# Cost effectiveness of testing HIV infected individuals for TB in a low TB/HIV setting

**Running title:** Cost effectiveness of TB testing in HIV clinic

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**Declaration of interests**

Potential competing interests: Margaret Johnson and Marc Lipman contributed to the British HIV Association Guidelines on TB/HIV coinfection, 2011 and 2018 update. Ibrahim Abubakar co-chaired and Marc Lipman was a member of the NICE TB clinical guidance development group (2013–2016). Stephen Morris is a member of the Public

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**ABSTRACT**

**Objectives:** Guidelines recommend routine testing for latent TB infection (LTBI) in people living with HIV. However there are few cost-effectiveness studies to justify this in contemporary high resource, low TB/HIV incidence settings. We sought to assess the uptake, yield and cost-effectiveness of testing for latent and active TB.

**Methods:** Adults attending an ambulatory HIV clinic in London, UK were prospectively recruited by stratified selection and tested for TB infection using symptom questionnaires, chest radiograph (CXR), tuberculin skin test (TST), T-Spot.TB and induced sputum. From this, 30 testing strategies were compared in a cost-effectiveness model including probabilistic sensitivity analysis using Monte Carlo simulation.

**Results:** 219 subjects were assessed; 95% were using antiretroviral therapy (ART). Smear negative, culture positive TB was present in 0.9% asymptomatic subjects, LTBI in 9%. Only strategies testing those from subSaharan Africa with a TST or interferon gamma release assay (IGRA) with or without CXR, or testing those from countries with a TB incidence of >40/100,000 with TST alone were cost-effective using a £30,000/QALY threshold.

**Conclusions:** Cost-effectiveness analysis in an adult HIV cohort with high ART usage suggests there is limited benefit beyond routine testing for latent TB in people from high and possibly medium TB incidence settings.

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**Keywords:** Tuberculosis, HIV infection, Costs and Cost analysis, adult, screening

**INTRODUCTION**

Human immunodeficiency virus (HIV) infection increases the risk of active tuberculosis

(TB) disease up to 40 fold compared to background rates.[1] Testing and treating latent

TB infection (LTBI) in people living with HIV (PLWH) in high TB incidence countries

decreased the risk of active TB by 62% in those with a positive tuberculin skin test

(TST), whilst use of antiretroviral therapy (ART) also reduces TB reactivation risk by at

least 65%.[2,3]


International guidelines advocate testing in low TB incidence settings, but the evidence

comes from studies published before near universal use of antiretroviral therapy.[4-16]

Only one also estimated the cost-effectiveness of testing in low TB incidence areas

such as the United States (US) and Western Europe.[7,8] This is important given the

potential costs associated with large-scale testing for latent or active TB.


Guideline advice ranges from frontal chest radiograph (CXR) plus interferon gamma

release assay (IGRA) in high risk populations, with TST if CD4 >400 cells/µL (European

AIDS Clinical Society, EACS) to CXR and TST or IGRA in everyone at HIV diagnosis,

plus sputum culture or yearly TST screening in some higher risk groups (US Centers for

Disease Control & Prevention - CDC).[4-10,16] The UK has two different

guidelines.[8,9] A potential consequence is that clinicians may be uncertain how to

manage their patients. European reports suggest given that less than half of HIV

centres follow national latent TB testing in PLWH guidelines.[17,18]

In response to this, we sought to determine the uptake and yield of testing for TB in a contemporary adult UK HIV ambulatory care clinic using extensive assessments for active and latent TB infection. From this, we determined the most cost-effective strategy to identify latent and active TB.

