Cost-effectiveness of testing for latent tuberculosis infection in people living with human immunodeficiency virus

Running head: Testing for LTBI in people living with HIV

Abstract: 250 words (exclusive of headings)

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Abstract

Objective: The aim of this study was to estimate the cost-effectiveness of screening strategies for predicting LTBI that progresses to active TB in people living with HIV.

Design: We developed a decision-analytical model that comprised a decision tree covering diagnosis of LTBI and a Markov model covering progression to active TB. The model represents the lifetime experience following testing for LTBI, and discounting costs, and benefits at 3.5% per annum in line with UK standards. We undertook probabilistic and one-way sensitivity analyses.

Setting: UK National Health Service and Personal Social Service perspective in a primary care setting.

Participants: Hypothetical cohort of adults recently diagnosed with HIV.

Interventions: Interferon-gamma release assays and tuberculin skin test.

Main outcome measure: Cost per quality-adjusted life year (QALY).

Results: All strategies except T-SPOT.TB were cost-effective at identifying LTBI, with the QFT-GIT -ve followed by TST5mm strategy being the most costly and effective. Results indicated that there was little preference between strategies at a willingness-to-pay threshold of £20,000. At thresholds above £40,000 per QALY, there was a clear preference for the QFT-GIT -ve followed by TST5mm, with a probability of 0.41 of being cost-effective. Results showed that specificity for QFT-GIT and TST5mm were the main drivers of the economic model.

Conclusion: Screening for LTBI has important public health and clinical benefits. Most of the strategies are cost-effective. These results should be interpreted with caution due to the paucity of studies included in the meta-analysis of test accuracy studies. Additional high-quality

primary studies are needed to have a definitive answer about which strategy is the most effective.

Keywords

HIV, latent tuberculosis infection, cost-effectiveness analysis, interferon gamma release assays, tuberculin skin test

Background

Tuberculosis (TB) has become the most prevalent opportunistic infection and is a leading cause of death in people living with human immunodeficiency virus (PLHIV).[1, 2] TB is more aggressive and accelerates the clinical course of HIV.[1, 3] Co-infection with HIV is an important risk factor for the progression of latent tuberculosis infection (LTBI) to active TB; increasing the rate of progression by 20-fold.[4] In 2019, it was estimated that there were approximately 105,200 PLHIV in the UK, with 98% on antiretroviral therapy (ART). TB incidence in PLHIV was 1.3 (95% CI:1.2, 1.4) per 1000 person-years, with the majority (58.1%) of the TB events occurring after initiation of ART.[5] Rate of progression can be reduced if people with LTBI receive anti-tuberculous prophylactic treatment,[2] that is, six months of isoniazid plus pyridoxine or three months of isoniazid plus rifampicin plus pyridoxine.[6] Thus, identifying and treating LTBI in an HIV population is a key public health priority in the elimination of TB.

The tuberculin skin test (TST) is widely used to diagnose LTBI, despite its limitations. Evidence suggests that TST can lead to a high number of false positive and false negative cases, especially in an HIV population.[7] False positive results can occur due to cross-reactivity in people who are Bacilli Calmette-Guérin (BCG) vaccinated and those who are infected with non-tubercular mycobacteria.[8] Whereas false negative results can occur in people who are immunosuppressed.[2] Additionally, TST requires two health care visits, and there is a possibility of error when measuring the size of the induration of the skin reaction,[9, 10] but this should not be a major issue in clinics with well trained professional..

Interferon gamma release assays (IGRAs) were developed to address the limitations of the tuberculin skin test. Two IGRAs are commercially available for the diagnosis of LTBI: QuantiFERON Gold In-tube (QFT-GIT) (Cellestis Ltd., Carnegie, Australia) and T-SPOT.TB (Oxford Immunotec Ltd, Oxford, UK). IGRAs have been more sensitive and specific compared with TST regardless of an individual's BCG status and, people are not required to make a

second health care visit.[11] UK guidelines[12] recommend the use of IGRAs and a concurrent TST for the diagnosis of LTBI in PLHIV. From this guideline,[12] the clinical evidence that underpins these recommendations for screening in an HIV population are based on immunocompromised people collectively. Though useful, this offers little insight on the prognostic value of these tests for identifying LTBI that progresses to active TB in PLHIV and hence, their cost-effectiveness in this population.

