Cost-effectiveness of a novel lipoarabinomannan test for tuberculosis in patients with HIV

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Summary: Testing hospitalized patients with HIV in South Africa and Malawi for tuberculosis by the novel FujiLAM urine assay is likely to increase life expectancy and be cost-effective. These results can inform decisions about implementing FujiLAM testing.

ABSTRACT

Background: A novel urine lipoarabinomannan assay (FujiLAM) has higher sensitivity and higher cost than the first-generation AlereLAM assay. We evaluated the cost-effectiveness of FujiLAM for tuberculosis testing among hospitalized people with HIV irrespective of symptoms.

Methods: We used a microsimulation model to project clinical and economic outcomes of three testing strategies: 1) sputum Xpert MTB/RIF (*Xpert*); 2) sputum Xpert plus urine AlereLAM (*Xpert+AlereLAM)*; 3) sputum Xpert plus urine FujiLAM (*Xpert+FujiLAM)*. The modelled cohort matched that of a two-country clinical trial. We applied diagnostic yields from a retrospective study (yields for *Xpert*/*Xpert+AlereLAM*/*Xpert+FujiLAM* among those with CD4<200/μL: 33%/62%/70%; among those with CD4≥200/μL: 33%/35%/47%). Costs of Xpert/AlereLAM/FujiLAM were USD15/3/6 (South Africa) and USD25/3/6 (Malawi). *Xpert+FujiLAM* was considered cost-effective if its incremental cost-effectiveness ratio (USD/year-of-life saved) was <$940 (South Africa) and <$750 (Malawi). We varied key parameters in sensitivity analysis and performed a budget impact analysis of implementing FujiLAM countrywide.

Results: Compared with *Xpert+AlereLAM*, *Xpert+FujiLAM* increased life expectancy by 0.2 years for those tested in South Africa and Malawi. *Xpert+FujiLAM* was cost-effective in both countries. *Xpert+FujiLAM* for all patients remained cost-effective compared with sequential testing and CD4-stratified testing strategies. FujiLAM use added 3.5% (South Africa) and 4.7% (Malawi) to five-year healthcare costs of tested patients, primarily reflecting ongoing HIV treatment costs among survivors.

Conclusions: FujiLAM with Xpert for tuberculosis testing in hospitalized people with HIV is likely to increase life expectancy and be cost-effective at the currently anticipated price in South Africa and Malawi. Additional studies should evaluate FujiLAM in clinical practice settings.

Keywords: tuberculosis, HIV, diagnosis, lipoarabinomannan, cost-effectiveness

INTRODUCTION

Tuberculosis (TB) is the leading cause of death of people with HIV (PWH) worldwide [1]. In sub-Saharan Africa, TB accounts for approximately 40% of hospital deaths among PWH, and half of these are undiagnosed before death [2,3]. Sputum-based diagnostics, the current standard, suffer from the inability of some patients to produce sputum, the low sensitivity of smear, and the cost of molecular diagnostics. Moreover, extrapulmonary TB may be missed by sputum-based testing.

Urine-based assays for lipoarabinomannan (LAM) are a promising TB testing approach. Testing hospitalized PWH using a first-generation LAM lateral flow assay (Determine TB-LAM®; Alere; hereupon called AlereLAM) increases TB diagnostic yield and, in some subgroups, reduces mortality [4,5]. However, AlereLAM's limited sensitivity hinders more widespread clinical benefit.

The next-generation Fujifilm SILVAMP TB-LAM assay (FujiLAM) offers higher sensitivity than AlereLAM for TB detection [6–8]. A study using biobanked urine from hospitalized PWH in South Africa found FujiLAM's sensitivity against a microbiologic reference standard to be 70%, compared with 42% for AlereLAM [6]. Specificity for both assays was over 90%. Although both can provide a result in under one hour without additional instrumentation, FujiLAM involves additional steps, time, and cost compared with AlereLAM [6].

Weighing additional TB detections and potential prevented deaths against additional costs is critical in deciding whether to implement FujiLAM in resource-limited settings. We therefore performed a cost-effectiveness analysis of urine FujiLAM added to sputum Xpert for TB testing among hospitalized PWH in South Africa and Malawi.

METHODS

Analytic Overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model, a validated microsimulation of HIV- and TB-related disease and treatment [9–11]. The population of interest was adults with HIV, regardless of CD4 count or symptoms, hospitalized in medical units. We compared three TB testing strategies: 1) sputum Xpert alone (*Xpert*); 2) sputum Xpert and urine AlereLAM (*Xpert+AlereLAM*); 3) sputum Xpert and urine FujiLAM (*Xpert+FujiLAM*). To attain stable per-person results, we modelled cohorts of one million hospitalized PWH separately in South Africa and Malawi. We based our modelled population on participants in the Rapid Urine-based Screening for Tuberculosis to Reduce AIDS-related Mortality in Hospitalized Patients in Africa (STAMP) trial in South Africa and Malawi, in which hospitalized PWH, irrespective of CD4 count or symptoms, were tested for TB by either sputum Xpert or sputum Xpert plus urine Xpert plus urine AlereLAM [5,12]. While the STAMP trial represented our target population, it did not include FujiLAM. Therefore, we based performance characteristics of all diagnostic assays on a study that used biobanked specimens from hospitalized PWH in South Africa [6].

Model outcomes included mortality, life expectancy, and TB- and HIV-related costs from the health system perspective. The primary outcome was the incremental cost-effectiveness ratio (ICER) – the difference in lifetime healthcare costs (2017 US dollars [USD]) divided by the difference in life expectancy – between testing strategies. A strategy was strongly dominated if it resulted in lower life expectancy than a less costly strategy. A strategy was weakly dominated if it resulted in a higher ICER than a strategy that provided higher life expectancy [13]. Because second-line antiretroviral therapy (ART) is relatively expensive but implemented and recommended in national HIV care guidelines in both South Africa and Malawi, we defined an ICER less than that of second-line ART as

cost-effective, i.e., offering good value (Supplement) [14–16]. These thresholds were USD940/year-of-life saved (YLS) in South Africa and USD750/YLS in Malawi [9].