**METHODS**

**Study population and patient selection**

Subjects were approached from those attending routine appointments at the Royal Free Hospital, London, UK using stratified selection, unless they had a new diagnosis of HIV in the past four weeks, in which case all were contacted. Exclusion criteria are listed in the Appendix. The service provides ambulatory care to approximately 2500 people living with HIV annually, a third of whom are black African (BA), most originating from countries with an estimated TB incidence of >300 per 100,000.[19]

**Study procedures**

Symptom and medical questionnaires including any history of TB disease or known TB exposure, quality of life scores, chest radiograph (CXR), blood IGRA (T-Spot.TB, Oxford Immunotec, Abingdon, UK), TST (using 2U/0.1ml purified protein derivative, Statens Serum Institut, Denmark), and a single induced sputum were offered to all subjects and were usually performed over two visits 48–72 hours apart. CXR were reported by a Specialist Radiologist at the Royal Free Hospital. T-Spot.TB assays were performed by ODL (Oxford Immunotec, Abingdon, Oxford) within 24 hours. Those with borderline and

indeterminate results (definitions in the Appendix) had the T-Spot.TB test repeated. TSTs were interpreted after 48–72 hours by trained staff. Those who could not return to have the TST read in person were given instructions and a ruler to report on the size of any induration.

Sputum induction was performed with 3.5% saline in a negative-pressure isolation tent. Sputum samples were analysed using Xpert MTB/RIF (Cepheid, Sunnyvale, California, USA) within 48 hours, and by liquid mycobacterial culture (Bactec - Becton Dickinson MGIT 960, New Jersey USA) for 42 days.

Those with CXR suggestive of active TB were investigated and treated accordingly with rifampicin, isoniazid, pyrazinamide and ethambutol. Those with CXR not suggestive of active TB, with a negative sputum mycobacterial culture, and a positive T-Spot.TB or TST, were informed and offered TB preventive therapy with six months isoniazid or three months rifampicin and isoniazid depending on drug interactions.[16]
Subjects continued to be followed up to see if they developed active TB.

Subjects were reimbursed for any travel costs, 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.

**Case definitions**

LTBI was defined as a TST result at 48–72 hours of ≥5mm (irrespective of Bacille Calmette–Guérin, BCG, vaccination status), or a positive T-Spot.TB.[6,20,21] Active TB disease was defined as symptoms and radiographic changes consistent with tuberculosis and positive sputum microscopy and culture for *Mycobacterium tuberculosis*. Asymptomatic, smear negative, culture positive 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 40–300 and <40/100 000 population respectively.[5,19]

**Economic analysis model structure and assumptions**

TB testing strategies:

The results of the tests above, along with participant characteristics and uptake in the study, were used to undertake an economic analysis based on thirty predefined testing strategies. The assumptions used within the different strategies are listed in Table 1 and Appendix Table 1. The full table of strategies are in Appendix Table 2, and reflect national guidelines, or incremental combinations of readily-available tests to detect TB infection and disease.[4-10,16]

Baseline risk of TB:

We assumed a 10% lifetime risk of active TB in those with a positive IGRA,[22-24] 2% with positive TST, negative IGRA and 0.02% with negative IGRA and TST.[13,23]

Using these, we estimated the expected total number of cases of active TB that would prospectively develop without LTBI testing and treatment (see Appendix Figure 1). 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.[11]

Utilities:

Reduction in QALYs due to active TB, treatment of asymptomatic, smear negative, culture positive TB and treatment of latent TB were 0.676, 0.2 and 0.007 respectively.[7]

Costs:

Costs of testing using TST and T-Spot.TB, latent TB treatment, and active TB treatment were taken from local charges or published studies and measured from an English NHS perspective in £ Sterling, with costs updated to 2018/19 using the Hospital and Community Health Services Index.[7,8,25,26] The time horizon was lifelong and costs and benefits discounted at 3.5% per year.[27]

Costings, assumptions and sources are given in Appendix Table 1.

