9759.	251	51.5	71	95.8	3796.6	1.6
All IGRA&TST	88.1	69.8	D	223.4	54.9	88.1	88.1	5613.3	CS
All IGRA&CXR	83.3	73.6	438.1	214.3	51.7	73.3	89.7	2045.9	1.2
All IGRA&TST&CXR	100.1	85.2	D	271.1	61.4	88.3	107.7	3662.8	3.4
All TST&CXR&IS	122.8	108.9	558.5	365.3	73.8	98.6	141	3768.4	14.4
All IGRA&CXR&IS	110.5	99.4	351.4	292.4	68.1	93.9	121.9	2345.4	9.7
All IGRA&TST&CXR&IS	124.4	108.3	1395.	343.9	75.9	105.9	137	3677.7	11.2
All IGRA&TST&CXR & IS&PCR	149.2	130	1673. 7	412.6	91.1	127.1	164.3	3987.8	18.5

ART - antiretroviral therapy, BHIVA - British HIV Association, CD4 - blood CD4 cell count in cells/μL, CS - Cost saving, CXR - chest X ray, D - dominated, IGRA - Interferon-gamma release assay, LI - low [TB] incidence countries, MI - middle [TB] incidence countries, NICE - National Institute of Health and Care Excellence, PLHIV - People living with HIV, QALY - Quality adjusted life year, TB - tuberculosis, TST - tuberculin skin test.

BHIVA 2011: IGRA only in subSaharan Africa with any CD4 on ART < 2 years, MI with CD4 <500 on ART < 2 years, LI with CD4 <350 on ART < 6 months.
NICE 2011: IGRA + TST if blood CD4 <200 and IGRA alone if blood CD4 <500.
NICE 2016: IGRA + TST if blood CD4 <200 and IGRA alone in all others.

5.4 Discussion

5.4.1 Summary

In this cost-effectiveness analysis of real-world TB testing in a contemporary HIV clinic in a low HIV and TB incidence region, only three of thirty strategies had cost-effective point estimates. Compared with no testing, testing black Africans with a TST or IGRA was cost effective at under £30,000/QALY, as was testing both black Africans and people from middle TB incidence countries (approximating to all those from outside Western Europe or North America) with a TST. Using IGRA in these groups would be just above this threshold. When subjected to probabilistic sensitivity analysis, 'No testing' was most likely cost-effective up to £30,000/QALY.

Despite the low up-front costs, the efficiency of strategies involving TST was substantially reduced due to the number of people who did not return to have their TST interpreted. Routine sputum induction for mycobacterial culture also added significant cost for very little yield. Given the low TB bacillary burden in the patients with subclinical TB, routine sputum TB PCR testing also provided no further information. No strategies that used both a TST and IGRA, or CXR or sputum induction were cost-effective. This included all current national and international guidelines reviewed. [43,44,75,134,241]

5.4.2 Sensitivity analyses

If the cost of an IGRA fell, or its predictive value increased, the strategies were much better value. Testing also became better value if uptake of LTBI testing

and treatment increased, although even if both of these were 100%, testing all attendees was not cost-effective.

5.4.3 Implementation

Whilst this model suggested that no testing is most cost effective using UK NICE criteria, other countries with low TB incidence may use different cost/QALY threshold criteria. [180] Similarly, our study models from an NHS perspective and, given the WHO aim of eliminating tuberculosis by 2050 to under one in a million cases per year, public health bodies may be willing to pay more in order to prevent disease in those at the highest risk of TB reactivation. [141,244,245]

The selection of either TST or an IGRA as a preferred test may also depend on factors such as the availability of Purified Protein Derivative (PPD) for TST, or the advantage of not needing to recall for reading results in those having a blood IGRA. [246] Testing using an IGRA alone may be operationally more locally appropriate.

5.4.5 Variables and need for more data

5.4.5.1 Uncertainty ranges

There were large uncertainty ranges around the final point estimates from the probabilistic analysis. This was in part due to a lack of contemporary data for HIV/TB treatment. The lower sample numbers led to large standard deviations and hence wide variables used in the probabilistic sensitivity analysis. There were also a large number of parameters that were varied, further increasing the ranges.

5.4.5.2 Predictive value of TST and IGRA

There are very few studies on the predictive value of a positive TST or IGRA in a contemporary HIV population using ART and calculating this more accurately would take prolonged follow-up over years. We therefore had to estimate this from the few studies available in order to determine the number of cases of active TB that would be likely to occur, with or without LTBI treatment (also see Section 1.6.7). [173,175]

Early reports indicated that active TB could occur in people with negative skin tests (possibly due to new TB exposure). [78,247] This was therefore included the model, though this may underestimate the effectiveness of testing, as more contemporary studies find zero or a very low risk of active TB in those with negative IGRA results or those with LTBI who take preventive therapy. [77,173,175]

5.4.5.3 Quality of life change and costs

In the study, the sample numbers with subclinical TB and LTBI, and those taking preventive treatment were too small to make a precise estimate of quality of life change. However, the adverse events associated with preventive treatment were greater than would have been expected from estimates used in other cost-effectiveness models. In most previous cost-effectiveness models, LTBI treatment has not been associated with any loss in quality of life (except relating to hepatotoxicity). [192,193] Where is accounted for, the only data are from Guo et al. where the QALY loss is estimated at 0.003, or from the study by Kruijshaar et al. in the UK, which NICE also use in their analysis, estimating this at 0.007. [43,190,248-250] These quality of life studies were also from the general

population, rather that people with HIV co-infection, where there may be more morbidity associated with preventive treatment. If so, this would make LTBI testing less cost-effective.

Some TB quality of life studies have quoted a large drop in quality of life due to bronchiectasis or loss in lung function due to active TB disease. [195] We found respiratory symptoms were very common in the whole study cohort, but there were few sequelae of previous pulmonary TB. Again, the estimates used in the cost-effectiveness model were from NICE data for adults in the general population with active TB. [43]

Along with a much larger study on quality of life data in people being treated for TB/HIV coinfection or LTBI, a more contemporary estimate of the cost of LTBI and active TB treatment would be would be useful in providing variables for cost-effectiveness in this modelling.

5.4.6 Other Limitations

Since ART use is now so widespread in higher resource countries, and is likely to increase with international guidelines (such as recommendations to treat soon after HIV diagnosis irrespective of blood CD4 count), there may be a further decline in the risk of TB disease due to reactivation – reducing the cost-effectiveness of TB testing even more. [49,251] This is consistent with the retrospective analysis in Chapter 3, where cost-effectiveness reduced as ART uptake increased.

The study and model is appropriate for testing entire clinics of HIV infected individuals – both those with new HIV diagnoses and in established care. There were low numbers of individuals newly diagnosed with HIV in the study and

hence it is difficult to extrapolate to estimate the cost-effectiveness of testing just this group. Similarly, there were low numbers of injecting drug users and none in this study with subclinical TB or LTBI and so their risk could not be extrapolated, but the incidence of active TB disease is higher than the general population and it could be that they should be tested as much as individuals from high TB incidence countries. [252]

The benefits of reducing TB transmission were also not included in this model – although, even if one case of active TB resulted in a single further case of active disease, testing all HIV clinic attendees was calculated to not be cost-effective.

5.5 Conclusion

Even the most targeted testing for TB in a contemporary HIV clinic is only marginally cost effective at a £30,000/QALY threshold. Using more than one test was even more expensive. Pragmatically, either not testing routinely, or testing only those at the highest risk of reactivation of TB with a TST or IGRA alone may be the most cost-effective and convenient strategy. This is at odds with the majority of contemporary national guidelines.

CHAPTER 6: RESPIRATORY SYMPTOMS AND AIRWAYS DISEASE

6.1 Introduction

6.1.1 History of lung disease in HIV

A series of patients with Pneumocystis pneumonia (PCP) led to the initial description of AIDS. [3] HIV infection is also a risk factor for Pneumococcal pneumonia [253,254] Since then, opportunistic lung infections have been recognised as a cause of morbidity and mortality in people with HIV.

As antiretroviral treatment has become more effective, respiratory infections have become less prevalent, but there is still an increased burden of chronic lung disease compared to the general population. These include chronic obstructive pulmonary disease (COPD) and bronchiectasis. [255,256] One pre-ART study showed HIV infection was associated with a low carbon monoxide transfer factor, but fairly well-preserved spirometry. [257] Another, using high-resolution computerised tomography (HRCT) scans of the lungs, found 37% of HIV-infected smokers had emphysema on CT. Previous pneumonia, PCP, injecting drug use and low blood CD4 count were implicated as risk factors for lung disease. [258] In these studies, as in many since, the prevalence of smoking was higher (63%) than the general population, and there was a history of previous respiratory infection in those with emphysema. [259]

Since 1996, when ART became much more widespread, epidemiological data have shown a higher prevalence of COPD in HIV-infected versus non-infected

US veterans, although the association with lower CD4 and higher HIV viral load has become less consistent. [254,256,260,261] Three prospective studies have shown a prevalence of obstructive lung disease of 3.4-21% with a high frequency of respiratory symptoms. [258,262] In one study, ART was found to be a risk factor for airway obstruction (despite adjustment for age and smoking history). These were all from large US cross-sectional or cohort studies, however, where HIV demographics differ from the UK. Contrastingly, in the pulmonary substudy of START (a large, randomised control trial in 20 countries of early versus deferred treatment of HIV) there were similar rates of obstructive lung disease in both early and deferred ART groups. The follow-up time may have been too short to show a significant difference. [263]

6.1.2 Cause of chronic lung disease in HIV

These findings have led to a hypothesis that the aetiology of chronic lung disease in HIV may be due to a vicious circle of smoking and substance abuse damage (with malnutrition in some), defective immune responses and an increase in microbial colonisation with inflammatory cytokine and protease release. [11] The overwhelming epidemiological confounder, however, seems to be tobacco smoking. Smoking prevalence is higher in people living with HIV (up to three times that in the general population), although even when adjusting for this, the burden of lung disease remains high. [264,265] A Danish cohort study found that the number of years of premature death due to smoking was greater than that from HIV alone, provided patients were adherent with ART. [265]

6.1.3 Diagnosis and aetiology of COPD

A diagnosis of COPD is made using obstructive spirometry in people with a risk factor (the greatest being smoking), but COPD only affects a fifth of smokers. It may be that individuals that develop COPD have a modified response to smoker or noxious particles that causes more lung inflammation parenchymal tissue disruption and have abnormal repair or defence mechanisms. [266] COPD tends to have an indolent onset, although symptoms such as exertional breathlessness, chronic cough, sputum production, winter bronchitis and wheeze are often present and may precede changes in lung function. More noticeable breathlessness and disability may only occur after substantial irreversible damage has occurred. [209]

6.1.4 Respiratory symptoms

Compared to non-smokers, smokers with normal spirometry seem to have more respiratory symptoms, and it is speculated that these symptomatic patients may have a form of smoking related lung disease, an early predictor of COPD before measurable airways obstruction occurs. Alternatively the symptoms could be a marker of co-existent asthma. [267] These individuals also seem to have exacerbations, a feature of COPD. Smoking cessation and timely treatment of exacerbations could be useful interventions at this point.