Model Overview

In this analysis, simulated PWH enter the model upon TB testing and are tracked monthly until death. Initially, the model draws randomly from user-defined characteristics in each country, such as distributions of CD4 count and TB status [10]. The model tracks clinical outcomes and costs as each individual transitions through various "states" of TB and HIV disease and treatment. Details about the model, validation, and treatment parameters are in the Supplementary Text, Supplementary Figure 1, Supplementary Table 1, and at massgeneral.org/medicine/mpec/research/cpac-model.

Tuberculosis Diagnostics

In the model, TB can be diagnosed from a positive test result. After diagnosis, individuals start treatment for drug-susceptible or multidrug-resistant TB (Supplement). In case of only negative microbiological tests, empiric treatment can be initiated according to patterns in local practice or in studies.

Input Parameters

Tuberculosis Diagnostics

We characterized the simulated population using STAMP trial data [5] (Table 1). Diagnostic data came from a cohort of hospitalized PWH, all of whom were tested for TB regardless of CD4 count or symptoms [6,17]. We used CD4-stratified (<200/μL or ≥200/μL) diagnostic performance data that were not included in the published report (Table 1).

For performance characteristics of each testing strategy (*Xpert*, *Xpert+AlereLAM*, and *Xpert+FujiLAM*) in the model, we applied diagnostic yields, calculated as: the number of subjects who had a correct positive TB result by at least one test in the strategy, divided by the number of subjects diagnosed with TB by the composite reference standard, all from Broger et al. (Supplement) [6]. The diagnostic yield accounted for the number of subjects able to provide a specimen and the incremental diagnostic yield of the LAM tests over sputum Xpert (i.e., the additional cases detected by LAM that were not diagnosed by sputum Xpert, Supplement). We assumed 50% of individuals would provide a sputum specimen (Supplement). The diagnostic yields applied in our base case analysis were, for CD4/μL <200/≥200: *Xpert*, 33%/33%; *Xpert+AlereLAM*, 62%/35%; *Xpert+FujiLAM*, 70%/47% (Table 1 and Supplement). We applied specificity of Xpert from a meta-analysis and specificity of AlereLAM and FujiLAM from Broger et al. [6,18].

Costs

In South Africa/Malawi, sputum Xpert costs were USD15/25 and urine AlereLAM costs were USD3/3 [9,19–21]. Though the price of urine FujiLAM has not yet been established, we used in the base case a best estimate of the anticipated cost, USD6, which is also in line with the World Health Organization's (WHO) target product profile [22]. We varied this cost from USD3 to USD20 in sensitivity analysis. We included additional TB and HIV care costs (Supplement).

Uncertainty Analysis

Deterministic Sensitivity Analysis

We performed one-way and multi-way deterministic sensitivity analysis by varying key parameters across ranges (Table 1). When varying FujiLAM sensitivity, we accounted for its impact on the diagnostic yield of *Xpert+FujiLAM* (Supplement).

Probabilistic Sensitivity Analysis

In a probabilistic sensitivity analysis, we simultaneously varied several parameters across beta distributions to understand how results would vary in other settings or scenarios (Supplement). These parameters were TB prevalence, sputum provision, empiric TB treatment, loss to follow-up from TB care, and death from untreated TB. We used the results to generate a cost-effectiveness acceptability curve.

Alternative Testing Strategies

We evaluated alternative TB testing strategies, including: solo strategies (Xpert, AlereLAM, or FujiLAM alone); sequential strategies (whereby a urine LAM test is done and, if positive, is followed by sputum Xpert for rifampicin-resistance testing); and CD4-stratified strategies (sputum Xpert plus urine LAM for those with CD4<200/μL; sputum Xpert alone for those with CD4≥200/μL). We compared the outcomes of these strategies to those of the three strategies of the base case, generating a cost-effectiveness frontier; strategies that lie on the frontier are economically efficient. We also evaluated a scenario in which Xpert Ultra was substituted for Xpert in each of the three base case strategies, offering higher sensitivity and lower specificity at similar cost to Xpert (Table 1 and Supplement) [23].

Budget Impact Analysis

We conducted a budget impact analysis of performing *Xpert+FujiLAM* instead of *Xpert* countrywide among all hospitalized PWH over one year and five years, assuming 500,000 and 70,000 annual hospitalizations among PWH in South Africa and Malawi (Supplement) [9]. We considered FujiLAM per-test cost of either USD6 or USD20.

RESULTS

Base Case

LAM strategies increased the number of positive TB results (Supplementary Table 2). In the base case analysis in South Africa and Malawi, *Xpert+AlereLAM* and *Xpert+FujiLAM* both reduced two-year mortality and increased life expectancy compared with *Xpert* (Table 2). Undiscounted life expectancy with *Xpert*/*Xpert+AlereLAM*/*Xpert+FujiLAM* was 13.2/13.7/13.9 years in South Africa and 12.7/13.1/13.3 years in Malawi. Regarding cost-effectiveness, *Xpert+AlereLAM* was weakly dominated by the more effective *Xpert+FujiLAM*. In both countries, *Xpert+FujiLAM* was cost-effective compared with *Xpert*, with ICER USD830/YLS in South Africa and USD440/YLS in Malawi (Table 2).

Sensitivity and Uncertainty Analysis

When varying key parameters in one-way sensitivity analysis, *Xpert+AlereLAM* was weakly dominated by *Xpert+FujiLAM* in most analyses in South Africa and Malawi (Supplementary Table 3). *Xpert+FujiLAM* remained cost-effective compared with *Xpert* in all these analyses except in South Africa when *Xpert+FujiLAM* yield was decreased by 20 percentage points (i.e., <50%/<27% for low/high CD4).