**Statistics**

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

**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 the previous (non-dominated) strategy, ranked according to total cost. Incremental cost-effectiveness ratios were calculated as the difference in costs between the two strategies divided by the difference in outcomes (either cases averted or QALYs gained). We used the England and Wales National Institute for Health and Care Excellence (NICE) threshold of £20–30,000/QALY gained as our measure of cost-effectiveness.[27]

**Sensitivity analysis**

Univariate and multivariate (best and worst case) deterministic sensitivity analyses were performed. We halved and doubled costs for TST, T-Spot.TB, CXR, sputum induction, latent, asymptomatic, smear negative, culture positive and active TB treatment. We also modeled the effect of ongoing transmission of TB, based on NICE methodology and assumptions.[8] The 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 within realistic margins (see Appendix Table 1).

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 most likely cost-effective at different cost-effectiveness thresholds with and without the effect of transmission.

**RESULTS**

**Uptake, and cases of active and asymptomatic, smear negative, culture positive TB**

Between June 2013 and September 2014, 982 adult outpatient attendees were eligible to be recruited, 683 were approached and 219 took part within the 14 months recruitment period (Figure 1). Seventeen (8%) had a new diagnosis of HIV. There had been no previous systematic TB testing in the clinic. The study participants were representative of the total clinic population (Table 2) with 95% taking ART, of which 88% had an undetectable HIV load. Median CD4 cell count was 643 cells/µL. There were no incidental cases of symptomatic, active tuberculosis disease.

Of the 219 participants, 162 (74%) returned to have their TST result read, another 40 (18%) read their own skin test after 48–72 hours (all of whom either had TB previously, had a TST result of <5mm, or had a positive IGRA). Twelve subjects (5%) did not attend or make contact after testing. Five (2%) patients declined to have a TST performed.

T-Spot.TB results were available for 217/219 (99%). Two hundred and fourteen of 219 (98%) had chest radiographs. Seventeen (8%) were consistent with a history of previous TB, 16 (7%) had other abnormalities (see Appendix) and 181 (85%) were

normal. Sputum induction was performed on 208 subjects, of whom 178 (86%) were productive. No samples had *M. tuberculosis* detected by Xpert MTB/RIF. Two (0.7%) were positive for *M. tuberculosis* on sputum culture (both cultured at 40-42 days incubation and had unique mycobacterial interspersed repetitive unit variable nucleotide tandem repeat (MIRU-VNTR) results. The two participants were classified as having asymptomatic, smear negative, culture positive TB.

Of the 217 subjects with T-Spot.TB results, 11 (7%) had a history of previous TB. Fourteen participants were diagnosed with LTBI: eight (3.7%) who did not report previous TB had a positive T-Spot.TB and six (2.8%) a positive TST with negative T-Spot.TB (all of whom returned to have their TST read by trained staff). Thirteen percent were subSaharan African (8/62), and 6.5% (2/31) and 3% (4/126) respectively in those from middle and low TB incidence countries.

Of those with latent TB infection, all were offered preventive therapy, but only 9/14 (64%) started and seven (50%) completed treatment. Two subjects with positive T.Spot-TB results declined treatment. Two stopped due to adverse effects and one was lost to follow-up despite multiple attempts to maintain contact. Over 72 months (IQR 68-74) follow-up, there have been no reported cases of active TB in those tested (irrespective of TST/T-Spot.TB result).

**Cost effectiveness**

We estimated that over their lifetime, 92 of 10,000 PLWH in care in England and Wales would develop active tuberculosis due to reactivation of latent infection in the absence of preventive treatment (see Appendix Figure 1). Thirty different testing strategies (full list in Appendix Table 2) were then applied using the results obtained from the observational study.

The estimated costs, cases prevented and QALYs gained for each strategy in order of increasing expense are given in Table 3 and Appendix Table 2.

Compared with no testing, six strategies met the NICE cost-effectiveness criteria of £20-30,000/QALY. A single TST in black Africans was the least expensive at £15,868/QALY. Testing BA and those from middle TB incidence countries (MI) with a TST cost £18,221/QALY. The strategy that prevented the most cases was testing all BA with a single IGRA and chest X ray (cost/QALY £28,575). All of these point estimates had wide, overlapping uncertainty ranges. Testing all BA and MI with a single IGRA cost just over the threshold at £31,138/QALY gained. Compared to the previous most costly (non-dominated) intervention, only testing with TST and CXR in black Africans had an incremental cost effectiveness ratio of less than £30,000/QALY gained.