6.1.5 Testing for COPD in primary care

There has been interest in testing smokers in order to detect COPD and intervene before more noticeable disability occurs. Given the large populations and

resource associated with spirometry as a diagnostic test, pre-screening to find those at higher risk using questionnaires has been trialed. In a study in primary care in Leicester: age, breathlessness on exertion and wheeze identified COPD patients with a sensitivity of 77.4%-87.1%. [268] The COPD Diagnostic Questionnaire, another example, records smoking history, sputum production outside of viral infections, morning cough productive of sputum, and wheeze. [269,270] Screening for COPD in asymptomatic individuals, however, has not been shown to improve health outcomes and has been discouraged by the US Preventive Services Task Force. [271]

6.1.6 Sputum Microbiology

Despite smoking as a confounder, the presence of pathogenic bacteria, such as *Haemophilus influenza*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* have been associated with exacerbations of COPD, and their presence correlates with markers of neutrophilic inflammation. [272] There are data to suggest that the bacterial load increases at exacerbation and the presence of these bacteria are associated with lung function decline in patients with COPD and bronchiectasis, and perhaps in exacerbating smokers with normal lung function. [273,274] The risk of pneumococcal pneumonia is also increased in both people with COPD or HIV infection. Pulmonary macrophages are central to airway innate immunity and it there is evidence that in both conditions, dysfunctional apoptosis by macrophages could be the cause of impaired immunity, leading to colonisation. [274-276].

Quantitative polymerase chain reaction (qPCR) is more sensitive than culture at detecting airway bacteria [273], and *H. influenzae* can exist intracellularly,

resulting in negative standard bacterial culture. QPCR can also be analysed in a batch on frozen samples.

6.1.7 Aims and objectives

Given the increased prevalence of COPD in HIV-infected individuals in epidemiological studies, we sought to determine the frequency of respiratory symptoms and airways disease using spirometry in an HIV-infected cohort in London with very high ART use, and identity their risk factors.

6.2 Methods

6.2.1 Setting and recruitment

A sample of subjects already undergoing care at the Ian Charleson Centre for HIV care at the Royal Free Hospital, plus all those with a new diagnosis of HIV were invited to take part in a TB-testing study. Selection method and criteria have been outlined in previous chapters (Chapter 2).

6.2.2 Study questions

In the study questionnaire (see Appendix 1.5, participants were asked about a history of asthma, bronchiectasis, inhaler use, smoking (tobacco and cannabis), injecting drug use, previous infection with Pneumocystis pneumonia (PCP), bacterial pneumonia and active tuberculosis disease.

We enquired about:

- recent and winter cough
- sputum production

- history of wheeze
- tight chest
- breathlessness

A quality of life EQ5D score was included. Subjects were asked to self-report their height when filling in the questionnaire.

6.2.3 Pathology and radiology data

Blood tests including:

- renal function
- recent and nadir blood CD4 cell count
- recent HIV viral load
- hepatitis B and C serology

were taken from the hospital pathology database, and a frontal chest radiograph (CXR) performed. Any previous chest radiology reports were reviewed from the radiology database.

6.2.4 Spirometry and sputum induction

Spirometry and sputum induction methods are described in the methods chapter (2.3.4.5 and 2.3.4.6). Spirometry was performed before sputum induction then repeated 5 minutes after inhaling 3.5% saline. Where enough sputum was obtained at induction, samples were saved for research purposes. These samples were later thawed, the DNA extracted and tested using multiplex qPCR used for evidence of airway bacteria including *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Legionella pneumophila, Chlamydia pneumoniae, Mycoplasma pneumoniae.* This work was performed by Dr Camus Nimmo and

Sarah Thurston from the Department for Microbiology, University College London, Royal Free Campus.

6.2.5 Statistical methods

Data were analysed using SPSS version 20 (IBM SPSS Statistics, USA) for Mac, Excel 10 for Windows and Excel 2011 for Mac (Microsoft, Seattle, USA). This is further detailed in the methods chapter (2.5).

Significance was calculated using the Mann Whitney U test for independent samples with a significance level at 0.05 for non parametric distributions, or the Pearson Chi-square test. Odds ratios were calculated using univariate analysis for variables relating to respiratory symptoms and smoking status and confidence intervals calculated using the Pearson Chi-square test (or Fisher's exact test if n<5).

Forced expiratory volume in one second (FEV_1) percent predicted, forced vital capacity (FVC) percent predicted and were calculated for each participant where a height had been recorded. European Respiratory Society equation and tables were used to calculated predicted FEV_1 and FVC for an individual's age and height. [277] The FEV_1/FVC ratio was calculated for all the participants that performed spirometry.

6.3 Results

6.3.1 Demographics

The study was performed between 10th June 2013 and 6th September 2014 at the Ian Charleson Centre. Of the 1205 outpatients that were eligible, 219 participated.

Demographics are described in Chapter 4 (Figure 4.3.2).

Table 6.3.3: Demographics and differences between groups by smoking status

	Total (n=204)	Current/ex-Smokers (n=111)	Never smokers (n=93)	p
Female (%)	51 (25%)	12 (10.8%)	39 (41.9%)	<0.005
Age - years (IQR)	46 (41-53)	47 (12)	46 (13)	0.999 (MWU)
Median CD4 (IQR)	612 (457-789.5)	597 (336)	625 (277)	0.533 (MWU)
Number with VL <40	173 (83%)	88 (79.3%)	85 (91.4%)	0.016
On ART	201 (99%)	108 (98.2%)	93 (100%)	0.501
Indoor fire exposure	47 (23%)	27 (24.3%)	20 (21.5%)	0.688
Still smoking	47/111	47 (42.3%)	0	
Hx cannabis smoking	83 (40.7%)	70 (63.1%)	13 (14%)	<0.005
History IDU	21 (10.3%)	16 (14.4%)	5 (5.4%)	0.106
HIV Risk Factor				<0.005
Heterosexual	79 (38.7%)	29 (26.1%)	50 (53.8%)	
IDU	4 (2%)	4 (3.6%)	0	
MSM	116 (56.9%)	78 (70.3%)	38 (40.9%)	
Vertical	2 (1%)	0	2 (2.2%)	
Other	2 (1%)	0	2 (2.2%)	
Place of birth/ethnicity				<0.005
BA	54 (26.5%)	13 (11.7%)	41 (44.1%)	
Middle TB incidence	29 (14.2%)	20 (18%)	9 (9.7%)	
Low TB incidence	121 (59.3%)	78 (70.3%)	43 (46.2%)	

Table 6.3.3: Demographics and differences between groups by smoking status (continued)

	Total (n=204)	Current/ex-Smokers (n=111)	Never smokers (n=93)	p
≥1 Respiratory symptom	121 (59.3%)	73 (65.8%)	48 (51.6%)	0.046
Winter cough	80 (39.2%)	45 (40.5%)	35 (37.6%)	0.373
Wheeze	53 (26%)	35 (31.5%)	18 (19.4%)	0.121
Tight chest	63 (30.9%)	38 (34.2%)	25 (26.9%)	0.348
Breathlessness	61 (29.9%)	38 (34.2%)	23 (24.7%)	0.077
Cough past 4 weeks	73 (35.8%)	44 (39.6%)	29 (31.2%)	0.209
Sputum past 4 weeks	65 (32.2%)	40 (36.7%)	25 (26.9%)	0.137
Abnormal CXR	37 (18.1%)	16 (14.4%)	21 (22.6%)	0.167
History of asthma	22/192 (11.5%)	12/103 (11.7%)	10/89 (11.2%)	0.928
History of bronchiectasis	6/188 (3.2%)	4/101 (4%)	2/87 (2.3%)	0.688
Obstructive spirometry	16 (7.8%)	13 (11.7%)	3 (3.2%)	0.025
Previous TB	15/202 (7.4%)	6/110 (5.5%)	9/92 (9.8%)	0.243
Previous PCP	24/189 (12.7%)	16/105 (15.2%)	8/84 (9.5%)	0.277
Previous bacterial pneumonia	34/188 (18.1%)	22/107 (20.6%)	12/81 (14.8%)	0.311
Hepatitis B coinfection	59/194 (30.4%)	30/105 (28.6%)	29/89 (32.6%)	0.545
Hepatitis C coinfection	21 (10.8%)	12/106 (11.3%)	9/89 (10.1%)	0.786

6.3.2 Uptake and symptoms

Both symptoms and spirometry were available for 204 subjects. Five (2.2%) participants did not fill in the questionnaire, and ten (4.5%) did not perform spirometry.

Of the 204, 135 (63%) had a height available in order to calculate the predicted FEV_1 %.

Of the questionnaire responses, 121 participants (59%) had at least one respiratory symptom, five (2.6%) had three and 20 (9.8%) had four symptoms. Eighty-three individuals (41%) denied having any symptoms at all.

6.3.3 Smoking status

Of 204 participants with questionnaire responses, 93 (46%) were never smokers and 47 (23%) current smokers and 64 (31%) ex-smokers.