A scoping search of the literature identified five studies[13-17] that assessed the cost-effectiveness of diagnostic strategies for identifying LTBI in PLHIV. These studies provide useful clinical and economic evidence that may be used to support recommendations but there were several limitations noted. First, the sensitivity and specificity used in two economic analyses[13, 14] were obtained from systematic reviews[18-20] where the authors excluded studies with participants who were immunocompromised/immunosuppressed. Also, the sensitivities reported for QFT-GIT and T-SPOT.TB were for identifying active TB, and not LTBI. Second, in one analysis[14] the sensitivity and specificity of TST were obtained from different sources; hence, the bivariate nature of sensitivity and specificity was not accounted for. Third, the authors assumed the sensitivity of IGRAs collectively.[16] These studies all have limitations because of the test accuracy estimates, which were not based on empirical evidence.

Hence, the aim of this paper is to develop a decision analytical model to measure the costs and benefits of using TST, IGRAs, or a combination of both tests for predicting the progression of LTBI to TB in PLHIV. Using empirical evidence in an economic analysis would provide decision makers with the evidence-base required to support the development of guidance for identifying LTBI in PLHIV.

Methods

We published a systematic review and meta-analysis of the clinical evidence about the performance of tests.[21] We found two studies that directly compared an IGRA with TST,[22, 23]

and a further three studies that compared IGRAs or used an IGRA/TST[7, 24, 25] in a cohort of PLHIV who had not been treated for LTBI. From these studies, we used a Bayesian bivariate modelling framework to synthesise the evidence to derive pooled estimates for sensitivity and specificity of TST and IGRAs for predicting the progression of LTBI to active TB in PLHIV. We defined sensitivity as the proportion of people with positive results among those who progressed to active TB, who were correctly identified by the test as positive, and specificity as the proportion of people with negative results among those who did not progress to active TB, who were correctly identified by the test as negative. Table 1 presents the results for sensitivity and specificity of these tests.

Model structures

To assess the cost-effectiveness of strategies for the diagnosis of LTBI, we draw on the illustrative model structure reported by Auguste et al.(2016).[26] The model was developed with clinical input and programmed in TreeAge Pro Healthcare 2020 (Williamstown, MA, USA), and represents the clinical pathway PLHIV would take whilst being screened for LTBI. The model structure is presented in the appendix. The model comprises two stages, diagnosis of LTBI and disease progression to active TB. In the first stage of the model we used a decision tree structure to represent the clinical pathway people would take whilst being diagnosed for LTBI. Five strategies were examined in the model: TST alone, QFT-GIT alone, T-SPOT.TB alone, sequential testing with IGRA then TST, and a no testing strategy. The second stage is a Markov model that models the progression from LTBI to active TB.

Data required for the model

We populated the model with clinical information obtained from a meta-analysis.[21] Information was required on the prevalence, sensitivity and specificity, and adverse events. Resource use and costs, and utilities were obtained from several sources.

Resource use and costs

Table 1 presents the costs used in the model. The resource use and costs included were those directly related to the UK National Health Service (NHS). Costs for diagnostic tests, chest x-ray, sputum examination, treatment of LTBI/TB and isoniazid (INH) induced hepatitis were included in the analysis. Cost for QFT-GIT (testing kit, consumables, processing, and phlebotomy) and TST (disposables, administration and reading) were obtained from Pooran et al. (2010).[27] Costs for chest x-ray and sputum examination were obtained from the NHS reference costs 2017/18.[28] Costs for the treatment of LTBI were obtained from the NHS drug tariff 2018. Cost for the treatment of TB were obtained from Bothamley et al. (2002).[29] Management of LTBI included further blood tests, outpatient visits, and treating with INH 300mg daily for six months. Estimated costs for treating INH-induced hepatitis were obtained from Pareek et al. (2013).[30] We excluded wider societal costs (e.g. loss of productivity) in line with our perspective and research question. All costs obtained from the literature were adjusted to 2018/19 prices using the Hospital and Community Health Service (HCHS) pay and price index Curtis et al. (2019).[31]

<Insert Table 1: Model input parameters required>

Outcomes

Three different outcome measures were used in the analysis, diagnostic error avoided, correct diagnosis and QALYs. To derive the diagnostic error avoided, we did not use effectiveness information. We allocated the value of one to true positive and true negative cases and assigned the value of zero for an error (false positives and false negatives) in the diagnosis. To derive QALYs, utility weights for PLHIV and the utility decrement of 0.15 for people who received treatment for active TB were obtained from the published literature (Maheswaran & Barton 2012).[40]

Analysis

The economic analysis was conducted according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[41] The cost-effectiveness analysis adopts the NHS and personal social services (PSS) perspective in a primary care setting. The results of the analysis are presented in terms of an incremental cost-effectiveness ratio (ICER), expressed as cost per QALY gained over a lifetime horizon. We also presented secondary outcomes in the form of cost per diagnostic error avoided. All costs incurred and benefits accrued were discounted at a 3.5% annual rate. Univariate and probabilistic sensitivity analyses (PSA) were undertaken to estimate the impact on the ICER by varying key model input parameters. In the base-case analysis we used pooled estimates for sensitivity and specificity based on studies that directly compared an IGRA with TST, then in scenario analysis we used pooled estimates that include data from single-arm studies.

