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Cost-Utility of Lateral-Flow Urine Lipoarabinomannan for Tuberculosis Diagnosis in HIV-infected African Adults

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Abstract

Setting—Inpatient hospitals in South Africa and Uganda

Objective—To evaluate the cost-effectiveness of a lateral flow urine lipoarabinomannan (LAM) test when added to existing strategies for tuberculosis (TB) diagnosis in HIV-infected adults ($CD4^+$ T-cell counts<100 cells/μL) with symptoms of active TB.

Design—Decision-analytic cost-utility model with the primary outcome being the incremental cost-effectiveness ratio (ICER), expressed in 2010 US dollars per disability-adjusted life year (DALY) averted, from the perspective of a public-sector TB control program.

Results and Conclusion—For every 1000 patients tested, adding lateral-flow urine LAM generated 80 incremental appropriate TB treatments and averted 224 DALYs. Estimated cost-utility was $353 per DALY averted (95% uncertainty range: $192–$1161) in South Africa and $86 per DALY averted (95% uncertainty range: $49–$239) in Uganda, reflecting the lower treatment costs in Uganda. Cost-utility was most sensitive to assay specificity, cost of TB treatment, life expectancy after TB cure, and cohort TB prevalence but did not rise above $1500 per DALY averted in South Africa under any one-way sensitivity analysis. The probability of acceptability was >99.8% at a per-DALY willingness-to-pay threshold equal to the per-capita gross domestic product in South Africa ($7275) and Uganda ($509).

INTRODUCTION

Tuberculosis (TB) is the leading cause of infectious death among people living with HIV/AIDS (PLWHA),[1,2] accounting for 26% of AIDS-related deaths worldwide.[3] Standard diagnostics for TB (e.g., chest X-ray, sputum smear microscopy) perform poorly in PLWHA, and many patients die prior to diagnosis.[4–6] Better TB diagnostic tests may substantially reduce mortality in PLWHA,[7] but they may also increase costs.[8–10] A newly developed lateral flow immunochromatographic assay (Determine TB-LAM Alere, Waltham, MA, USA) detects lipoarabinomannan (LAM)—an immunogenic glycolipid in the cell wall of *Mycobacterium tuberculosis*[11,12]—in urine, diagnosing TB with excellent

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specificity and higher sensitivity than sputum smear among highly immunocompromised adults.[13] This lateral-flow assay is the first true point-of-care diagnostic test for TB,[14,15] and although inexpensive, its specificity is imperfect and it is optimized for use only in individuals with high underlying mortality rates. Thus, its cost-effectiveness remains uncertain. We performed a cost-utility analysis of lateral-flow LAM detection using data from a cohort of severely immunocompromised HIV-infected individuals with symptoms of TB in a South African hospital.

METHODS

Study Data

We conducted a diagnostic accuracy study in South Africa and Uganda to determine the sensitivity and specificity of Determine TB-LAM.[16] We evaluated consenting HIV-infected adults (≥ 18 years) with clinical suspicion of TB based on any one or more of cough, fever, night sweats and weight loss. Individuals on TB treatment for more than 2 days during the prior 2 months were excluded. At enrollment, each participant underwent $CD4^+$ T-cell testing, chest radiograph, sputum smear microscopy (two sputa), culture of blood and sputum for mycobacteria, and urine collection. We performed lateral-flow LAM testing immediately after urine collection in accordance with the manufacturer's instructions. We defined sensitivity as the probability of a positive test (2+ or higher) among individuals who exhibited clinical improvement with empiric TB treatment or had a positive culture for *M. tuberculosis*. Using this case definition, specificity was markedly lower among individuals with $CD4^+$ T-cell counts <50 cells/μL, potentially representing occult TB. Thus, we measured specificity (test result negative or 1+) among individuals with $CD4^+$ T-cell counts of 50 or higher who had neither a positive culture nor clinical response to TB chemotherapy. We performed a retrospective modeling analysis using aggregate data from this study; the parent study was approved by the institutional review boards of the participating institutions, but ethical approval was not required for this model-based analysis.