Table 6.3.4a Respiratory symptoms

Symptom	Percentage	Number
Tight chest	31%	69/207
Wheeze	26%	60/209
Winter cough	39%	85/213
Breathlessness	30%	67/212
Tight chest and wheeze	20%	42/207
Wheeze and breathless	16%	34/207
Tight chest, wheeze and breathless	11%	23/207
Breathlessness alone	3%	6/212

Table 6.3.4b Odds Ratios for respiratory symptoms

	Respiratory symptoms (n=121)	No respiratory symptoms (n=83)	OR	95% CI	p
Age					
<40	26 (62%)	16 (38%)	1.20	0.55-2.61	0.90
40-50	53 (60%)	36 (40%)	1.09	0.58-2.04	
50+	42 (58%)	31 (42%)	1.00*		
Ever smoker	73 (65.8%)	38 (34.2%)	1.80	1.02-3.17	0.046
Current smoker	39/47 (83%)	8/47 (17%)	4.42	1.78-11.0	0.001
Cannabis ever smoker	56 (67.5%)	27 (32.5%)	1.94	1.10-3.48	0.026
Biofuel exposure	31 (66%)	16 (34%)	1.51	0.76-2.99	0.235
Female	28 (54.9%)	23 (45.1%)	0.79	0.41-1.49	0.459
History of asthma	18 (81%)	4 (18.2%)	3.55	1.15-10.94	0.02
History of bronchiectasis	5 (83.3%)	1 (16.7%)	3.59	0.41-31.30	0.219
On ART	120 (59.7%)	81 (40.3%)	0.68	0.04-10.95	0.781
Undetectable VL	100 (57.8%)	73 (42.2%)	0.65	0.29-1.47	0.300
From low TB incidence country	76 (62.8%)	45 (37.2%)	1.16	0.60-2.24	0.209
Medium TB incidence country	13 (44.8%)	16 (55.2%)	0.56	0.23-1.39	
High TB incidence country	32 (59.3%)	22 (40.7%)	1.00*		
History IDU	15 (71.4%)	6 (28.6%)	1.85	0.69-4.99	0.218
Previous TB	9 (60%)	6 (40%)	1.02	0.35-3.00	0.961
Previous PCP	14 (58.3%)	10 (41.7%)	0.93	0.39-2.23	0.876
Previous bacterial pneumonia	24 (70.6%)	10 (29.4%)	1.75	0.78-3.92	0.168
Abnormal CXR	24 (64.9%)	13 (35.1%)	1.35	0.64-2.83	0.431

* - reference value. Confidence intervals and p values are calculated using the likelihood ratio Chi square test or Fishers exact test if n <5.

Smokers were more likely to be male (p<0.005) and to have a detectable plasma HIV viral load (>40 copies/ml) (p=0.016). Seventy-four percent of men who have sex with men (MSM) were smokers or ex-smokers, whereas only 24% of black Africans had ever smoked. Smokers were more likely to have more than one respiratory symptom (p=0.046) and have obstructive spirometry (p=0.025), but apart from these factors, the smokers and non-smokers had similar frequencies of symptoms, history of asthma, TB, PCP, pneumonia or bronchiectasis, and also to have an abnormal CXR.

6.3.4 Respiratory symptoms

The frequency of respiratory symptoms was 59% (121/204) in all, 66% in smokers and 52% in non-smokers.

The frequency of symptoms are listed below.

The most common symptom was winter cough (39%), although 11% had three symptoms and 3% complained of breathlessness alone.

Of those with self-reported tight chest and breathlessness, only three had obstructive spirometry.

Respiratory symptoms were more frequent in current rather than ex-smokers (OR 4.3, CI 1.74-10.6, p=0.002), but ex-smokers were no more likely to have symptoms than never smokers (OR 1.06, CI 0.56-2.0, p=0.82).

6.3.5 History of asthma

Twenty-three participants (11%) had a self-reported history of asthma. Fourteen (61%) had been diagnosed before the age of 30 years and 15 (79% of those

that answered) had inhalers. Three participants used inhaled corticosteroids and long acting beta agonist combined, one salbutamol alone, eleven did not specifically identify their inhaler.

Nineteen of the self-reported asthmatics (83%) reported airways disease symptoms. Six (26%) were current smokers and seven (30%) were ex-smokers. Seven of 13 (54%) had a greater than 20 pack year smoking history. Three subjects had injected drugs.

Four of 23 (17%) participants with a self-reported asthma diagnosis also had

Table 6.3.6.2: Table of odds ratios for those with and without obstructive spirometry

	Obstructive spirometry (n=16)	Not obstructive spirometry (n=188)	OR	95% CI	p
Age					
<40	2 (5%)	40 (95%)	1.00*	-	0.02
40-50	6 (7%)	83 (93%)	1.45	0.28-7.48	
50+	8 (11%)	65 (89%)	2.46	0.50- 12.18	
Ever smoker	13 (12%)	98 (88%)	3.98	1.10-14.42	0.03
Current smoker	5 (11%)	42 (89%)	0.79	0.24-2.59	0.70
Cannabis ever smoker	11 (13%)	72 (87%)	3.39	1.13-10.17	0.02
Biofuel exposure	6 (13%)	41 (87%)	2.65	0.87-8.08	0.10
Female	3 (6%)	48 (94%)	0.67	0.18-2.46	0.55
History of asthma	4 (18%)	18 (82%)	2.93	0.85-10.03	0.09
History of bronchiectasis	3 (50%)	3 (50%)	13.0	2.38-70.93	0.009

Table 6.3.6.2: Table of odds ratios for those with and without obstructive spirometry (continued)

	Obstructive spirometry (n=16)	Not obstructive spirometry (n=188)	OR	95% CI	p
Not on ART	1 (50%)	1 (50%)	12.4	0.74-208.3	0.15
Undetectable VL	11 (6%)	162 (94%)	0.35	0.11-1.10	0.07
From low TB incidence country	10 (8%)	111 (92%)	1.00*	-	0.96
Medium TB incidence country	2 (7%)	27 (93%)	0.82	0.17-3.97	
High TB incidence country	4 (7%)	50 (93%)	0.89	0.27-2.97	
History IDU	2 (10%)	19 (90%)	1.26	0.27-5.95	0.68
Previous TB	3 (20%)	12 (80%)	3.35	0.84-13.37	0.10
Previous PCP	2 (8%)	22 (92%)	1.16	0.24-5.53	0.69
Previous bacterial pneumonia	5 (15%)	29 (85%)	2.48	0.79-7.8	0.15
Abnormal CXR	5 (13%)	32 (86%)	2.20	0.72-6.77	0.18
≥1 respiratory symptom	14 (12%)	107 (88%)	5.30	1.17-23.97	0.02
Cough in past 4 weeks	10 (14%)	63 (86%)	3.31	1.15-9.51	0.02
Sputum in past 4 weeks	8 (12%)	57 (88%)	2.26	0.81-6.33	0.11
Tight chest	10 (16%)	53 (84%)	4.25	1.47-12.26	0.01
Wheeze	7 (13%)	46 (87%)	2.35	0.83-6.67	0.14
Breathlessness	6 (10%)	55 (90%)	1.59	0.54-4.68	0.39
Cough in the winter	5 (6%)	75 (94%)	0.67	0.23-2.02	0.48

* - reference value. Confidence intervals and p values are calculated using the likelihood ratio Chi square test or Fishers exact test if n <5.

obstructive lung function.

Of the other respondents in the study, 181 did not report a previous diagnosis of asthma, but despite this, 62 (53%) had symptoms of airways disease, of whom 10 (8.5%) also had obstructive spirometry.

6.3.6 Spirometry

Sixty five percent (142/219) of participants performed spirometry and had also recorded their height (to calculate FEV_1 % predicted). Sixty-four (29%) had spirometric values but no height, and 13 (6%) did not attend for sputum induction nor performed spirometry.

Thirteen of 206 (6%) had obstructive spirometry initially and one (0.5%) developed obstructive spirometry after five minutes inhaling nebulised 3.5% hypertonic saline.

6.3.6.2 Risk factors for obstructive lung disease

Ex-smokers were more likely to have obstructive lung function than never smokers (OR 4.3, CI 1.1-16.8, p=0.04), but current smokers no more likely than ex-smokers (OR 1.2, CI 0.37-3.93, p=0.76). Ever use of cannabis had an OR of 3.4 (p=0.022). Self reported asthmatics, those with a tight chest and those with a cough over the past four weeks were also more likely to have obstructive lung function. Those with a self-reported history of bronchiectasis had an even higher risk (OR=13.0, p=0.009).

The sensitivity of one respiratory symptom for obstructive spirometry was 87.5%, specificity was 46%, positive predictive value was 11.6% and negative predictive value was 46%.

Table 6.3.6.3 Characteristics of non-self-reporting asthmatics with obstructive lung function

StudyNo	Age	Sex	Place of birth	Smoking status	Pack years	Cannabis history	Indoor stove	Prev PCP/ pneumonia/ TB	Chest X ray	On ART	Recent CD4	Nadir CD4	Symptoms	FEV_1 (L)	FEV_1 % pred	FEV_1/ FVC ratio	FEV_1 fall >100ml
137	52	M	England	Ex	18	Heavy (8 yrs)	Yes	Nil	N	Yes	423	368	All	1.75	51%	0.39	No
36	54	M	UK	Curr	34	10 yrs	No	Nil	N	Yes	881	302	Wheeze	2.25	63%	0.47	23%, 510ml
99	43	M	England	Curr	15	Rare	Missing	Nil	Pericardial cyst	Yes	283	200	All	2.26	64%	0.68	No
138	52	M	England	Ex	70	Little	Yes	PCP	N	Yes	464	36	Tight, breathless, winter cough	2.54	73%	0.68	No
161	63	M	England	Ex	40	Heavy (16 yrs)	No	Pneumonia	N	Yes	361	NA	None	2.35	81%	0.61	No
56	49	M	UK	Ex	20	Heavy (20 yrs)	No	Nil	Hyperinflated	Yes	379	110	Breathless, winter cough	3.12	81%	0.69	No
6	26	F	Uganda	Curr	0.8	Never	No	Pneumonia	N	No	749	749	Tight chest	2.52	85%	0.47	No
103	47	M	Zambia	Ex	30	Heavy (2 yrs)	No	TB and pneumonia	N	Yes	523	3	Breathless	3.19	87%	0.52	5.6%, 190ml
93	43	F	Nigeria	Never	0	0	Yes	Nil	N	Yes	728	NA	Breathless only	2	NA	0.68	No
218	48	M	Ivory Coast	Never	0	0	No	TB	Fibrosis LUL	Yes	29	NA	Tight chest	2.15	NA	0.64	7%, 150ml

6.3.6.3 Characteristics of participants with obstructive lung function

After excluding those with a history of asthma or bronchiectasis, 102/181 (56%) subjects had at least one symptom, and 10 (5.5%, CIs 2.2-8.9%) had obstructive spirometry. Of these, 10 (see Table 6.3.6.3), eight had documented heights available of which four had an FEV_1 <80% predicted and four had an FEV_1 of 50-80% predicted. All but one subject had at least one respiratory symptom, wheeze was reported in three, and winter cough in four. None had a history of injecting drug use, but 80% had smoked at some point.