In multi-way deterministic sensitivity analyses in which we varied TB prevalence, sputum provision, and empiric TB treatment probability, *Xpert+FujiLAM* was cost-effective compared with *Xpert* in South Africa except when both TB prevalence was relatively low (15%) and sputum provision probability was high (90%); *Xpert+FujiLAM* was cost-effective compared with *Xpert* in Malawi in all scenarios (Supplementary Figure 2). In a two-way sensitivity analysis where FujiLAM sensitivity and FujiLAM cost were varied, *Xpert+FujiLAM* remained cost-effective compared with *Xpert* in South Africa and Malawi except when FujiLAM had both relatively low sensitivity (≤42%) and higher cost (≥USD10/test) (Figure 1).

In the probabilistic sensitivity analysis, there was a >95% probability that *Xpert+FujiLAM* offered the highest net monetary benefit when willingness-to-pay was >USD930/YLS in South Africa and >USD460/YLS in Malawi (Supplementary Figure 3).

Alternative Testing Strategies

Most solo, sequential, and CD4-stratified testing strategies were dominated by *Xpert+FujiLAM* (Supplementary Table 4). In South Africa, only *AlereLAM alone*, *Xpert alone*, and *Xpert+FujiLAM* were on the cost-effectiveness efficiency frontier (strategies below the frontier are dominated, Figure 2A). In Malawi, only *AlereLAM alone*, *FujiLAM alone*, and *Xpert+FujiLAM* were on the efficiency frontier (Figure 2B). Strategies that added LAM testing to Xpert provided notable gains in life expectancy at modest additional cost compared with *Xpert alone*, the more established strategy. *Xpert+FujiLAM* provided the most life-years in both countries. Strategies that included Xpert Ultra instead of Xpert reduced 2-year mortality modestly (<0.8%); cost-effectiveness results were similar to those of the base case (Supplementary Table 5).

Budget Impact Analysis

Over five years, testing all hospitalized PWH for TB with *Xpert+FujiLAM* instead of *Xpert* saved approximately 172,200 and 26,700 years of life in South Africa and Malawi. When FujiLAM per-test cost was USD6, *Xpert+FujiLAM* increased cumulative healthcare expenditures among tested individuals by approximately USD336million (3.5%) in South Africa and USD17 million (4.7%) in Malawi over five years, compared with *Xpert* (Figure 3). The largest contributors to the increase were non-TB, non-ART HIV care costs (70%/40% of increase in South Africa/Malawi). When excluding HIV care costs, *Xpert+FujiLAM* compared with *Xpert* increased five-year TB healthcare expenditures among tested individuals by approximately USD56 million (46%) in South Africa and USD7 million (40%) in Malawi. FujiLAM itself, at USD6 per test, contributed USD15 million (South Africa) and USD2 million (Malawi) to these additional costs. When FujiLAM per-test cost was USD20, the increases in cumulative healthcare expenditures for both TB and HIV care were USD370 million (3.9%) in South Africa and USD22 million (6.1%) in Malawi. One-year budget impact results are in the Supplementary Text and Supplementary Figure 4.

DISCUSSION

In our model-based analysis, we found that testing hospitalized PWH for TB with sputum Xpert and urine FujiLAM together decreased mortality, increased life expectancy by 0.6-0.7 years, and was cost-effective compared with sputum Xpert testing alone in South Africa and Malawi. A testing strategy of Xpert plus FujiLAM outperformed and economically dominated an Xpert plus AlereLAM strategy. The results remained robust in sensitivity analysis in which key parameters were varied to reflect other possible settings and scenarios. A novel aspect of this analysis was our comparison of clinically-relevant parallel, solo, sequential, and CD4-stratified testing strategies – Xpert plus FujiLAM for all remained cost-effective.

In 2019, WHO expanded its recommendations for AlereLAM use for TB diagnosis – for inpatient PWH, WHO strongly recommends AlereLAM for those with signs and symptoms of TB, those with advanced HIV disease or who are seriously ill, and those with CD4 count <200/µL irrespective of signs and symptoms [24]. With its improved sensitivity, FujiLAM might be considered for broader use [6–8]. However, prospective studies to demonstrate feasibility, clinical outcomes, and cost in clinical practice settings will be important, as FujiLAM compared with AlereLAM requires additional steps (silver amplification) and time (50-60 minutes versus 25 minutes, including incubation) [6]. While we attempted to capture these operational factors by increasing the cost of FujiLAM, they are challenging to account for in cost-effectiveness analysis. Operational variability could influence FujiLAM accuracy and uptake but is unlikely to prolong time to treatment initiation after a positive result.

The per-test price of FujiLAM has not been finalized, and there are no published microcosting estimates of FujiLAM in practice. A preliminary cost has been estimated at USD6 per test, in line with WHO's target for a new TB diagnostic [22]. Our sensitivity analysis showed that, even at a higher per-test cost, a testing strategy combining FujiLAM with sputum Xpert would be cost-effective compared with Xpert alone. Increasing the FujiLAM cost has little influence on the ICER – indeed, most incremental costs of FujiLAM strategies reflect years of HIV care for individuals who otherwise would die of undiagnosed TB.

However, FujiLAM cost has a greater influence in the budget impact analysis, which accounts for the total number of people who would be tested. Though we did not fully account for the operational factors associated with implementation and scale-up of FujiLAM testing or for the logistics of

increasing TB treatment capacity, our budget impact analysis of FujiLAM at a cost of USD20 per test indirectly reflects some of these factors by incorporating operational costs into the test cost. We show that adding FujiLAM would contribute a relatively small amount to the total healthcare costs for this patient population, and that much of the increase in costs is due to downstream positive effects of longer survival and not due to the test itself. Nonetheless, when considered in the isolated context of a TB control program, adding FujiLAM would consume a greater proportion of the program's budget. Overall, FujiLAM offers clinical benefit and good value based on the ICER, but affordability must be considered in the context of budget and other resource constraints and the full costs of implementation.