Modeled Scenarios

Using data from the study above, we constructed a decision-analytic cost-utility model of lateral-flow urine LAM, as used for hospitalized adults with known HIV infection, $CD4^+$ T-cell count <100 cells/mm^3 (most patients in this setting have either a known or low CD4 count), and clinical suspicion of TB. We compared a reference scenario in which diagnosis is based on sputum smear, clinical judgment, and the existing array of available additional diagnostic tests, to an alternative scenario in which lateral-flow urine LAM detection is added to that array. We excluded the use of culture in this scenario as medical decisions must be made rapidly in these seriously ill patients. We assumed that the probabilities of positive results using existing diagnostics and urine LAM were independent, and that a positive result with either strategy would trigger treatment for TB. Among those testing negative with existing diagnostics (and LAM, in the intervention scenario), we assumed that a proportion of patients would be treated based on other test results and clinical judgment, and that this proportion was unchanged by the availability of urine LAM detection. We estimated the case-fatality rate of treated TB in this seriously ill population at 20%[17] and assumed untreated TB to be uniformly fatal within 1 month. We assumed a life expectancy of 5 years for survivors and patients without TB, based on cohort studies of African populations on antiretroviral therapy. Assuming differential mortality or life expectancy according to LAM positivity status did not change our results of incremental cost-effectiveness, as LAM neither benefitted nor harmed individuals testing negative in our analysis; thus, for parsimony, we assumed that LAM-negative individuals had the same outcomes as those for LAM-positive individuals reported in Table 1. Costs and effectiveness of antiretroviral therapy were not modeled. We assumed that neither the effectiveness of

urine LAM detection nor the cost of the lateral-flow assay would vary by country, but that the cost of TB treatment, as well as the willingness-to-pay, would be lower in Uganda. Model parameters are shown in Table 1.

Our primary outcome was the incremental cost-effectiveness ratio (ICER), measured from the perspective of the public-sector TB control program and reported in 2010 USD per disability-adjusted life year (DALY) averted. Patient costs were not assessed. We modeled the time horizon as the lifetime of the cohort, assuming that incremental costs would not accrue beyond the period of active TB treatment. Since all costs were reported in 2010 USD, inflation of costs was unnecessary. Future DALYs and costs were discounted at 3% per year.[18]

Sensitivity and Uncertainty Analysis

We performed one-way sensitivity analyses on all variables across reasonable ranges and three-way sensitivity analysis on the variables to which the primary outcome was most sensitive. When data on sensitivity ranges were not available from the literature, we varied parameters over a range of +/−15% of their base value, using wider ranges for parameters with greater uncertainty. Given that Xpert MTB/RIF, an automated molecular test for TB,[19] is being scaled up in South Africa (and, to a lesser extent, in Uganda), we also modeled a scenario in which smear was replaced by Xpert (sensitivity 85%, no change to specificity of the overall diagnostic algorithm) in both arms. To generate 95% uncertainty ranges and cost-effectiveness acceptability curves, we performed a probabilistic uncertainty analysis in which we simultaneously varied all parameters using 10,000 Monte Carlo methods across systematically defined distributions. For variables bounded from 0 to 1, we assumed an underlying beta distribution; for variables bounded from 0 to infinity, we assumed a gamma distribution. Parameters for both types of underlying distribution were derived from the most likely value listed in Table 1, assuming a standard deviation equal to 12.5% of that value. This was an arbitrarily chosen value that standardized the variation of parameter values for the multivariable uncertainty analysis. Analyses were conducted in TreeAge Pro 2011 (TreeAge Software Inc, Williamston MA, USA).

RESULTS

Cost-effectiveness of adding lateral-flow urine LAM

The prevalence of TB was 38% in this cohort of severely immunocompromised, symptomatic individuals. For every 1,000 patients in the reference scenario (no LAM detection), we estimated that 262 of the projected 380 people with culture-positive TB would be appropriately diagnosed and treated, and that 130 patients without TB would be inappropriately treated based on clinical suspicion (Table 2). Addition of lateral-flow urine LAM to this scenario resulted in 80 additional true-positive TB diagnoses (13 of whom nonetheless died) and 25 additional false-positives, at a cost of $79 per individual tested in South Africa and $19 per person tested in Uganda. Of this cost, $3.50 represented the diagnostic test price, and the remainder represented treatment of people who tested positive (either true-positive or false-positive). In South Africa, addition of urine LAM was estimated to avert 224 DALYs at an incremental cost of $353 per DALY averted (95% uncertainty range: $192–$1161). In Uganda, incremental cost-utility was $86 per DALY averted (95% uncertainty range: $49–$239), reflecting lower costs of first-line TB treatment in that country. The probability of acceptability at a per-DALY willingness-to-pay threshold equal to the per-capita gross domestic product (GDP, $7275 in South Africa and $509 in Uganda)[20] was >99.8% in both countries (Figure 1, solid lines).