Four subjects had a history of smoking, wheeze and an FEV_1 of 50-80% predicted. One had a 510ml drop in FEV_1 after 3.5% saline. There were two African participants with obstructive lung function, both of whom were non-smokers (although one with biomass exposure, the other with previous TB) but they had not supplied their heights and so FEV_1 predicted could not be calculated.

The remaining four subjects had mild obstruction (FEV_1 80-100% predicted), of which one was African with a very short smoking history, another an African with a heavy smoking history. Two were British with substantial smoking histories.

6.3.7 Chest radiographs

Chest radiographs were available on 214 (98%). Five participants did not return for CXR. Normal and abnormal radiographs are discussed further in the Chapter on the prospective study results (Chapter 4, section 4.3.10).

Six participants had radiographic features of airways disease. One had left lower lobe bronchiectasis, two had possible bronchial wall thickening (207,174), three had hyperinflated lungs.

The subject with bronchiectasis had cough, but no obstructive lung function.

A subject whose radiograph was reported as having bronchial wall thickening had a self-reported history of asthma using inhalers, was an ex-smoker and had normal spirometry. He reported no respiratory symptoms. The second had radiological signs of previous TB infection (described further in Results Chapter 4), but no airway symptoms and normal spirometry.

Of the three participants with hyperinflated lungs: one subject had obstructive spirometry; another had never smoked, had no respiratory symptoms, no history of asthma and had an FEV_1 of 115% predicted; a third had never smoked, reported no airways symptoms but had noted a recent cough. He had an FEV_1 of 95% predicted.

Of those participants with obstructive spirometry, one subject had left apical scarring and volume loss, another had left upper lobe fibrosis consistent with old TB and a third had hyperinflated lung fields.

Ever-smokers were no more likely to have an abnormal chest radiograph than never-smokers (OR 1.8, CI 0.86-3.6, p=0.13), and ex-smokers as likely as current smokers (OR 1.43, CI 0.5-4.2), p=0.50).

6.3.8 Old TB or PCP

Of the 15 participants with self-reported previous active TB disease, two had a self-reported history of asthma, five had abnormal CXR (one with bronchiectasis), three had obstructive spirometry. Nine (60%) had one or more respiratory symptoms.

Twenty-four patients reported previous PCP, of which four (17%) had asthma (three of whom diagnosed in childhood), 14 (58%) had respiratory symptoms

and two (8%) had obstructive spirometry.

6.3.9 Quality of life

Those patients with at least one airway symptom had a median quality of life score of 71/100, (IQR 60-80) and those without of 88/100 (IQR 75-95, p=0.00).

Those with obstructive spirometry had a median quality of life of score 80 (IQR 66.5-90) and those without 80 also (IQR 60-90, p=0.943).

6.3.10 Sputum culture and qPCR

Fifty-three patients also provided sputum for research purposes. This group was demographically similar to the entire cohort (see Table 6.3.10). Median CD4 cell count was 643 cells/μL and 84% had an undetectable blood HIV viral load. They were more likely to have reported a history of winter cough (p=0.01) or a cough in the previous week (p=0.04).

The sputum had DNA extracted and multiplex quantitative PCR performed for airway bacteria. Airway bacteria were present in 23/52 (44%) of samples.

Table 6.3.10a Demographics of those with or without sputum samples

	Sputum samples (n=52)	No sputum samples	p
Female	11 (21%)	46 (27%)	0.14
Age years (median, IQR)	47 (40-52)	46 (41-53)	0.50
UK born	21 (40%)	69 (41%)	0.86

	Sputum samples (n=52)	No sputum samples	p
Black African	14 (27%)	47 (28%)	0.95
White British	31 (59%)	95 (57%)	
Ever smoker	24 (46%)	89 (54%)	0.29
Current smoker	14/24 (58%)	34/89 (38%)	0.12
Smoking pack years (median, IQR)	15 (5-30)	10 (5-25)	0.62
Injecting drug use ever	3 (6%)	18 (11%)	0.45
Smoked cannabis ever	21 (40%)	64 (39%)	0.82
Any respiratory symptom	40 (77%)	92 (56%)	0.007
Recent cough	27 (52%)	51 (31%)	0.007
Recent sputum	24 (46%)	46 (29%)	0.02
Wheeze	21 (40%)	39 (24%)	0.03
Tight chest	23 (44%)	46 (29%)	0.10
Breathless	17 (33%)	50 (31%)	0.83
Winter cough	32 (62%)	53 (33%)	0.00
Asthma	7 (14%)	18 (12%)	0.71
Bronchiectasis	2 (3.8%)	4 (2.7%)	0.68
Obstructive lung function	6 (11.5%)	10 (6.6%)	0.25
FEV1 % predicted (median, IQR)	90%	98%	0.12
Previous TB	5 (9.6%)	12 (7.2%)	0.61
Prev PCP	8 (15%)	19 (13%)	0.90
Previous bacterial pneumonia	8 (15%)	26 (17%)	0.87
On ART	52 (100%)	161 (97%)	0.26
Recent CD4 (median, IQR)	709 (436-806)	606 (461-778)	0.777
On Septrin	1 (2%)	7 (4.3%)	0.32

Table 6.3.10b Demographics of those with or without sputum bacteria

	No bacteria	Bacteria	p
n	29	23	
Female	7 (24%)	4 (17%)	0.46
Age (median, IQR)	45 (39-50)	47 (43-53)	0.84
UK born	12 (41%)	9 (39%)	0.87
Black African	9 (31%)	5 (22%)	0.73
White British	16 (55%)	15 (65%)	
Ever smoker	9 (31%)	15 (63%)	0.01
Current smoker	3 (33%)	11 (79%)	0.07
Smoking pack years (median, IQR)	5 (5-30)	15 (6-30)	0.85
Injecting drug use ever	0 (0%)	3 (14%)	0.04
Smoked cannabis ever	10 (36%)	11 (48%)	0.38
Any respiratory symptom	20 (69%)	20 (87%)	0.13
Recent cough	16 (55%)	11 (48%)	0.60
Recent sputum	11 (38%)	13 (57%)	0.18
Wheeze	10 (35%)	11 (48%)	0.33
Tight chest	11 (38%)	12 (52%)	0.30
Breathless	8 (28%)	9 (39%)	0.38
Winter cough	17 (59%)	15 (65%)	0.63
Asthma	5 (18%)	2 (9%)	0.34
Bronchiectasis	1 (3%)	1 (4%)	0.87
Obstructive lung function	3 (10%)	3 (13%)	0.76
FEV1 % predicted (median, IQR)	95 (81-104)	88 (82-104)	0.70
Previous TB	3 (10%)	2 (8.7%)	0.84
Previous PCP	2 (7%)	4 (17%)	0.28
Previous bacterial pneumonia	5 (19%)	3 (13%)	0.56
On ART	29 (100%)	23 (100%)	NA
Recent CD4 (median, IQR)	712 (451-805)	707 (433-801)	0.92
On Septrin	1 (3%)	0 (0%)	0.37

In 16/52 (31%) *Streptococcus pneumoniae* was isolated, *Haemophilus influenza* in 10/53 (19%) and *Moraxella catarrhalis* in 1/53 (1.9%).

The participants with bacteria detectable in their sputum were more likely to be smokers, or to have injected drugs (Table 6.3.10b). Those with a winter cough were more likely to have a higher total bacterial load (p=0.04). In those with *S. pneumoniae* detected, those who were breathless had a higher *S. pneumoniae* load (p=0.01)

6.4 Discussion

The absence of respiratory symptoms was moderately useful in ruling out obstructive spirometry in this group.

6.4.1 Summary of findings

There was a high prevalence of respiratory symptoms in this group (59.3% complained of one or more symptom), and this was even more frequent in smokers (65.8%). George et al. described symptoms in 31.5% of an HIV infected cohort in Southern California, whilst Diaz et al. found each symptom was present in around 40% HIV infected participants compared to 7-20% HIV negative controls. [258,259] Our figure is similar to that seen in HIV-negative individuals with COPD, where macrophage dysfunction is thought to play a role in lower airway bacterial colonisation and lead to lung damage. [266,273]

Despite the high prevalence of symptoms, there was relatively little obstructive lung disease (7.8%), although significantly more in smokers (11.7%) than in non-smokers (3.2%), especially when participants with asthma were excluded.

There are few published studies of respiratory symptom prevalence and airways diseases in cohorts of European HIV patients. Our cohort had a median age of 46 years, 24% were current smokers (similar to the prevalence in the general UK population) and 31% were ex-smokers. [278]

6.4.2 Obstructive lung function

Ten participants had obstructive lung function (from those without a self-reported history of asthma or bronchiectasis). Three of these were African and also never smokers/very light smokers. Participants with more than one respiratory symptom were more likely to have obstructive lung disease (OR 5.3), especially those who reported tight-chestedness. One participant had changes consistent with previous TB on chest radiograph and this may be consistent with residual bronchiectasis or small airways disease. Of the others, one subject had a significant drop in FEV_1 after five minutes nebulised 3.5% saline which could be a feature of previously undiagnosed asthma.