There is no consensus on appropriate cost-effectiveness thresholds in a given country [16]. As in a prior study, we used as our cost-effectiveness threshold the ICER of second-line ART, which is recommended for care by national guidelines in both South Africa and Malawi [9,14,15]. Alternative thresholds could affect interpretations of cost-effectiveness but would not change the model-generated ICER results.

Urine LAM assays are more sensitive in those with low CD4 compared with high CD4 counts [6]. Nonetheless, our analysis of CD4-stratified testing strategies showed that adding FujiLAM testing for all patients, rather than only for those with CD4<200/μL, would provide greater clinical benefit and be cost-effective. As CD4 testing for the diagnostic algorithm would add time delay, cost, and complexity (and it is being phased out in many settings), performing FujiLAM for all hospitalized PWH rather than only for those with low CD4 counts offers practical advantages.

We previously conducted a cost-effectiveness analysis of the STAMP trial, finding that adding AlereLAM to Xpert was cost-effective compared with Xpert alone [9]. In the present study, *Xpert+AlereLAM* remained cost-effective compared with *Xpert*, but *Xpert+FujiLAM* was cost-effective compared with *Xpert* and *Xpert+AlereLAM* and yielded higher life expectancy than those strategies. Compared with the prior study's results, we project fewer life-years in South Africa and a smaller difference in life-years between testing strategies in Malawi. These discrepancies are due to differences in diagnostic yields and other model parameters between the two studies. In our previous study, we applied parameters directly from the STAMP trial in which there were differences between South Africa and Malawi, including a much higher probability of sputum provision (75% versus 39%), higher probability of empiric treatment (10% versus 4%), and lower incremental diagnostic yield of AlereLAM (approximately 19% versus 52%) in South Africa compared with Malawi [5]. We assumed here that sputum provision probability, empiric treatment probability, and diagnostic yield would be similar in the two countries. Despite modest changes in these assumptions, both studies showed that adding LAM to Xpert would be cost-effective, and our sensitivity analyses in this study (which included the base case values from the STAMP cost-effectiveness analysis) provide insight into results when parameters differ by country. Additional testing of urine by Xpert, as in the STAMP trial, could be considered. However, urine Xpert had only limited additional diagnostic yield above urine AlereLAM and sputum Xpert in STAMP, and it had disadvantages of requiring centrifugation and costing more than AlereLAM [5,9]. Xpert Ultra may offer greater yield.

Like all model-based analyses, our study has limitations. We applied diagnostic yields from a retrospective study (with the attendant potential biases) that included all assays of interest, except for applying a base case sputum provision probability of 50% [5,6,17,25,26]. We chose this retrospective study because it included helpful details about the additional diagnostic yields of

AlereLAM and FujiLAM above sputum Xpert alone [6]. Our analysis accounted for false-positive test results in terms of costs of unnecessary TB treatment and of managing treatment toxicities but did not account for potential mortality from misdiagnosis and unnecessary treatment, which could temper the enthusiasm for more widespread implementation (though, because of an imperfect reference standard, some "false-positives" may be true-positives). Lacking data, we did not account for TB transmission, thus potentially underestimating population-level benefits of LAM testing in detecting TB, prompting treatment, and decreasing transmission. Finally, we adopted a health system perspective for costs and did not include patient costs, non-health system costs, or economic gains from improved survival.

In conclusion, our model-based analysis found that adding urine FujiLAM to sputum Xpert for TB testing among unselected hospitalized PWH in South Africa and Malawi would increase life expectancy and be cost-effective. Though additional feasibility studies of FujiLAM are needed in clinical practice settings, the rapidity of the test procedure and its improved sensitivity over an earlier-generation LAM assay suggest that it would reduce deaths among hospitalized PWH in TB-endemic settings while offering good value when its cost is in line with WHO targets.

NOTES

Authors' Contributions:

KPR, CMD, TB, and RPW conceived the study. KPR, NCM, KAF, and RPW developed the model structure and designed the cost-effectiveness analysis. KPR, NCM, PPP, FMS, CRH, and RW developed model input parameters. CMD, TB, AGW, ADK, KLF, MPN, and GM collected and analyzed primary trial data for use in the model. KPR and NCM implemented the model and analyzed the data. KPR wrote the first manuscript draft. All authors contributed to the study design and interpretation of the results, revised the manuscript for important intellectual content, and approved the final version.

DISCLAIMER

The funding sources had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript, or in the decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the Massachusetts General Hospital Executive Committee on Research, or other funders.

FUNDING

This work was supported by awards from the National Institute of Allergy and Infectious Diseases [grant numbers R37 AI093269, R37 AI058736] of the National Institutes of Health; Massachusetts General Hospital [Steve and Deborah Gorlin Research Scholars Award to RPW]; and the Joint Global Health Trials Scheme of the UK Department of Health and Social Care, the Department for International Development, the Global Challenges Research Fund, the Medical Research Council, and