When including cases that may have been prevented by interrupting ongoing TB transmission, a strategy of testing all BI and MI with an IGRA and CXR became cost effective at £29,818. From a health service's perspective, neither of the CDC, EACS, WHO, nor the NICE UK strategies were cost-effective (Appendix Table 2).[4-10,16] The

BHIVA 2018 strategy would be cost effective if the effect of transmission was included.[9]

**Sensitivity analysis**

Univariate cost-effectiveness analysis showed that: TST in BA alone remained the most cost effective strategy, even if TST cost more than £40 (from its assumed price of £18.51). If the cost of a CXR fell below £30 then CXR and TST in BA was most cost effective, whilst IGRA in BA became cost-effective if the cost of T-Spot.TB fell to £22 (from £53). If the average cost of an active case of TB rose from £9,6474 to £19,000, then testing with TST in BA and MI became cost saving, and if the cost of TB disease fell to ≤£2 300 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, and if there was 80% uptake and completion, testing all PLWH with T-Spot.TB alone cost less than £30,000/QALY. This strategy was also cost-effective if the positive T-Spot.TB progression rate were ≥13%.

Using a Monte Carlo analysis, a cost-effectiveness acceptability curve was calculated for cost-effectiveness thresholds of 0–£100,000/QALY gained. Most regimens were not cost effective in this range. Of the nine that were, no testing was most likely cost effective up to £20,000; above which, testing using TST in BA became the strategy most likely to be cost effective (Figure 2). At just over £50,000/QALY, testing BA and middle incidence groups with IGRA and CXR was the most likely cost-effective.

**DISCUSSION**

In this real world analysis of testing for TB in a low HIV and TB incidence setting with widespread use of antiretroviral therapy, only six strategies in targeted populations were cost effective. Strategies that tested all clinic attendees, used both a TST and IGRA, or those including sputum induction and examination, were not cost-effective, even when the effect of transmission was included. This is important as nearly all current national and international guidelines reviewed by us either test all attendees, use both a TST and IGRA, or require sputum sampling within their recommendations.[4-10,16]

Testing black Africans (representative of PLWH from a high TB incidence setting) with a TST or IGRA with a CXR was cost-effective at under £30,000/QALY compared to no testing, as was testing both black Africans and people from middle TB incidence countries (approximating to all those from outside Western Europe, North America and Australasia) with a TST and CXR. Using an IGRA in this context would be just above this threshold, although when ongoing transmission is incorporated, this becomes cost-effective compared to no testing. When subjected to probabilistic sensitivity analysis, 'No testing' was most likely cost-effective up to £20,000/QALY and testing black Africans with a TST at £30,000/QALY (whether transmission is included or not).

Our sensitivity analysis suggested that if the cost of an T-Spot.TB fell by 60%, or its predictive value increased, the strategies using an IGRA were cost-effective. However, given the low overall incidence of LTBI in Western Europe, testing all clinic attendees

with any test was not cost-effective, unless population transmission was as high as one per active case of TB.

The efficiency of strategies involving TST was substantially reduced by the poor participant return rate required for TST to be read, although there may be processes to improve this, such as better remote reading.[28] Routine sputum induction for mycobacterial culture also added significant cost for very little yield; and given the low TB bacillary burden in the patients with asymptomatic, smear negative, culture positive TB, routine sputum TB molecular testing provided no further information.

Although no symptomatic, active TB was identified, there were two cases of asymptomatic, smear negative, culture positive TB (0.9%) – which is similar to 0.6%-1% in other studies in similar settings.[24,29] Also, the proportion of patients with latent infection was comparable to that from elsewhere: 13% in subSaharan Africans, measured by IGRA only, in London and Denmark; and 15%, determined using TST in a Swiss study.[13,29,30] Apart from one patient (later diagnosed with sarcoidosis), all subjects with a positive IGRA result also had a positive tuberculin skin test (≥5mm).