Twenty-seven percent of subjects in one published United States cohort had obstructive spirometry, although their median age was 50 years, 68% were current smokers, and 44% had a history of injecting drug use. [256] A number needed to test was 5 in this study to detect abnormal spirometry irrespective of respiratory symptoms. In our cohort, this would be 18.

6.4.3 Chest radiographs

There were few subjects with abnormalities on chest radiograph in this cohort, and smokers, nor those with respiratory symptoms were no more likely to abnormal CXRs.

6.4.4 Sputum bacteria

Despite seemingly good immune function in this cohort, respiratory symptoms are common and bacteria frequently detected in the samples. Nearly half had qPCR evidence of chronic bacterial colonisation (predominantly in smokers), a similar frequency to that seen in stable state COPD – although with lower bacterial loads than seen in the COPD cohort. [273] This HIV cohort also had high rates of *Streptococcus pneumoniae* (in contrast to patients with COPD who are more likely to have *Haemophilus influenzae*), but *H. influenzae* and *M. catarrhalis* were also found. [279]

It is difficult to ascertain if the increased frequency of bacterial isolation is a cause or consequence of symptoms, although total bacterial load was associated with winter cough and history of breathlessness. These 52 participants with sputum samples available for analysis were more likely to be smokers and have a cough, so there may be a selection bias to those that were more productive.

Despite there being a similar prevalence of airways disease in the bacteria and non-bacteria groups, could airway bacteria be a marker of smokers who may go on to develop COPD in this cohort?

Unfortunately, there were no matched HIV negative controls to compare with this group, although one study has shown that the health HIV lung microbiome does not seem to differ to that in non-HIV controls. [280]

6.4.5 Limitations

This cohort, although recruited using stratified selection, may have been self-selecting as part of a tuberculosis testing study. It is conceivable that they had a higher frequency of respiratory symptoms than an entire clinic cohort, as these

symptoms may have motivated them to take part in the study. Unfortunately, we could not record respiratory symptoms in those who had declined or not attended. In order to limit the time burden on participants less, a systematic respiratory questionnaire such as the St Georges Respiratory Questionnaire was not included. The EQ5D may be too insensitive to ascertain loss of quality of life due to respiratory disease alone.

A relatively large number of participants did not self-reported their height – we feel most overlooked this. Our spirometry data therefore was less complete and formal anthropomorphics would have been a valuable part of the study protocol.

Many of our participants had not performed spirometry before and there was an appreciable learning effect, with some participants increasing their FEV_1 by over 500mls over four attempts. Using a hand held spirometer, our results may not have been as reliable as those in a lung function laboratory. We also did not perform carbon monoxide transfer factor (due to logistics and resources involved with testing), which may have better characterised lung damage.

With respect to bacterial testing on sputum, only those who could produce a larger volume of sputum could have a qPCR assay performed. Although those producing sputum were no more likely to have symptoms or obstructive spirometry, the high frequency of airway bacteria could be confounded by this.

Finally, there was no HIV-negative control group in which to compare frequency of symptoms, lung function or presence of sputum bacteria. Also, this was a single cross-sectional study – serial measurements may give more insight into FEV_1 decline in HIV-infected symptomatic smokers.

CHAPTER 7: SUMMARY AND FUTURE DIRECTIONS

7.1 Summary

This is the first study of systematic, extensive testing of an HIV infected contemporary population for active, subclinical and latent TB with a cost-effectiveness analysis in a low TB incidence area. Retrospective modelling showed decreasing cost-effectiveness of testing for latent TB infection with time over the past 15 years – testing in all with blood CD4 <500 cells/μL with an IGRA (NICE 2011 guidance) was cost-effective up to 2005, then more targeted testing in those at the highest risk (BHIVA 2011) up to 2010. Modelling using prospective data shows that even the most targeted testing for LTBI in those at the highest risk of reactivation is only just cost-effective from an NHS perspective in a contemporary HIV infected population. It also shows that neither testing all attendees nor using more than one test was cost-effective, contradicting nearly all of the current national or regional LTBI testing guidance.

One participant in the study had a positive sputum culture for *M. tuberculosis*, but with no symptoms or radiological or immunological evidence of TB disease. Previous cases from other low TB settings have been presented in the literature but all have had positive immunological tests.

The prevalence of subclinical TB and LTBI in this study was very similar to other recent estimates in Western Europe as was the uptake of LTBI treatment – perhaps many clinic patients were not convinced that this was beneficial, which

also reflects the views of clinicians in many centres. [201]

This study found a high number of adverse events with LTBI preventive treatment, although these were sought pro-actively, there are more than are usually described when estimating the quality of life utility for LTBI. This has implications for future cost-effectiveness models.

There was a high frequency of respiratory symptoms amongst the whole cohort, even higher in smokers, although the prevalence of obstructive spirometry was much lower. In those who produced adequate sputum samples, nearly 50% had molecular evidence of bacterial colonisation. This was also more common in smokers.

The participants in the study will continue to serve as part of a cohort to help calculate the predictive value of TST and IGRA over the next 15-20 years.

7.2 Application of the work

Although two cases of subclinical tuberculosis were detected in this cohort, the low frequency of active disease implies that more comprehensive testing than just using immunological tests for latent TB infection in this context (asymptomatic patients in HIV clinics in low TB prevalence areas) is not economically viable.

As the risk of reactivation is a reflection of TB prevalence, it could be suggested that guidelines should also test injecting drug users (who have a high incidence of active TB disease) as well as those from high TB incidence countries. [281] The

work from this study has already influenced the British HIV Association draft guidelines for testing people living with HIV for latent TB infection, who will suggest testing using a single immune-based test in only those from subSaharan Africa, TB contacts or in those that inject drugs.

7.3 Future directions

Although modelling is cited as always wrong but sometimes useful, the analysis has highlighted certain areas with little data. There are very few studies into the quality of life of patients with both HIV (on ART) and LTBI or active TB disease. Even the suitability of the questionnaires used are controversial. [189,248] Nor are there up to date costs of treatment for these groups. There are also few data on the predictive value of TST or IGRA in HIV infected individuals who adhere to ART. The available information will improve as more studies report their long-term outcomes, newer immunological or even RNA transcriptomic tests that identify those at highest risk of reactivation are developed, and better-tolerated, shorter LTBI treatments become available. [282] All of these interventions may make testing for TB in this group more cost-effective in the future.

There still seems to be a need to convince both patients and clinicians that TB prevention is worth implementing. The number of patients in this study with new HIV diagnoses was too low to make a prediction of the effectiveness of LTBI testing in this group, but their risk of reactivation is higher. A larger study using just immunological tests, with more costing and quality of life data and higher recruitment amongst individuals with new HIV diagnoses, may resolve

this. In anticipation of that, some centres are only testing those with new HIV diagnoses and TB contacts, whilst some national guidelines already suggest only testing only those from the highest incidence countries and those with chaotic lifestyles (such as injecting drug users). [283]

Up to now, the majority of diagnoses of active TB in people with HIV have been made before the HIV status of the patient is known. Perhaps HIV prevention, increasing HIV testing and prompt treatment with ART will have consequences to prevent active TB, and this, again, could be modelled to assess its impact.

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APPENDIX I

Study Protocol

Title
Testing for tuberculosis in a UK HIV infected population

Study Type
Single Centre study

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Background
Despite effective antituberculosis medication, the number of cases of (active) tuberculosis (TB) disease worldwide has continued to increase over time (1). The main driver of this is HIV infection. People living with HIV have a 20-40 times higher risk of developing TB disease compared to individuals without HIV (2,3). This results from the immune dysregulation associated with HIV infection, and has a number of consequences: 1. An increased risk of developing active TB disease soon after exposure to *Mycobacterium tuberculosis* (Mtb), 2. An increased risk of progression of latent TB infection (LTBI) to TB disease, 3. A worse overall outcome (4).

The majority of cases of TB result from inhalation of Mtb, usually from contact with another person. It is thought that around seventy percent of those exposed clear the infection and have no evidence of ongoing infection. Up to five percent of those exposed develop active TB disease, often characterised by weight loss, fever, night sweats and other localising symptoms such as cough, within 2 years of exposure. The remainder, who may have a short, self-limiting illness, remain infected, and have latent infection. This can be defined as a clinical state, where an individual is well and their Mtb infection is controlled by their immune response. For often unknown reasons, in approximately 5-15% of those without HIV, LTBI can progress to active tuberculosis during the person's lifetime (4-6).

In the UK and other low TB incidence areas, reactivation of LTBI is thought to be the cause of the majority of active TB disease. In those with HIV infection, the risk of reactivation is estimated to be much higher at 5-14% per year (2,7). More recently, a state between active and latent TB, with detectable Mtb in sputum but no symptoms or chest radiographic (CXR) abnormalities, has been described in high TB prevalence countries. This is now referred to as subclinical disease (8-10).

LTBI almost certainly encompasses a spectrum, from near sterilisation of the infecting microbe to low level/paucibacillary infection with replicating bacteria. This is usually diagnosed with positive markers of cellular immunity – classically the tuberculin skin test (TST) and more recently the Interferon Gamma Release Assay (IGRA) – e.g. the T-Spot.*TB* and QuantiFERON-TB Gold tests. Inevitably, with such immune based tests, their accuracy is less certain in the context of HIV co-infection. As systemic immunity declines (reflected in falling blood CD4 count), skin tests are less reactive in people with Mtb infection, whilst IGRAs maybe indeterminate (defined as a QuantiFERON-TB Gold mitogen nil result of <0.5 IU/ml, a T-Spot.TB positive control of <20 spots in the context of a negative sample result or nil control >10 spots). Within the same subjects, there is up to 30% discordance between TST and either IGRA, and also discordance between the Quantiferon and TSpot.TB tests (11-13).