Wellcome Trust [grant number MR/M007375/1], a UK funded award that is part of the EDCTP2 programme supported by the European Union. CRH is also supported by the Providence/Boston Center for AIDS Research [grant number P30 AI042853 from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health] and the Boston University/Rutgers Tuberculosis Research Unit [grant number U19 AI111276 from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health]. GM was supported by the Wellcome Trust [grant numbers 098316, 203135/Z/16/Z], the South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation (NRF) of South Africa [grant number 64787], NRF incentive funding [UID: 85858], and the South African Medical Research Council through its TB and HIV Collaborating Centres Programme with funds received from the National Department of Health [RFA# SAMRC-RFA-CC: TB/HIV/AIDS-01-2014]. MPN reports grants from the Foundation for Innovative New Diagnostics during the conduct of the study. KLF reports grants from Global Health Trials (MRC/DFID/WT) during the conduct of the study. CMD reports working for FIND until April 2019. FIND is a non-for-profit foundation, whose mission is to find diagnostic solutions to overcome diseases of poverty in LMICs. It works closely with the private and public sectors and receives funding from some of its industry partners. It has organizational firewalls to protect it against any undue influences in its work or the publication of its findings. All industry partnerships are subject to review by an independent Scientific Advisory Committee or another independent review body, based on due diligence, TTPs and public sector requirements. FIND catalyzes product development, leads evaluations, takes positions, and accelerates access to tools identified as serving its mission. It provides indirect support to industry (e.g., access to open specimen banks, a clinical trial platform, technical support, expertise, laboratory capacity strengthening in LMICs, etc.) to facilitate the development and use of products in these areas. FIND also supports the evaluation of prioritized assays and the early stages of implementation of WHO-approved (guidance & PQ) assays using donor grants. In order to carry out test validations and evaluations, has product evaluation agreements with several private sector companies for the

diseases FIND works in which strictly define its independence and neutrality vis-a-vis the companies whose products get evaluated, and describes roles and responsibilities. Additionally, CMD reports grants for the development and evaluation of FujiLAM (Not directly for this modelling work) from UK Department for International Development, German Federal Ministry of Education and Research (BMBF) through KfW, Dutch Ministry of Foreign Affairs, Australian Department of Foreign Affairs and Trade, and Global Health Innovative Technology, during the conduct of the study. TB reports a patent pending (WO/2019/186486), as only inventor, now with ownership/commercial rights.

REFERENCES

1. UNAIDS. Tuberculosis. Available at: https://www.unaids.org/en/topic/tuberculosis. Accessed 28 April 2020.

2. Cohen T, Murray M, Wallengren K, Alvarez GG, Samuel EY, Wilson D. The prevalence and drug sensitivity of tuberculosis among patients dying in hospital in KwaZulu-Natal, South Africa: a postmortem study. PLoS Med **2010**; 7:e1000296.

3. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS **2015**; 29:1987–2002.

4. Peter JG, Zijenah LS, Chanda D, et al. Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. Lancet **2016**; 387:1187–1197.

5. Gupta-Wright A, Corbett EL, van Oosterhout JJ, et al. Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial. Lancet **2018**; 392:292–301.

6. Broger T, Sossen B, du Toit E, et al. Novel lipoarabinomannan point-of-care tuberculosis test for people with HIV: a diagnostic accuracy study. Lancet Infect Dis **2019**; 19:852–861.

7. Kerkhoff AD, Sossen B, Schutz C, et al. Diagnostic sensitivity of SILVAMP TB-LAM (FujiLAM) point-of-care urine assay for extra-pulmonary tuberculosis in people living with HIV. Eur Respir J **2020**; 55:1901259.

8. Bjerrum S, Broger T, Székely R, et al. Diagnostic accuracy of a novel and rapid lipoarabinomannan test for diagnosing tuberculosis among people living with HIV. Open Forum Infect Dis **2019**; 7:ofz530.

9. Reddy KP, Gupta-Wright A, Fielding KL, et al. Cost-effectiveness of urine-based tuberculosis screening in hospitalised patients with HIV in Africa: a microsimulation modelling study. Lancet Glob Health **2019**; 7:e200–e208.

10. Walensky RP, Ross EL, Kumarasamy N, et al. Cost-effectiveness of HIV treatment as prevention in serodiscordant couples. N Engl J Med **2013**; 369:1715–1725.

11. Reddy KP, Horsburgh CR, Wood R, et al. Shortened tuberculosis treatment for people with HIV in South Africa: a model-based evaluation and cost-effectiveness analysis. Ann Am Thorac Soc **2020**; 17:202–211.

12. Gupta-Wright A, Fielding KL, van Oosterhout JJ, et al. Rapid urine-based screening for tuberculosis to reduce AIDS-related mortality in hospitalized patients in Africa (the STAMP trial): study protocol for a randomised controlled trial. BMC Infect Dis **2016**; 16:501.

13. Siegel JE, Weinstein MC, Torrance GW. Reporting cost-effectiveness studies and results. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. Oxford, New York: Oxford University Press, 1996: 276–303.

14. Ministry of Health, Malawi. Malawi Guidelines for Clinical Management of HIV in Children and Adults. 2016; Available at: https://aidsfree.usaid.gov/sites/default/files/malawi_art_2016.pdf.

15. Meintjes G, Moorhouse MA, Carmona S, et al. Adult antiretroviral therapy guidelines 2017. South Afr J HIV Med **2017**; 18:776.

16. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. Bull World Health Organ **2015**; 93:118–124.

17. Lawn SD, Kerkhoff AD, Burton R, et al. Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort. BMC Med **2017**; 15:67.

18. Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev **2019**; 6:CD009593.

19. National Health Laboratory Service. Available at: http://www.nhls.ac.za/. Accessed 28 April 2020.

20. Maheswaran H, Petrou S, Cohen D, et al. Economic costs and health-related quality of life outcomes of hospitalised patients with high HIV prevalence: a prospective hospital cohort study in Malawi. PLoS One **2018**; 13:e0192991.

21. Sun D, Dorman S, Shah M, et al. Cost utility of lateral-flow urine lipoarabinomannan for tuberculosis diagnosis in HIV-infected African adults. Int J Tuberc Lung Dis **2013**; 17:552–558.

22. Denkinger CM, Kik SV, Cirillo DM, et al. Defining the needs for next generation assays for tuberculosis. J Infect Dis **2015**; 211 Suppl 2:S29-38.

23. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. Lancet Infect Dis **2018**; 18:76–84.

24. World Health Organization. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV. 2019. Available at: http://www.who.int/tb/publications/2019/LAMPolicyUpdate2019/en/. Accessed 28 April 2020.