PSA was undertaken to determine the joint uncertainty for the outcome cost per QALY. Due to heterogeneity of the studies included in the meta-analysis,[21] results from the PSA, which explicitly includes the impact of that uncertainty were considered to provide more plausible estimates of costs and outcomes than the deterministic analysis. Therefore, costs and outcomes used to produce ICERs were calculated as the means of the costs and outcomes in each of the 10,000 PSA simulations. In Table 1 we present the parameters varied along with their distributions. These simulations were plotted along a cost-effectiveness plane, with each point representing uncertainty in the expected mean costs and QALYs for each strategy. In addition, these simulations were also used to obtain cost-effectiveness acceptability curves (CEACs), which illustrate the effect of sampling uncertainty, and presents the probability that an intervention is optimal at a range of willingness-to-pay (WTP) values.[42]

Results

We assumed a hypothetical cohort of adults with HIV undergoing screening for LTBI. Appendix Table 1 and 2 gives a breakdown of the estimated mean diagnostic costs per strategy, as well as corresponding diagnostic errors (false positives and false negatives), total diagnostic errors and cost per diagnostic error avoided.

These results showed that screening with QFT-GIT -ve followed by TST5mm in PLHIV led to the most diagnostic errors overall, with the majority being false positive errors. Screening with QFT-GIT resulted in the least number of errors, with majority being false positives. TST5mm alone dominated the QFT-GIT -ve followed by TST5mm, and the T-SPOT.TB strategies, by being less costly and more effective, in this case having less errors. The comparison between TST5mm and QFT-GIT was extendedly dominated by the results of the comparison between TST5mm and no screening, with an ICER of approximately £780 per diagnostic error avoided.

As with the results of cost per diagnostic error avoided, results in terms of cost per correct diagnosis (Appendix Table 2) showed that QFT-GIT dominated most screening strategies by being less costly and identifying more cases of LTBI likely to progress to active TB in PLHIV. In comparison to screening with TST, QFT-GIT identifies 0.0785 more cases at an additional cost of approximately £30 which equates to an ICER of approximately £340 per correct diagnosis.

<Insert Table 2: Deterministic analysis results based on cost per QALY (2018/19 prices)>

Results in terms of QALYs (Table 2) showed that no screening for PLHIV for LTBI is likely to yield 21.2881 QALYs. Screening and treatment for LTBI in this population is likely to lead to modest gains in QALYs. The incremental results showed that screening with T-SPOT.TB was dominated by QFT-GIT. Excluding the dominated strategy showed that TST compared to no

screening had an ICER of approximately £10,200 per QALY. Other strategies had incremental results of approximately £12,100 and £20,200 per QALY.

Characterising uncertainty

In Appendix Table 3, the QALY outcomes of the 10,000 Monte Carlo iterations show that the results are robust to the parametric distributions used for key model input parameters; with the ordering of strategies remaining the same, and the results in the same ball-park as the deterministic results.

Figure 1 displays the iterations of the expected mean costs and QALYs for each strategy. The scatterplot shows that there is good dispersion of points for all testing strategies, and less so for the no testing strategy. However, this is expected because of the zero costs associated with the no testing strategy; any spread is a result of the uncertainty around the expected QALYs.

Figure 2 presents a five-way cost-effectiveness acceptability curve (CEAC) for these strategies, with the probability of each being cost-effective at different willingness-to-pay thresholds. Assuming a willingness-to-pay threshold of £20,000 per QALY, QFT-GIT had the highest probability of 0.33 of being cost-effective. T-SPOT and TST5mm had probabilities of 0.28 and 0.27, respectively. These results indicate that there is little preference between these three strategies at this threshold. At thresholds above £40,000 per QALY, these results show that there is a clear preference for the IGRA -ve followed by TST5mm strategy, with a probability of 0.41 of being cost-effective.

Scenario analysis

Appendix Tables 4 to 6 present the scenario analyses results based on using alternative sensitivity and specificity estimates for TST5mm, QFT-GIT and T-SPOT.TB obtained from

Auguste et al. (2019).[21] Using these alternative estimates for sensitivity and specificity resulted in a modest reduction to the ICERs in terms of cost per QALY (see Appendix Table 6).