Given the natural history of tuberculosis infection, much work has focused on treating asymptomatic LTBI to prevent active disease. This is important as globally, it is estimated that a third of the world's population may have LTBI. The use of preventive therapy (with antituberculous agents, e.g. 6 months of isoniazid treatment) in high TB prevalence countries has been shown to result in reduced risk of reactivation by up to 60%, with an effect lasting up to

4 years (14,15). Antiretroviral therapy (ART) for HIV also decreases the risk of active TB disease (by up to as much as 80% in low and high TB prevalence areas) (16-18). Hence, the use of combination of isoniazid preventative treatment (IPT) and ART is an attractive option, although the drugs can have significant interactions and lead to severe adverse events. However, in high TB prevalence areas (especially in countries also with high HIV prevalence, such as those in sub-Saharan Africa) the benefit to risk ratio is clearly in favour of treatment (19,20). In low TB prevalence areas, for example, the UK, this is less certain. There is a need for guidance.

In England and Wales, NICE guidelines suggest using IGRA testing alone or TST and IGRA together in patients with a blood CD4 count of 200-500 cells/μL and both IGRA and TST with blood CD4 <200 cells/μL (21). The British HIV Association (BHIVA) use data from a European cohort to calculate the risk of progression to active TB and test depending on country of origin, CD4 count and use of ART using IGRA alone (Table 1) (22). Testing is only performed in those where the risk of progression to active TB is higher than the risk of serious liver toxicity from preventive treatment. If the IGRA is positive, the individuals are recommended treatment (23,24). Both sets of guidance make an implicit assumption that the majority of cases of active TB are as a result of reactivation of latent disease.

Table 1: BHIVA testing criteria

	Sub-Saharan Africa	Medium incidence country	Low incidence country
Blood CD4 count	Any	<500 cells/μl	<500 cells/μl
Duration of ART use	< 24 months	< 24 months	< 6 months

NICE guidance is often underpinned by economic evaluation, typically using cost-utility analyses expressed in terms of Quality Adjusted Life Years (QALYs). The EQ-5D is a standardised, generic quality of life questionnaire used to calculate loss of QALYs and has been a widely used instrument for NICE appraisals including the assessment of asthma interventions and drug treatments in rheumatoid arthritis. Previous estimations of QALY change in LTBI (on preventive treatment) and active TB disease vary considerably and there are no empirical data to support QALY differences in those with active or latent TB and HIV co-infection (25-27).

Exclusion of active TB is required before starting latent TB treatment. To do this, the World Health Organisation (WHO) and others advocate symptom

screening questionnaires (28,29). This is to prevent both inadequate treatment of active disease with the smaller number of drugs and shorter duration of treatment used to treat LTBI, and hence to avoid drug resistance. The questionnaires ask about cough, sweats, fever, fatigue and loss of appetite. In high TB prevalence areas, when used without CXR or sputum analysis, these still appear to miss 3-16% of cases with active or subclinical disease (29,30). In low prevalence areas, their utility has not been assessed.

Diagnosis of active TB depends upon identification of the organism. Pulmonary tuberculosis occurs in at least 50% of individuals and therefore sputum analysis with microscopy (AFB smear) and culture has been used as the mainstay of TB diagnosis for over fifty years. However, microscopy has a low sensitivity (even lower in HIV infection) and culture results can take several weeks to become positive. There is an urgent need to develop new techniques that can improve detection compared to microscopy and decrease the time to diagnosis when compared to standard culture. These include nucleic acid amplification of specific gene regions in the mycobacterial genome e.g. polymerase chain reaction (PCR) and transcriptome, e.g. detection of 16S ribosomal RNA (16S rRNA). In a study from South Africa, Xpert.TB PCR testing detected up to 60% of culture-proven TB cases in HIV infected subjects, compared to 5% that were smear positive (30). 16S rRNA analysis has been used to identify Mtb and other non-tuberculous mycobacteria and, importantly, to quantify bacterial load (31,32).

ART improves life expectancy in those infected with HIV, and as these individuals age, pulmonary diseases that affect the general population become more prevalent. In particular, as rates of smoking are higher in people with HIV, the prevalence of non-infective respiratory conditions such COPD or lung cancer will increase (33,34). The synergistic impact of smoking (both cigarettes and other drugs), plus recurrent pulmonary infections, creates a milieu within the lung that predisposes the individual to significant long term risk of further pulmonary disease. This can include reactivation of pulmonary tuberculosis (35).

Given the undoubted beneficial effect of ART in HIV, and the high levels of access to good quality care in the UK, plus lack of UK data, there is an urgent need to evaluate the role of assessments for tuberculosis (latent, subclinical and active) in UK HIV infected individuals at risk of TB who also are likely to receive sustained ART.

Hypotheses

1. Systematic testing for Mtb infection (with IGRA) is feasible and cost-

effective in a UK HIV population.
2. Tuberculin skin testing provides no further information compared to single step blood Interferon Gamma Release Assay in the detection of Mtb infection in a UK HIV infected clinic population.
3. Within our clinic population, asymptomatic HIV infected individuals with normal chest radiographs have negative mycobacterial sputum microscopy and culture despite originating from high TB prevalence areas.

Aim

We propose to investigate the frequency of TB sensitisation (by TST and IGRA), abnormal radiology (by chest radiograph) and mycobacterial smear/ culture positivity (by spontaneous and induced sputum) in a cohort of HIV infected individuals in a London centre with an incidence of TB of >40 per 100 000. These data will allow us to understand the role of testing for TB using IGRA, TST, chest radiograph and sputum analysis in people in a low incidence setting. This population can then be followed to determine the short and longer term risks of reactivation with or without concomitant antiretroviral therapy.

Primary objectives

To determine the feasibility, yield and cost-effectiveness of systematic testing for *M. tuberculosis* infection in UK HIV infected individuals.

Secondary objectives

For all subjects:

1. To determine the prevalence of subclinical and active TB in a UK HIV infected clinic
2. To determine the sensitivity and specificity of systematic screening questionnaires for detecting cases of active TB outside of high TB prevalence settings
3. To determine concordance between TST and blood T-Spot.*TB* in latent TB infection
4. To identify risk factors for latent TB infection in the clinic population
5. To determine the underlying frequency of airways disease (using spirometry) and of respiratory symptoms
6. To determine the sensitivity and specificity of Xpert MTB/RIF PCR testing of sputum and induced sputum compared to mycobacterial microscopy and culture
7. To compare the Molecular Bacterial Load (MBL) assay, based on 16S rRNA, and other available molecular assays, with Xpert MTB/RIF for detection of Mtb
8. To determine quality of life scores (EQ-5D) for those with HIV infection, with

and without latent TB infection and/or undergoing treatment

On those with evidence of LTBI:
9. To determine uptake of latent TB therapy (6 months isoniazid treatment)
10. To determine cost of latent TB treatment (including screening costs, clinic time)
11. To determine quality of life and rate and severity of adverse events on latent TB treatment
12. To determine rate and time until active TB in those with LTBI on or off ART and/or isoniazid prophylaxis

In all patients (over 20 year follow up):
13. To determine the rate of incident active TB
14. To determine the time until progression to active TB with in patients with abnormal radiographic changes consistent with old tuberculosis exposure or disease

Methods

Study design

1. Cross sectional study of the prevalence of active, subclinical and latent tuberculosis in people living with HIV undergoing care at the Royal Free Hospital.
2. Quality of life and economic analysis of systematic TB testing and latent tuberculosis treatment in this group
3. Establishment of baseline measures for a cohort that can be followed over time whilst receiving long term HIV care.

Study numbers

300 HIV infected adults will be recruited from the Ian Charleson Centre, Royal Free Hospital, London.
A control group will be formed from the other patients not approached for testing but that attend the Ian Charleson Centre, Royal Free Hospital, London during the period of recruitment. Retrospective diagnoses of tuberculosis can be identified using previously obtained ethical approval for the HIV cohort as a whole.
The study is powered to identify a difference between all TB (latent infection and active disease) between subjects from sub-Saharan Africa and low TB prevalence areas (such as the UK) with 80% power, allowing a 5% Type I error.

Selection criteria

All patients with a new diagnosis of HIV will be approached, plus stratified

sampling of existing patients undergoing care (by approaching 3 patients in each HIV clinic, 1st, 4th and 7th on each clinic list on Mondays, Tuesdays, Wednesdays and Fridays) in order to recruit 180 subjects originating from sub-Saharan Africa and 120 from lower TB prevalence areas. After recruitment of 100 subjects, certain clinics (for example, with a predominance of African patients) will be selected in order to enrich the cohort. Due to a delay of 48-72 hours being required between Mantoux skin testing and reading, we will not be able to recruit on a Thursday.

Data will be collected on patients already known to the service and prospectively on those newly diagnosed with HIV infection and consist of:

- a record of baseline characteristics (including country of birth, time in UK, blood CD4 lymphocyte subset count at diagnosis),
- a symptom questionnaire (based on WHO and Cain questionnaires (29)),
- EQ-5D quality of life scores, respiratory symptoms,
- history of previous BCG,
- blood T-Spot.*TB* testing,
- PA chest radiograph,
- tuberculin skin testing,
- spontaneous sputum analysis where possible,
- spirometry according to international guidelines,
- sputum induction for mycobacterial smear and culture, Xpert MTB/RIF and 16S rRNA testing.

In subjects with evidence of LTBI:

- EQ-5D in all and adverse event questionnaires for subjects prescribed LTBI treatment,
- Comprehensive costings and resources used by subjects whilst receiving LTBI treatment.

Recruitment and informed consent

Patients will be approached by their usual clinical care team during routine appointments. All patients with a new diagnosis of HIV will be approached by their nominated consultant. Those already undergoing care will be identified by the researchers or Ian Charleson Centre nurses as the 1st, 4th or 7th patient in a clinic from clinic lists only – without access to the medical history. The patient's regular doctor will then approach the patient during routine consultation if he/she fits inclusion criteria. Patients will be given an information sheet and any questions can be answered by the researchers. Written informed consent will be obtained at this point.

Participants can be reimbursed for reasonable transportation costs for visits that do not form part of their routine treatment/healthcare.

Storage of sputum and blood samples
Sputum samples will be tested in the Department for Clinical Microbiology, Royal Free Hospital. Any leftover sputum sample will be stored in the Department for Clinical Microbiology and identifiable by study number only. Blood samples: Blood samples for T.Spot.*TB* tests will be sent by secure courier to Oxford Immunotec laboratories on the day of sampling. 3 further blood samples (2xEDTA, 1xLiHep) will be stored in the Department for Clinical Microbiology, Royal Free Hospital. Plasma or human cells from these may be sent to the University of Southampton and University College London for further analysis after recruitment finishes. They will be identifiable by study number only.