25. Boyles TH, Griesel R, Stewart A, Mendelson M, Maartens G. Incremental yield and cost of urine Determine TB-LAM and sputum induction in seriously ill adults with HIV. Int J Infect Dis **2018**; 75:67–73.

26. Huerga H, Ferlazzo G, Bevilacqua P, et al. Incremental yield of including Determine-TB LAM assay in diagnostic algorithms for hospitalized and ambulatory HIV-positive patients in Kenya. PLoS One **2017**; 12:e0170976.

27. Ford N, Matteelli A, Shubber Z, et al. TB as a cause of hospitalization and in-hospital mortality among people living with HIV worldwide: a systematic review and meta-analysis. J Int AIDS Soc **2016**; 19:20714.

28. Kerkhoff AD, Barr DA, Schutz C, et al. Disseminated tuberculosis among hospitalised HIV patients in South Africa: a common condition that can be rapidly diagnosed using urine-based assays. Sci Rep **2017**; 7:10931.

29. Abouyannis M, Dacombe R, Dambe I, et al. Drug resistance of Mycobacterium tuberculosis in Malawi: a cross-sectional survey. Bull World Health Organ **2014**; 92:798–806.

30. Katagira W, Walter ND, den Boon S, et al. Empiric TB treatment of severely ill patients with HIV and presumed pulmonary TB improves survival. J Acquir Immune Defic Syndr **2016**; 72:297–303.

31. Claassens MM, du Toit E, Dunbar R, et al. Tuberculosis patients in primary care do not start treatment. What role do health system delays play? Int J Tuberc Lung Dis **2013**; 17:603–607.

32. Pepper DJ, Marais S, Bhaijee F, Wilkinson RJ, De Azevedo V, Meintjes G. Assessment at antiretroviral clinics during TB treatment reduces loss to follow-up among HIV-infected patients. PLoS One **2012**; 7:e37634.

33. Lawn SD, Kranzer K, Edwards DJ, McNally M, Bekker L-G, Wood R. Tuberculosis during the first year of antiretroviral therapy in a South African cohort using an intensive pretreatment screening strategy. AIDS **2010**; 24:1323–1328.

34. Andrews JR, Lawn SD, Rusu C, et al. The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy: a model-based analysis. AIDS **2012**; 26:987–995.

35. Holmes CB, Wood R, Badri M, et al. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. J Acquir Immune Defic Syndr **2006**; 42:464–469.

36. Losina E, Yazdanpanah Y, Deuffic-Burban S, et al. The independent effect of highly active antiretroviral therapy on severe opportunistic disease incidence and mortality in HIV-infected adults in Côte d'Ivoire. Antivir Ther **2007**; 12:543–551.

37. Pooran A, Pieterson E, Davids M, Theron G, Dheda K. What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa? PLoS One **2013**; 8:e54587.

38. Clinton Health Access Initiative. 2016 Antiretroviral (ARV) CHAI Reference Price List. Available at: https://clintonhealthaccess.org/wp-content/uploads/2016/11/2016-CHAI-ARV-Reference-Price-List_FINAL.pdf. Accessed 28 April 2020.

39. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA **2016**; 316:1093–1103.

40. Cantor SB. Cost-effectiveness analysis, extended dominance, and ethics: a quantitative assessment. Med Decis Making **1994**; 14:259–265.

Table 1. Model input parameters.

Cohort characteristics	South Africa	Malawi	Deterministic sensitivity analysis range	References
Age, years, median [IQR]	37 [30-46]	38 [32-47]		[5]
Men/women, %	50/50	37/63		[5]
CD4 count at admission, cells/μL, median [IQR]	236 [70-445]	219 [86-431]		[5]
TB prevalence, %[a]	29	24	15-45[b]	[5,9,27,28]
MDR-TB prevalence among those with TB, %	3	1	1-7 (South Africa); 0.5-5 (Malawi)	[5,29]
Patients able to provide sputum, %	50	50	30-90[b]	Assumption / [5,6,25]
Probability of empiric treatment, *Xpert*, %[c]	11	11	0-20[b]	[5,30]
Probability of empiric treatment, *Xpert+AlereLAM* and *Xpert+FujiLAM*, %	10	10	0-20[b]	[5,6]
Loss to follow-up from TB care after hospital discharge, %/month	3.6	3.6	50%-200% of base case value[b]	[31,32]
Mortality				
Death from untreated TB, monthly probability	0.086	0.086	25%-200% of base case value[b]	[33,34]
Death from AIDS (besides TB), CD4-dependent, monthly probability	$6.2x10^{-5}$-0.2	$6.2x10^{-5}$-0.2		[35,36]
Cost of treatment[d]				
DS-TB treatment cost, monthly (6-month duration), USD	$7	$7		[37]
MDR-TB treatment cost, monthly (24-month duration), USD	$231	$231		[37]
First-line ART costs (TDF/3TC/EFV), monthly, USD	$11	$11	50-75% of base case value	[38]
Cost of TB diagnostic assay, per-test (USD)				
Sputum Xpert[e]	$15	$25		[19,20]
Urine AlereLAM	$3	$3		[21]
Urine FujiLAM	$6	$6	$3-20	Estimate

Table 1, continued.