One-way sensitivity analysis

Figure 3 shows the one-way sensitivity analysis results for the comparison between QFT-GIT and TST5mm based on the outcome cost per QALY. Changing key input parameters by using upper and lower limits showed that the specificity of both tests and the prevalence of the LTBI are the key inputs to the economic model. Changing one parameter at a time, an increase to the specificity of QFT-GIT resulted in a decrease to the ICER, while a decrease to the specificity resulted in an increase to the ICER. However, if the specificity of QFT-GIT is kept constant and there is a decrease to the specificity of TST, then there is a decrease to the ICER, and vice versa if there is an increase to the specificity, then the ICER increases. These results also show that an increase to the prevalence while keeping all other parameters constant increased the ICER.

Discussion

The exploratory economic analysis here offers some insight about the costs and effects associated with these strategies for identifying LTBI that is likely to progress to active TB in PLHIV. The results of the deterministic analysis based on the outcome cost per QALY show that there was a minimal increase in effectiveness at modest costs compared to no testing. Testing with TST was the least costly testing strategy, with IGRA negative followed by TST being the costliest. Excluding dominated strategies, the ICERs ranged from approximately £10,200 to £20,200 per QALY gained.

Other ICERs based on the outcomes cost per diagnostic errors avoided and cost per correct diagnosis were explored. These short-term results showed that testing with IGRA followed by TST resulted in the greatest number of false positive results and testing with QFT-GIT the least number of false positive results. However, testing with IGRA followed by TST resulted in the

least number of false negative results, but overall had the most errors of all testing strategies. Results in terms of cost per correct diagnosis indicates that TST5mm and QFT-GIT are both cost-effective testing strategies.

The cost-effectiveness threshold used by NICE is between £20,000 and £30,000 per QALY. Results from the PSA (Figure 2) indicates that there is no clear preference between the testing strategies at these thresholds; however, at willingness-to-pay thresholds beyond £40,000, testing with IGRA followed by TST is the most preferred strategy but never reaches a probability of one of being cost-effective.

The main results reported here indicate that the cost-effectiveness of these strategies were robust to most sensitivity and scenario analyses, with the exception of changes made to the specificity of QFT-GIT, the specificity of TST5mm and the prevalence of the disease. Our estimates for sensitivity and specificity were based on a recent systematic review and meta-analysis[21] with the ranges based on the lower and upper credible intervals. Wide credible intervals were noted due to the lack of studies that followed-up PLHIV who had not received TB preventative treatment following testing for LTBI.

Strength and limitations

The main strength of this economic evaluation is that to our knowledge this is the first economic analysis to determine the cost-effectiveness of strategies that can be used to identify LTBI likely to progress to TB in PLHIV. There are some limitations in the analysis that should be acknowledged and considered when interpreting the results. First, the test accuracy estimates were based on the best available recent evidence but there was a paucity of studies that compared between tests included in the meta-analysis, hence the exploratory nature of the economic analysis. Additional studies are likely to provide conclusive evidence about the predictive value of these tests. Second, there are other testing strategies (e.g., simultaneous testing) that could have been included in the economic analysis, which could have some impact

on the incremental results. These strategies were excluded because to our knowledge these were not explored in the primary studies. Methods are available to combine the results of tests but the underlying assumption would be that test results are independent (i.e., knowing someone's TST result doesn't change your expectation of their IGRA result) and using these methods could potentially invalidate the economic results, by overestimating and underestimating the sensitivity and specificity, respectively. Hence, we opted to exclude the strategy of simultaneous testing. Third, we have not included information about the levels of CD4 T cells at the time of screening and the effects of antiretroviral treatment and sustained suppression on risks for progression of LTBI to active TB nor have we characterised heterogeneity, by undertaking subgroup analysis (e.g. by CD4 T cells). Fourth, given the paucity of studies reporting the prevalence of LTBI that progresses to active TB in PLHIV, we used the probability for pregnant women who had LTBI that progressed to active TB.[13] Fifth, the model does not consider people with resolved TB being at risk of a new LTBI/TB diagnosis. Additionally, we have not included secondary cases of LTBI that may progress to active TB for each primary TB case. Each TB index case is likely to generate several secondary cases. Excluding these additional parameters might have underestimated the costs and benefits associated with testing and treatment. However, we consider the simple cohort model used here to be sufficient to address the exploratory nature of our research question.