Inclusion Criteria
Able to give informed consent
Over the age of 18
HIV infected, with confirmed positive HIV antibody status

Exclusion Criteria
Diagnosis of active TB or undergoing treatment for active or latent TB
Inability to produce sputum by coughing (e.g. recent rib fracture, chest pain, pneumothorax)
Pregnancy
Use of steroids (equivalent to 15mg prednisolone for ≥4 weeks) or any other immunosuppressive drugs (e.g. azathioprine)
Active solid organ or haematological malignancy (excluding Kaposi's sarcoma)
Previous hypersensitivity to purified protein derivative (PPD)
Extensive eczema

Study Procedures
Questionnaire (see Appendix B)
Subjects will be asked to complete a questionnaire including age, place of birth, previous time living abroad (if appreciable), symptoms (including cough, haemoptysis, fever, weight loss), smoking history, previous BCG vaccination for tuberculosis (with examination for BCG scar). Clinical and medication data will be added to this from subjects' medical records (including suspected route of infection with HIV, time of diagnosis with HIV, previous antiretroviral treatments, blood CD4 counts and HIV viral load).

Chest radiograph
Subjects will be asked to have a departmental posterior-anterior radiograph

(unless performed in last 4 weeks). If found to be abnormal (e.g. parenchymal lesion or pleural effusion), further testing may be necessary (see abnormal chest radiograph below) as part of routine care.
Women of childbearing age will have urine beta-hCG measured before undertaking this.

Sputum analysis
Any subjects with a productive cough will be asked to produce one sputum sample for mycobacterial microscopy and culture, Xpert MTB/RIF and MBL 16S rRNA testing in a negative pressure area.

Sputum induction
Sputum induction will be performed in a negative pressure closed unit within a side room. The procedure will be explained to the participants prior to sputum induction. Salbutamol 100 two puffs via metered dose inhaler and spacer will be given to prevent bronchospasm in those with underlying airways disease. Spirometric (FEV_1, FVC) and peak flow measurements will be performed as a precaution in order to identify airways disease before starting the procedure using a hand held spirometer and again 5 minutes after commencing the salbutamol nebuliser. 40mls 4% hypertonic saline will be nebulised over 20 minutes, re-measuring FEV_1 after 5 minutes, followed by active cycle of breathing to augment airway clearance. The procedure will be terminated if the subject complains of chest tightness, breathlessness or intense cough. Oxygen and nebulised salbutamol will be available if necessary for treatment of bronchospasm. All sputum will be expectorated into one pot and analysed for mycobacterial microscopy and culture, Xpert MTB/RIF and 16S rRNA testing. Sputum may be analysed for whole genome sequencing of the bacterial genome or sent to University College London and University of Southampton laboratories for further analysis of candidate biomarker molecules. 1 paired plasma (EDTA) samples will be taken (at the same time as T-Spot testing) for blood/sputum marker comparison.

If subjects have symptoms suggestive of active tuberculosis or a chest radiograph suggestive of active tuberculosis then tuberculin skin testing may be deferred.

TST (Tuberculin skin testing)
Intradermal administration of 2 TU=0.1ml purified protein derivative (SSI) with a (28 gauge) insulin needle on the upper third of the forearm (palm up) to form a wheal 6-10mm in diameter. Time and date of injection, lot number of solution and location of injection site will be documented and the subject advised to avoid pressure or bandage at the injection site. The diameter of the

lesion will be measured at follow up 48-72 hours later by the investigators. A lesion measuring 5mm or above will be considered a positive result.

T-Spot.*TB* testing
2 x 6ml lithium heparin tubes of whole blood, drawn simultaneously with routine clinic blood testing, will be sent to Oxford Diagnostic Laboratories using the DX same-day courier service in a robust, blood transport container for T-Spot.*TB* Testing. Samples will be identified by study number only. A difference of ≥6 spots between either CFP10 or ESAT6 antigen panels and the nil control panel will be considered a positive result, <6 spots a negative result. Where the difference between the higher of both panels and nil control is 5,6, or 7 spots, the result will be considered borderline. A positive control of <20 spots in the context of a negative sample or nil control >10 spots will be considered indeterminate. Borderline and indeterminate results will be recorded and a blood sample retested two weeks later.

Blood samples:
1 EDTA and 1 LiHep blood samples will be taken at the same time as T-Spot. *TB* testing and will be stored for possible future tests of immune function (including for the detection of biomarkers, microRNA and cell phenotyping associated with active and latent TB). Written consent will be obtained for these blood samples and they will only be used in ethically approved future studies.

Subjects with a positive result to tuberculin skin testing or T-Spot.*TB* testing will be referred to TB/HIV clinic for discussion of the results and consideration of LTBI treatment with 6 months of isoniazid. Costs and resources used during treatment will be calculated for each subject. Those undergoing treatment will have clinic follow up with assessment of adverse events using a standardised questionnaire and quality of life scores using EQ-5D. Those with LTBI and not undergoing treatment will also be asked to complete the EQ-5D questionnaire for comparison. (In this group, this can also be done by telephone).

Study measures
Questionnaire results:
Chest radiology – categorised as either:

(i) normal
(ii) abnormal suggestive of previous exposure but not active TB infection
(iii) abnormal suggestive of active TB infection
(iv) abnormal not suggestive of active TB infection

T-Spot.*TB* results (negative, equivocal, indeterminate, positive)
TST reaction size (defined as a reaction after 48-72 hours of intradermal injection of PPD of 0mm, 1-4mm, 5-10mm, 10-15mm, >15mm)
Spirometry (FEV_1, FVC and ratio) before and 5 minutes in to sputum induction.
Sputum quality and mycobacterial smear and culture status, and result of Xpert MTB/RIF and 16S rRNA testing for *M. tuberculosis*
Induced sputum quality and mycobacterial smear and culture status, and result of Xpert MTB/RIF and 16S rRNA testing for *M. tuberculosis*
Sputum stored for inflammatory and immunological markers

Follow up phase:
Uptake of latent TB treatment in those offered it
Completion rate of latent TB treatment in those offered it
Time to (incident) active TB over following 20 years

Quality of life:
Cost of resources and clinic appointment time related to latent TB treatment (including with TB nurses and Ian Charleson staff)
Adverse event rate whilst on latent TB treatment (see Appendix F)
Quality of life scores on those with and without LTBI and those on treatment for LTBI (using Euro-QoL/EQ-5D)
Time to active TB in those with and without latent TB treatment

Ethics and R&D
This study will not be commenced until approval from the local Ethics Committee and Hospital R&D department. The Ethics Committee will be informed of all subsequent study protocol amendments.
Prior to participation in the study, informed consent will be obtained from each patient. This consent must be retained as part of the study records.

Collaboration with external sites
All recruitment will take place within University College London (Royal Free Hospital Campus).
Transfer of tissues: Sputum samples and EDTA blood samples will be sent to the University of Southampton. All tissues will be labelled with study number only (pseudoanonymised). 2xLiHep blood samples will be transferred to Oxford Immunotec diagnostic laboratory for central T.Spot.*TB* testing using the specialist DX courier service. These will be identified by study number only.
Transfer of funds: Oxford Immunotec will be funded for commercial T.Spot.*TB* testing. There will be no other transfer of funds to external sites.

Transfer of data: Data on background risk of tuberculosis and immune status associated with blood and tissue samples will be transferred to the University of Southampton. All data will be pseudoanonymised.

Statistical analysis
Analysis will be performed using parametric and non-parametric measures in association with the Department of Infection and Population Studies, UCL.

Economic analysis
Economic Analysis will be performed with the UCL Department of Health Economics at the Centre for Applied Health Research.

Data and Quality Management
Data will be stored on a secure database. Participants will be followed through their clinical care pathway for up to 20 years. This will have as an endpoint of follow up: development of active TB. If participants no longer attend the Royal Free Hospital, other sources such as the Health Protection Agency or London TB Register may be contacted to look for newly diagnosed cases of active tuberculosis disease. This will be performed with patient anonymity and confidentiality, and within data protection requirements.
Data will be pseudoanonymised at data entry and files kept in an encrypted form on computers at the Royal Free Hospital and University College London (Royal Free Campus).
Patient details will not be sent to outside centres apart from those performing diagnostic tests (i.e. T-Spot.*TB* testing, which is performed at an external laboratory), in which case only hospital number and date of birth will be sent.
Data management will be subject to regular 3 monthly review by one study investigator to ensure records are complete and storage secure.
Explicit consent will be taken before subject's participation in the study is disclosed to their general practitioners.

Appendix A
In the event of an abnormal chest radiograph:
A medical history and examination will be undertaken. If there are no concerning features, no further action will be taken. Subjects will undergo investigations as part of routine care, as if they would were they presenting to hospital via their General Practitioner.
If the chest radiograph is suggestive of active TB, subjects will remain in the study for quality of life evaluations whilst on treatment and would undergo mycobacterial sputum microscopy and culture. Treatment of active TB and subsequent further radiological investigations would occur as routine care.
If there are any other abnormalities found, a medical history and examination

will be performed, the subject's General Practitioner will be notified (with patient consent) and the subject will have further investigations as part of routine care and not as part of this study. No data from subsequent radiological investigations form endpoints to this study.

Appendix B
Questionnaire

Appendix C
Consent form

Appendix D
Checklist

Appendix E
Flowcharts

Appendix F
Latent/active TB treatment adverse event symptom questionnaire and checklist

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Date:

INFORMATION ABOUT THE RESEARCH
Testing for Tuberculosis in a UK HIV Infected Population

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Why have I been invited?
We have asked people living with HIV to take part in this study. It is to see if there are things about you (your gender, where you were born, a skin test result) that make you more likely to develop tuberculosis (TB) in the future.