Using the health economic threshold criteria recommended by UK NICE, our data suggest that testing with only a TST in people from high TB incidence countries is most cost-effective. This finding should be interpreted carefully as different low TB incidence settings may vary in what they regard as a locally-relevant cost/QALY cut off.[31] Further, the selection of either TST or an IGRA as a preferred test can depend on

factors such as the availability of Purified Protein Derivative for TST, or the programmatic simplicity of not needing to recall people with a negative blood IGRA.[32]

Our study has several limitations. In the observational study, we found that less than 50% of the patients approached agreed to take part. This may have been due to the number of tests and time required during assessments for active TB. However, uptake throughout the study was similar to that reported elsewhere: for example three-quarters of our participants returning to have their TST read compares favourably with published figures of 30–80%.[33-35] In those with confirmed latent TB infection, 50% (7/14) completed preventive therapy. Again, this was similar or higher than seen in other European studies;[36] though less than reported by Kall et al who also investigated adult PLWH in London.[29]

Other issues include the difficulty of accurately determining the number of cases of TB disease likely to occur in those with a positive skin or blood test in a contemporary HIV population using ART – giving wide and overlapping uncertainty ranges for our estimates of cost-effectiveness. This is in part due to the need for prolonged follow-up to calculate the predictive value of these tests for TB disease. Despite this, it is interesting to note that there were no new cases of TB after a median of over 6 years of follow up in our study. Further, early reports indicated that active TB could occur in people with negative skin tests (possibly due to new TB exposure).[36] We have included this in our model, though this may underestimate the effectiveness of testing, as recent studies

find a zero or very low risk of active TB in people with negative IGRA results, or those with LTBI who take preventive therapy.[22,23,29]

Of the total population assessed, only 8% were new HIV diagnoses – yet these are a group not on ART who are at greatest risk of TB reactivation. The small numbers in our study make it hard to draw conclusions or develop guidance regarding testing for LTBI. Pragmatically, the offer of a TST or IGRA seems sensible in people from high TB incidence settings with a new diagnosis of HIV. If followed by prompt initiation of ART, their overall risk of TB would then fall. Indeed, as ART use is now so widespread in higher resource countries, and is likely to increase with international guidelines, there may be a further decline in the population-level risk of TB disease due to reactivation – reducing the cost-effectiveness of TB testing even more.[36,37] We have identified this in a recent retrospective analysis where testing became less useful as ART uptake increased.[38] We have not addressed TB testing in children with HIV.

Our sensitivity analysis suggests that if the costs of tests fall (e.g. cheaper IGRA or the use of low-cost digital chest radiography), more strategies may become cost-effective. This argues for the importance of regular re-evaluation of the data and testing strategies. The same holds true if new diagnostics such as host transcriptomic tests with greater positive predictive value for the development of active TB were applicable in PLWH and introduced into clinical practice.[39,40]

It is also important to note data from the UK, which find that only one in three people with TB/HIV coinfection have knowledge of their HIV status before TB diagnosis. Thus, testing for TB in an HIV clinic is one component of the approach needed to control TB/HIV.[41]

This is the first reported study to model different testing strategies for latent, asymptomatic and symptomatic TB disease in people living with HIV using real world data from a low TB and HIV incidence area. Despite current recommendations regarding widespread LTBI testing, we find there to be limited evidence for this approach. Testing people at greatest risk of TB/HIV (i.e. those from high TB incidence regions such as subSaharan African countries) in an HIV clinic with widespread ART use, appears cost-effective using cost/QALY of £20-30,000/QALY. Only a fall in the price of IGRA, an increase in the predictive value of IGRA or other tests, or an increase in costs for treatment of TB disease can, in the short-term, affect this.