Performance characteristics of diagnostic assays and strategies				
Diagnostic assay[f]	**Sensitivity**	**Specificity**	**Deterministic sensitivity analysis range**	**References**
Sputum Xpert, CD4<200/µL / ≥200/µL	65% / 65%	98% / 98%		[6], Assumption
Urine AlereLAM CD4<200/µL / ≥200/µL	48% / 2%	97% / 99%		[6], Assumption
Urine FujiLAM, CD4<200/µL / ≥200/µL	62% / 23%	94% / 98%	Sensitivity: 48%/8% to 77%/38% Specificity: 75%-90%	[6], Assumption
Xpert Ultra, CD4<200/µL / ≥200/µL	77% / 77%	96% / 96%		[23]
Diagnostic strategy[f]	**Diagnostic yield**			
Xpert, CD4<200/µL / ≥200/µL	33%/33%			[6], Assumption
Xpert+AlereLAM, CD4<200/µL / ≥200/µL	62%/35%		-20% to +20% of base case value	[6], Assumption
Xpert+FujiLAM, CD4<200/µL / ≥200/µL	70%/47%		-20% to +20% of base case value	[6], Assumption

Abbreviations: IQR, interquartile range; TB, tuberculosis; MDR, multidrug-resistant; DS, drug-susceptible; USD, United States dollars (2017); TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; LAM, lipoarabinomannan.

[a]TB prevalence is the true prevalence among the simulated group of hospitalized patients with HIV.

[b]These parameters were also examined in probabilistic sensitivity analysis using beta distributions (Supplement).

[c]Those who were diagnosed clinically without microbiologic confirmation were empirically treated in the first month of model simulation.

[d]We assumed that costs of TB drugs and ART drugs were equal across countries because they are imported across countries. Costs shown here are for drugs only.

[e]Xpert cost in a Malawi-specific costing study was higher than the cost reported in South African studies and by the South Africa National Health Laboratory Service [19]. This is due to factors such as different costs of maintenance and repair and different economies of scale.

[f]The indicated sensitivity of each assay is the sensitivity among those who provided a specimen and is independent of other test results. Italics reflect a diagnostic strategy rather than a single test. The diagnostic strategy yields applied in the model accounted for non-provision of sputum specimens and for concordance between test results – e.g., adding FujiLAM would increase diagnostic yield only if FujiLAM detected additional TB cases not detected by Xpert. In multi-test strategies, we applied the lowest specificity of any individual test.

Table 2. Base case model clinical, cost, and cost-effectiveness results.

South Africa				
Testing strategy	**Mortality at 2 years, %**	**Life-years, discounted[a] (undiscounted)**	**Cost, USD, Discounted[a,b]**	**ICER, USD/YLS[c]**
Xpert	35.8	8.9 (13.2)	8,230	-
Xpert+AlereLAM	33.3	9.2 (13.7)	8,500	dominated[d]
Xpert+FujiLAM	32.1	9.4 (13.9)	8,640	830
Malawi				
Testing strategy	**Mortality at 2 years, %**	**Life-years, discounted[a] (undiscounted)**	**Cost, USD, Discounted[a,b]**	**ICER, USD/YLS[c]**
Xpert	38.9	8.5 (12.7)	3,540	-
Xpert+AlereLAM	37.2	8.8 (13.1)	3,640	dominated[d]
Xpert+FujiLAM	36.2	8.9 (13.3)	3,710	440

Abbreviations: USD, 2017 US dollars; ICER, incremental cost-effectiveness ratio; YLS, year-of-life saved.

[a]Discounted 3% per year [39].

[b]This reflects lifetime healthcare costs.

[c]The ICER is the difference between two strategies in discounted costs divided by the difference in discounted life-years. The displayed life-years and costs are rounded, but the ICER was calculated using non-rounded life-years and costs. We considered a strategy cost-effective if its ICER was less than USD940/YLS in South Africa and less than USD750/YLS in Malawi (the ICERs of second-line antiretroviral therapy in these countries).

[d]This indicates "weak dominance" [40]. The ICER of *Xpert+AlereLAM* versus *Xpert* was higher (less attractive) than the ICER of *Xpert+FujiLAM* versus *Xpert+AlereLAM*, indicating an inefficient use of resources.

FIGURE LEGENDS

Figure 1. Two-way sensitivity analysis of FujiLAM sensitivity and cost.

Abbreviation: USD, 2017 US dollars.

We varied FujiLAM sensitivity and FujiLAM per-test cost across ranges and compared the cost-effectiveness of *Xpert*, *Xpert+AlereLAM*, and *Xpert+FujiLAM*. The displayed sensitivities are weighted averages of the sensitivities among those with CD4 count <200/µL and ≥200/µL. The numbers in parentheses show the difference in sensitivity between FujiLAM and AlereLAM. In the green areas, *Xpert+FujiLAM* is cost-effective compared with both *Xpert* and *Xpert+AlereLAM*; it weakly dominates *Xpert+AlereLAM*, meaning that it is more effective and has a lower cost-effectiveness ratio than *Xpert+AlereLAM*. In the red hatched areas, *Xpert+FujiLAM* is not cost-effective compared with *Xpert*, but *Xpert+AlereLAM* is cost-effective compared with *Xpert*.

*In the base case in both countries, FujiLAM is 15% more sensitive than AlereLAM and costs USD3 more per test.

Figure 2. Cost-effectiveness frontier of alternative tuberculosis testing strategies in hospitalized people with HIV.

We projected the life-years and lifetime costs associated with solo (green), parallel (orange), sequential (blue), and CD4-stratified (purple) tuberculosis testing strategies in South Africa (A) and Malawi (B). A square represents a strategy of Xpert alone, triangles represent strategies that include AlereLAM, and