What is the purpose of the study?
Many people are exposed to the bacteria that causes TB without knowing it. Most of these people won't get TB and the bacteria are completely removed from the body. In some people, a small amount of TB remains. Of these people who have a small amount of bacteria remaining, a few will go on to develop TB sometime in their life. The chance of this happening is higher in people with HIV, but lowered to a certain extent on effective HIV antiretroviral medication and also prevented by 6 months of an antibiotic called isoniazid (although we are not sure by how much in the UK). We don't know who will develop TB later in life and who won't, but there are some factors that increase the risk.

In TB high prevalence areas, such as Southern Africa, up to a third of patients with HIV but who are well are found to have TB in their sputum when they start antiretrovirals, but no one has looked for this systematically in the UK. We would like to look for this in sputum, which is produced either by deep coughing, or helped by breathing in a sterile mist of salty water. This sputum will be sent for TB testing including microscopy (looking for the TB bacteria under a microscope) and with a

PCR test (looking for the TB bacteria's DNA).

Do I have to take part?
It is up to you whether or not to take part. If you decide to do so, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are free to withdraw at any time, without giving a reason. Whether you take part or not will not affect your healthcare or treatment in any way.

What will happen to me if I take part?
The study only involves 2 visits. The first can be today and will take at most a couple of hours. The second is 2-3 days later and will only take a few minutes.
On the first visit, we will ask you to fill in a questionnaire. This covers things like your place of birth, time you've lived in areas that have a high TB rate and other questions that relate to your risk of exposure to TB. The risk of TB goes up in people who have been in prison or who have taken injectable drugs, so we've asked these questions in the questionnaire, although we appreciate they are sensitive. We would then like you to have a chest x-ray, some blood tests (including a T-Spot test) and a Mantoux test (which is a small injection on the forearm into the skin) to test for previous exposure to TB. We would also ask you to produce a sputum sample (using a water nebuliser) in which we will look for the TB bacteria. If positive, you will be told about the test results by us. If we find that you have been exposed to TB, you will see a doctor in clinic who will explain the advantages and disadvantages of having any treatment to stop TB causing you disease. All of your other treatments will remain the same during the study. It will be your decision as to whether or not you want to take the treatment. We will ask you some questions about how you feel each time you come to clinic, or if more convenient, over the telephone. If we find that your chest x ray is not completely normal, then you will be told this and we will explain what has caused the abnormality and do any necessary further tests.

What are the possible benefits of taking part?
As an individual, you may not benefit directly from the research carried out. If we do detect tuberculosis in your sputum, then catching this early may mean that you do not become as unwell as you might, had it been left, and you will be offered treatment. If we detect latent TB (previous exposure but no symptoms) with the skin or blood test then you will be offered treatment to stop you developing symptoms. The risks and benefits of this will be explained to you when it is offered and it is completely your own choice. Research from these types of studies will help us improve diagnosis of tuberculosis in the future and increase our understanding of how tuberculosis infection causes disease. If you wish, you can be informed of the tests performed. You can be reimbursed for travel expenses to visits additional to routine care. Please submit a claim to the researchers (Dr Santino Capocci or Research Nurse Janey Sewell) enclosing receipts.

What are the possible disadvantages and risks of taking part?
We do not envisage any significant risk to you if you decide to participate in this study. Sputum induction can make you cough but it is very unlikely to cause any harm. Anyone with a history of asthma or obstructive airways disease will be given 2 puffs of a salbutamol inhaler, which opens up the airways. This will prevent any wheeze when the salt water nebuliser is being breathed in.
The skin test may cause some discomfort on your skin. A chest x ray is required as part of the study and has negligible radiation risk, equivalent to a few days background radiation. A new x ray is not necessary if you have had a chest x ray within the last 4 weeks. We will ask any women under the age of 50 taking part to have a pregnancy test before a chest x ray as a precaution.

What will happen to the results of the research study?
Results generated from your tests will form part of a larger data set including results from other participants. The final results may be published in scientific journals or presented at conferences Please let us know if you would like to be informed of the outcome of this research. These results will be anonymous, so that people outside of the research group cannot identify you. If you wish, you will be informed of the results of your skin test, blood tests, x ray and sputum tests.

Will any additional information be collected?
To enable us to accurately interpret the results, we would like to collect information about your treatment details and progress including the results from your blood tests.

One of the aims of the study is to find out who gets tuberculosis in the future. Over the next 5-20 years we would like to check if you have been diagnosed with TB. If you are still treated at the Royal Free Hospital, we would like to recheck your records here; if not, then we may need to check via the TB database at the Health Protection Agency, which records this data. Just as now, all information gathered then will be kept securely at the Royal Free Hospital and be kept strictly confidential.

What will happen to my samples?
As part of the study, one blood test will be sent to a central laboratory in Oxford for a T.Spot.TB test, looking for previous exposure to tuberculosis. This will be transported by secure courier and no identifiable data will be used on the sample bottle or form. This and most of the other samples will be destroyed after analysis. However a small amount of the sample will have a chemical added that preserves any bacterial genetic information present. This will be stored in a freezer in a secure site at the Department of Microbiology at the Royal Free Hospital. This will be identified by a sample number only. This may be stored indefinitely. A very small amount of sputum and blood may be sent to the University of Southampton and to University College

London, where there are researchers that have a special interest in TB and HIV. These samples may be tested for biomarkers (chemicals secreted by human cells) that are associated with tuberculosis, or human cells may be extracted and tested to see why and how TB affects the cells in the lungs. All the research using these samples will be approved by an ethics committee and samples will not be identifiable. The data associated with the samples will also not contain any identifiable information. This extra analysis is very helpful for us, but is optional and you can still take part in the study without these samples being used in future research.

Who will have access to information about me?
All data collected will be held on a database at the Royal Free Hospital. Only the doctors, nurses and research personnel involved in running this study will have access to it. All information collected about you during the course of the research will be kept strictly confidential, and any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised. Any samples sent to University College London, the University of Southampton or Oxford Immunotec (for the IGRA blood test) will be identified only by a sample number (referred to as pseudoanonymised). Staff outside of the Ian Charleson Centre and the research group will not be able to access any personal information about you.

We will ask you if you would like the results of the TB tests we perform. We will specifically ask you if you would like your GP to be informed about your participation in the study. You will be able to see the GP letter before agreeing to this. You can still take part in the study without your GP being aware. We will also ask if you are happy for your GP to see the results of your TB tests.

Who is organising and funding the research?
The study is being organised by medical doctors from University College London who also work at the Ian Charleson Centre. It is funded by the HIV Department at the Royal Free Hospital.

Who has reviewed the study?
All research in the NHS is looked at by the independent group of people, called an Ethics Committee, to protect your safety, rights, wellbeing and dignity. The London City and East Research Ethics Committee, the Research and Development Office and a Senior Respiratory Consultant, Dr John Hurst, from University College London, have reviewed the study.

What if I have any other concerns or wish to seek independent advice about the study?
If you have any complaints about the way the investigator has carried out the study please contact the Patient Advocacy Liaison Service at the Royal Free Hospital;

telephone number 0207 472 6447.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (0207 794 0500 extension 31148).

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask your research doctor if you would like more information on this.
In the unlikely event that you are harmed by taking part in this study, compensation may be available.

If you suspect that the harm is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to Dr Marc Lipman who is the Chief Investigator for the research and is based at the Royal Free Hospital. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

Contacts for further information:
If you require any further information regarding the study at any stage, or in the event of an emergency please contact the following doctor or nurse:

Dr Santino Capocci 0207 794 0500 extension 31148 or 35151 Royal Free Hospital site
Research Nurse Janey Sewell 0207 794 0500 extension 34673 Royal Free Hospital site
Dr Marc Lipman 0207 317 7560 Royal Free Hospital site

Thank you for taking the time to read this information sheet.

You will be given a copy of this information sheet and a signed consent form to keep.

Royal Free Hospital
Pond Street
London
NW3 2QG

Tel: 020 7794 0500

Date:

CONSENT FORM
Testing for Tuberculosis in a UK HIV Infected Population

Name:

Hospital Number:

Study Number:

Researcher:

The participant should complete this sheet him/herself.
Please initial box.

1. I confirm that I have read and understood all the information contained in the information sheet above (Version 2, dated 26th October 2012). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. By completing and returning this form, I consent that the personal information I provide will only be used for the purposes of this project and not transferred to an organisation outside of the Royal Free Hospital/UCL. The information will be treated as strictly confidential

and handled in accordance with the provisions of the Data Protection Act 1998.

4. I give permission for blood results and certain data from my medical records to be used in the study and stored in a database kept at the Ian Charleson Centre at the Royal Free Hospital. I give permission for my Royal Free Medical records to be consulted again in the future to look for any diagnoses of tuberculosis.

5. I give permission for my blood and sputum samples to be stored in the Centre for Clinical Microbiology at the Royal Free Hospital and my blood sample to be sent to Oxford Immunotec (for latent TB blood testing).

6. I agree to take part in the Testing for tuberculosis in a UK HIV Infected Population study.

Optional: These parts are voluntary and you can still take part in the study without them:

7. I give permission for data about me and any leftover sample to be stored and used for future ethically approved studies. You will **not** be identifiable from this data or stored sample.

8. I agree to pseudo-anonymised samples of my sputum and blood to be sent for analysis within other departments in UCL and to the University of Southampton.

9. I agree to being informed of the results of my TB tests (blood IGRA test, tuberculin skin test, x ray result and induced sputum results) as clinically needed.

10. I agree to my GP being informed of my participation in the study (This is voluntary and you can still take part in the study without your GP being informed).

11. I agree to my GP being informed of the results of my TB tests (blood IGRA test, tuberculin skin test, x ray result and induced sputum results).

Name (block capitals)……

Signed……

Date……

DOCTOR/NURSE TAKING CONSENT (please delete)

Name (block capitals)……..

Signed……..

Date……

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

APPENDIX 2

Other published papers:

Yield and cost effectiveness of mycobacterial infection detection using a simple IGRA-based protocol in UK subjects with inflammatory bowel disease suitable for anti-TNFα therapy (2012)

Amikacin treatment for multidrug resistant tuberculosis: how much monitoring is required? (2013)

Expanded blood borne virus testing in a tuberculosis clinic. A cost and yield analysis (2014)