**Authors' contributions to the study:**

SC, MJ and ML designed the study. SC, JS and ML carried out the study with significant contributions by IC, SB, AS and ML. SM, CS and IA substantially contributed to the cost-effectiveness analysis. The first draft was written by SC and ML and was critically revised by all authors.

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**Table 1: Assumptions**

| |
|---|
| 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 |
| Fewer subjects would re-attend for TST interpretation (reflecting 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%[2] |

**Table 2: Subject demographics compared to those eligible and total Royal Free Cohort**

| | 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% |

| | Study group (n=219) | Subjects eligible, but not recruited (n=761) | p* | Total HIV cohort, Royal Free Hospital 2013 (n=2551) |
|---|---|---|---|---|
| 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 |

BCG - Bacille Calmette-Guérin, IQR - interquartile range, TB – tuberculosis

*Study group compared to those eligible but not recruited. Testing using Chi-squared or Mann-Witney U tests.

Low TB incidence country: TB incidence <40/100,000; middle TB incidence country: 40-300/100,000.

**Table 3: Costs for 18 selected strategies, discounted cost/case prevented and cost/QALY gained compared to no testing and last (non-dominated) strategy.**

| Strategy | Total cost of strategy per 10,000 PLWH (95% uncertainty ranges) | TB cases prevented (discounted) (95% uncertainty ranges) | QALYs gained compared to no testing (95% uncertainty ranges) | Cost/case averted (95% uncertainty ranges) | Cost/QALY compared to no testing (95% uncertainty ranges) | Incremental cost/QALY compared to last strategy (95% uncertainty ranges) |
|---|---|---|---|---|---|---|
| No testing | £889,527 (£153,844-£3,310,891) | 0 | 0 | £0 | £0 | |
| BA TST | £922,744 (£172,160-£3,338,385) | 3.9 (1.1-10.6) | 2.1 (0.4-8.6) | £8,510 (£2,603-£16,120) | £15,868 (£3,254-£49,229) | £15,868 |
| BA MI TST | £933,733 (£175,202-£3,353,942) | 4.5 (1.1-15.3) | 2.4 (0.4-12.4) | £9,837 (£2,831-£18,657) | £18,221 (£3,506-£56,938) | EXTENDEDLY DOMINATED |
| BHIVA 2011 - IGRA only in BA with any CD4 on ART < 2 years MI with CD4 <500 on ART < 2 years LI with CD4 <350 on ART < 6 months | £940,875 (£173,101-£3,389,891) | 2.3 (0.2-11.1) | 1.3 (0.1-9.2) | £22,552 (£7,126-£107,863) | £40,050 (£8,642-£303,159) | DOMINATED |
| BA TST&CXR | £970,468 (£215,217-£3,349,862) | 7.3 (1.8-19.2) | 3.7 (0.6-14.0) | £11,133 (£2,065-£34,518) | £21,900 (£2,843-£104,693) | £29,777 compared to BA TST |
| BHIVA 2011 strategy with CXR | £945,567 (£216,157-£3,400,455) | 5.6 (0.8-19.6) | 2.9 (0.3-14.7) | £17,554 (£4,634-£76,036) | £34,343 (£6,247-£224,611) | DOMINATED |
| BA IGRA | £997,509 (£221,671-£3,419,191) | 6.8 (2.0-18.3) | 3.8 (0.7-15.2) | £15,808 (£5,928-£34,016) | £28,074 (£7,189-£95,604) | EXTENDEDLY DOMINATED |
| NICE 2011: IGRA + TST if CD4 <200 and IGRA alone if CD4 <500 | £999,136 (£208,110-£3,487,781) | 1.1 (0.0-6.3) | 0.6 (0.0-5.2) | £98,334 (£28,263-£1,822,488) | £174,631 (£34,274-£5,122,253) | DOMINATED |