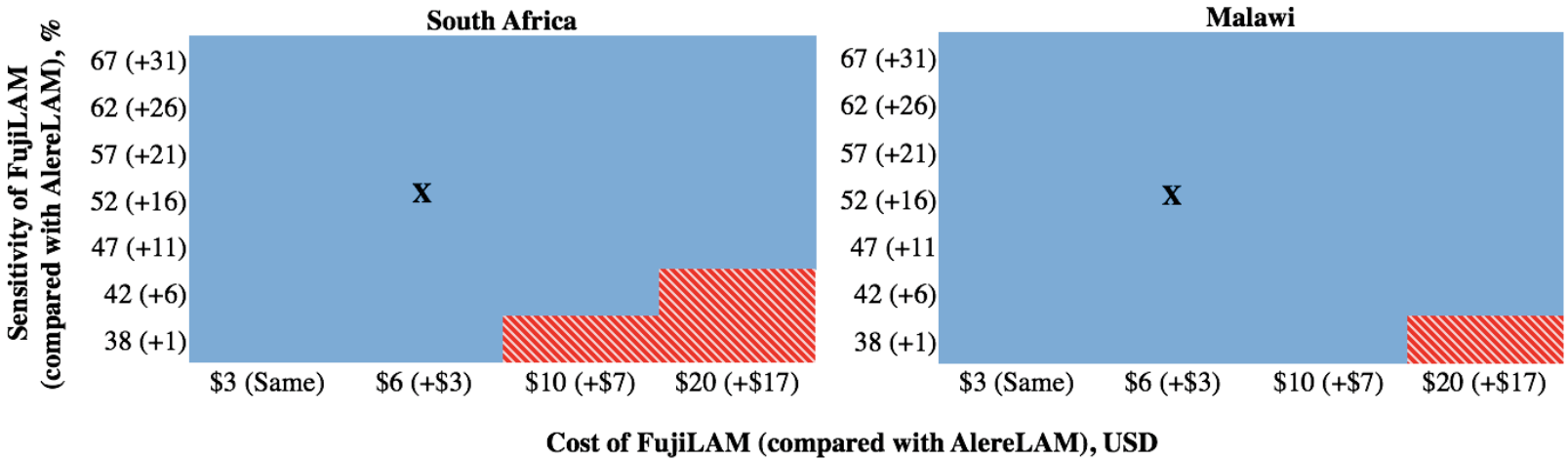
circles represent strategies that include FujiLAM. The testing strategies labelled on the cost-effectiveness frontier line are those that were not dominated. Other strategies, represented by symbols below the line, were dominated, reflecting an inefficient use of resources.

Figure 3. Budget impact analysis at five-year horizon: implementing FujiLAM testing countrywide in South Africa and Malawi among hospitalized patients with HIV.

Abbreviations: USD, 2017 US dollars; ART, antiretroviral therapy.

The vertical axis range is different between Panel A and Panel B. Budgetary projections are for the estimated 500,000 people with HIV who would be hospitalized each year in South Africa and 70,000 people with HIV who would be hospitalized each year in Malawi, all of whom would undergo tuberculosis testing. Within each panel, the left bar represents five-year cumulative healthcare costs among these people if *Xpert* was the tuberculosis testing strategy. The middle bar reflects the *Xpert+FujiLAM* testing strategy, with FujiLAM costing USD6 per test. The right bar reflects the *Xpert+FujiLAM* testing strategy, with FujiLAM costing USD20 per test.

Figure 1



Legend

***Xpert+FujiLAM* is cost-effective**

***Xpert+FujiLAM* is not cost-effective; *Xpert+AlereLAM* is cost-effective**

X **Base case**

Figure 2

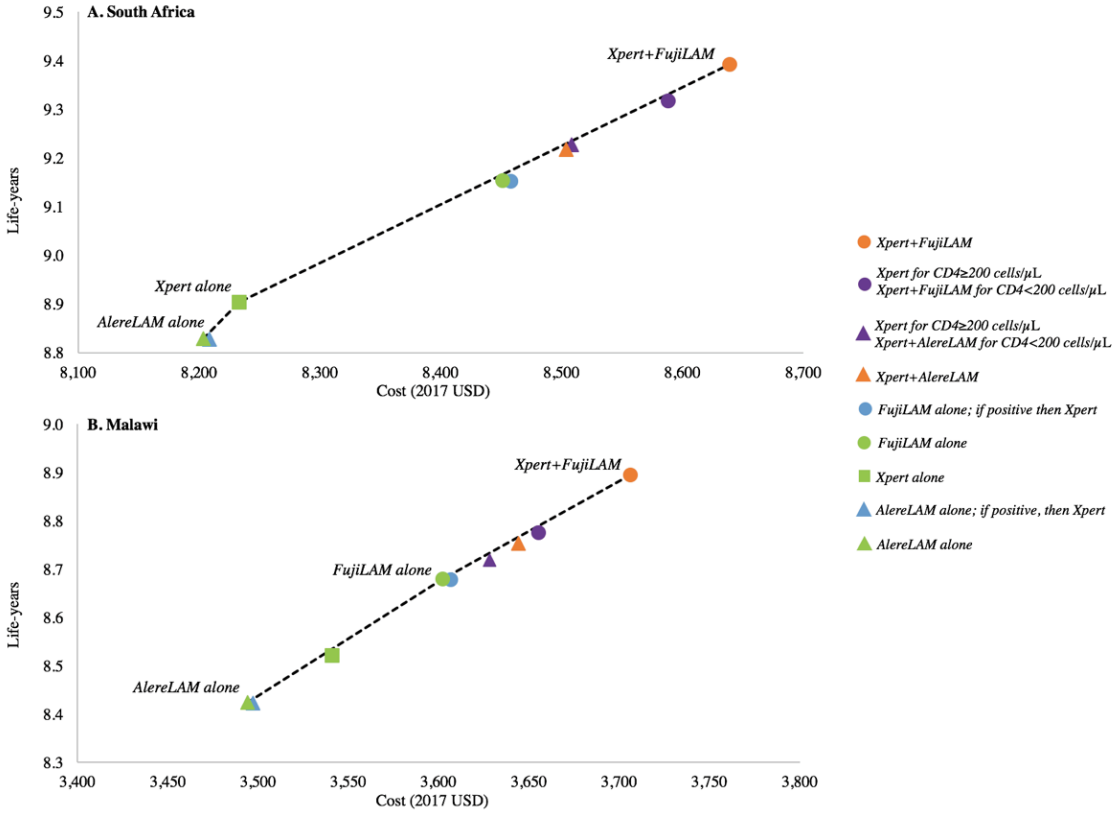


Figure 3