Comparison with other studies

When comparing our model with others from the literature, it should be noted that our definitions of sensitivity and specificity are not the same as those used in most studies, hence, we do not expect our analyses to be directly comparable. In the absence of an agreed reference standard we used LTBI that progresses to active TB, as a proxy reference standard to derive sensitivity and specificity. Sensitivity is defined as the proportion of PLHIV who progressed to active TB who were correctly identified by the test as positive, and specificity as the proportion of those who did not progress to active TB who were correctly identified as negative.[21]

As stated previously, our scoping review of the literature identified five economic analyses that assessed the cost-effectiveness of strategies used to identify LTBI in PLHIV.[13-17] Base-case results from Kowada[13] showed that T-SPOT.TB dominated all other strategies, while our results showed that T-SPOT.TB was dominated by QFT-GIT. Steffen et al.[14] showed that new emerging tests (e.g. Diaskintest and QFT-Plus) were cost-saving against TST. Diaskintest and QFT-Plus were not included in our economic analysis because at the point of publication of our systematic review and meta-analysis[21] there were no clinical studies with participants using these tests, who were untreated, and who were followed-up to ascertain the incidence of active TB. Jo et al.[16] showed that IGRAs collectively were cost-effective when compared to TST. Our findings were similar even though we assessed each IGRA separately. Capocci et al.[15] concluded that there is limited benefit beyond screening for LTBI in PLHIV with high antiretroviral usage from countries with a high incidence of TB; while our results showed that there may be benefit in screening for LTBI in PLHIV. Wong et al.[17] compared different strategies to assess how frequent should PLHIV be screened for LTBI, but only included TST as the main test; hence, did not compare between IGRAs and TST.

Meaning of the study

Our exploratory analysis results indicate that based on the model structure, assumptions, and clinical information about test accuracy, all strategies except T-SPOT.TB were cost-effective at identifying LTBI likely to progress to active TB. Our results may contradict those in the literature, as there were some differences noted. With respect to current UK practice in testing people who have recently been diagnosed with HIV, guidance suggests simultaneous testing with an IGRA and Mantoux test, and if either test is positive (for Mantoux, induration of ≥5mm), assess for active TB and if this assessment is negative offer treatment for LTBI.[12] Our economic evaluation uses alternative definitions for sensitivity and specificity for estimates of test accuracy for IGRAs and TST, which were based on a meta-analysis where the evidence was

scant. A decision was made before the analysis to exclude the simultaneous testing as there were no primary studies using this strategy and current methodology may provide biased estimates.

Our evaluation demonstrates that there were modest QALY gains (equating to approximately several days) between strategies and, there is no clear preference for these strategies at current acceptable willingness-to-pay thresholds used by NICE.

Unanswered questions for future research

We used a simple model, with estimates from a systematic review and meta-analysis,[21] to explore the cost-effectiveness of relevant strategies to identify LTBI that is likely to progress to active TB in people recently diagnosed with HIV. There was considerable uncertainty around the test accuracy estimates that transpired in the economic analysis. We have not undertaken a formal value of information analysis but would suggest that there is value in undertaking further primary studies to improve/have more robust accuracy estimates to have a definitive answer about which strategy is the most effective. Additionally, future primary studies should provide details stratifying by levels of CD4 T cells at baseline and take account of the impact of antiretroviral treatment and sustained viral suppression on risks for progression of LTBI to active TB. These studies could then be used in a future model-base economic analysis. When undertaking future economic analyses, analysts should also explore adopting the societal perspective.

Conclusion

Screening for LTBI has important public health and clinical benefits. Here, we have shown how test accuracy estimates based on a pre-defined construct can be used in an economic analysis to aid a decision-making progress. Our results suggest that most of the strategies included in the evaluation are cost-effective for screening PLHIV for LTBI that is likely to progress to active TB. These results should be interpreted with caution due to the paucity of studies available in

the systematic review and meta-analysis of test accuracy studies. Additional high-quality primary studies are needed to have a definitive answer about which strategy is the most effective.

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Disclosure of interest

All authors have completed the Unified Competing Interest form at

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and declare that: no authors have support from any company for the submitted work; no authors have any relationships from any company that might have an interest in the submitted work in the previous three years; their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and no authors have any nonfinancial interests that may be relevant to the submitted work.

Contributors to authorship

PA designed and undertook the economic analysis. HM and NMc supervised the economic evaluation. PA prepared the manuscript as the lead writer. NMc, AC, PS provided support and clinical input. All authors were involved in writing the drafts and final version of the report.

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Figure 1: Cost-effectiveness scatterplot

Figure 2: Cost-effectiveness acceptability curves for all strategies

Figure 3: Tornado diagram for the comparison between QFT-GIT versus TST 5mm