| All TST | £1,000,540 (£212,273-£3,447,275) | 5.6 (1.3-18.9) | 2.9 (0.4-14.9) | £19,729 (£7,213-£43,819) | £38,801 (£9,211-£147,999) | DOMINATED |
| BA MI TST&CXR | £1,015,938 (£230,785-£3,408,667) | 8.9 (1.8-28.9) | 4.5 (0.6-21.1) | £14,265 (£3,411-£42,302) | £28,059 (£4,699-£128,225) | EXTENDEDLY DOMINATED |
| BA IGRA&CXR | £1,045,234 (£264,728-£3,430,668) | 10.2 (2.6-26.8) | 5.4 (0.9-20.6) | £15,269 (£4,487-£42,076) | £28,575 (£5,873-£120,072) | EXTENDEDLY DOMINATED |
| BA MI IGRA | £1,056,145 (£238,982-£3,524,589) | 9.1 (2.1-31.6) | 5.1 (0.8-26.3) | £18,391 (£6,769-£40,170) | £32,660 (£8,209-£112,902) | DOMINATED |
| CXR in all | £1,095,328 (£338,835-£3,521,798) | 6.3 (0.7-20.3) | 3.0 (0.2-13.0) | £40,825 (£10,463-£271,789) | £85,768 (£16,502-£814,460) | DOMINATED |
| All IGRA | £1,303,929 (£411,809-£3,816,372) | 10.2 (2.2-36.0) | 5.7 (0.8-29.9) | £40,767 (£14,047-£119,309) | £72,397 (£17,035-£335,329) | DOMINATED |
| NICE 2016: IGRA + TST if CD4 <200 and IGRA in all others | £1,407,200 (£505,335-£3,776,864) | 10.2 (2.2-36.0) | 5.7 (0.8-29.9) | £50,926 (£15,899-£182,142) | £90,439 (£19,435-£547,239) | DOMINATED |
| All IGRA&TST | £1,475,296 (£504,165-£4,115,667) | 11.0 (2.3-38.9) | 5.9 (0.8-31.1) | £53,282 (£20,654-£152,474) | £99,566 (£26,060-£449,728) | DOMINATED |
| All IGRA&CXR | £1,559,576 (£596,801-£4,028,165) | 16.4 (2.8-56.4) | 8.7 (1.0-42.9) | £40,789 (£12,753-£155,815) | £76,975 (£16,874-£444,539) | EXTENDEDLY DOMINATED |
| All IGRA&TST&CXR | £1,730,943 (£689,157-£4,327,460) | 17.3 (3.0-59.3) | 8.9 (1.0-44.1) | £48,761 (£17,157-£179,740) | £94,926 (£23,243-£532,060) | EXTENDEDLY DOMINATED |

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 (TB incidence <40/100,000), MI - middle [TB] incidence countries (those with an incidence 40-300/100,000), NICE - National Institute of Health and Care Excellence, PCR - Xpert MTB/RIF M. tuberculosis polymerase chain reaction, PLWH - People living with HIV, QALY - Quality adjusted life year, TB - tuberculosis (includes active disease and subclinical tuberculosis cases), TST - tuberculin skin test.

Costs, cases and QALYs discounted by 3.5% per year.

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).
BHIVA 2011: IGRA only in BA 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 200-500.
NICE 2016: IGRA + TST if blood CD4 <200 and IGRA alone if blood CD4 ≥200.
Uptake was 82% for IGRA and CXR, 41% for TST and induced sputum.

All 30 strategies are listed in Appendix Table 2

**Figure titles and legends:**

**Figure 1: Consort diagram**

**Figure 2: Cost effectiveness acceptability curve for TB testing strategies**

Cost effectiveness acceptability curves for TB testing strategies using probabilistic sensitivity analysis. There is a 39% probability that testing all black African patients with a TST alone will be cost-effective where the health service is willing to pay a maximum of £30,000 per quality-adjusted life year (QALY) gained (vertical dashed line).