Sensitivity analysis

In one-way sensitivity analysis, incremental cost-utility was most sensitive to life expectancy after TB cure, assay specificity, cohort TB prevalence, and cost of TB treatment (Figure 2). Given the importance of the former three variables, we conducted a corresponding three-way sensitivity analysis (Figure 3). Under the reference-case assumption of test specificity (95%), lateral-flow urine LAM was cost-effective in South Africa (at a willingness-to-pay of $7275 per DALY averted) for hospitalized cohorts in which TB prevalence was as low as 5.0% even when assuming life expectancy of 1.5 years after TB cure (Figure 3A), and also in cohorts for whom the probability of death despite TB treatment was as high as 97%. Similarly, under a “worst-case” two-way sensitivity analysis in which we assumed a test specificity of 87% and probability of death from drug side effects of 1%, the cost of the lateral-flow urine LAM assay was $509/DALY averted. Results in Uganda were qualitatively similar to those in South Africa, although the cost-effectiveness ratios were lower (data not shown).

Xpert MTB/RIF scenario

Assuming that sputum smear was replaced by Xpert MTB/RIF increased the incremental cost of urine LAM detection to $731 per DALY averted in South Africa (95% uncertainty range: $234–$12,397) and $208 in Uganda (95% uncertainty range $113–$2847). The probability of acceptability at a per-DALY willingness-to-pay threshold equal to the per-capita GDP of South Africa was 95.8%, and in Uganda was 84%.

DISCUSSION

In this population of hospitalized, severely immunocompromised, HIV-infected African adults, the addition of lateral-flow urine LAM testing to standard TB diagnostics detected an additional 80 cases of TB at an incremental cost per DALY averted of $353 in South Africa and $86 in Uganda. Relative to widely-used standards (e.g., per-capita GDP), diagnosis of TB using lateral-flow urine LAM is likely to be cost-effective in these populations. Although cost-utility was sensitive to life expectancy after TB cure, cost of TB treatment, LAM specificity, and the prevalence of TB, it remained below the per-capita GDP of both countries despite variation across a wide range of parameter estimates.

Findings of the diagnostic accuracy of urine LAM detection in this study are similar to those reported elsewhere.[13,21] Lateral-flow urine LAM testing is a rapid point-of-care test, allowing for timely administration of TB therapy. However, patients with positive LAM results also tend to be the most ill, and there is currently no empirical evidence demonstrating that diagnosis of TB using urine LAM results in a survival benefit. Although the effectiveness of urine LAM detection depends on its ability to improve survival due to earlier diagnosis, patients who die also incur fewer TB treatment costs – which account for the majority of costs in our analysis. Thus, even though the total effectiveness (i.e., DALYs averted) of lateral-flow urine LAM detection varies closely with the projected survival of people who receive an early diagnosis, the cost-effectiveness (i.e., cost per DALY averted) of urine LAM does not depend strongly on offering a large survival benefit. We estimated that the cost of lateral-flow urine LAM detection per DALY averted would remain under South Africa's per-capita GDP even if it prevented death in only 3% of TB patients. Importantly, however, the question of whether a diagnostic test falls under a universal threshold of cost-effectiveness may be less important to decision-making than the determination of whether that test is more cost-effective than other available options. Future studies could directly compare the cost-effectiveness of the urine LAM assay directly with other HIV- and TB-related health interventions (e.g., Xpert MTB/RIF) to determine which interventions provide the most health impact per dollar invested.

In evaluating the determinants of cost-effectiveness for the lateral-flow urine LAM assay, treatment of patients without TB (i.e., false-positives) had great influence. For example, we estimated that, for every 1,000 patients in South Africa, $3,500 would be spent on materials for the lateral-flow assay, versus $21,250 to treat 25 false-positive cases. Additional empirical studies evaluating assay specificity under routine conditions and the mortality benefit provided by a positive test are necessary to better specify both the effectiveness and cost-effectiveness of lateral-flow urine LAM detection for TB diagnosis.

In addition to specificity, the cost-effectiveness of the LAM assay also depends on characteristics of the population in which it is used. Deployment of this assay in a population with lower TB prevalence and less immunosuppression (e.g., outpatients) might result in more false positives but might also provide more years of life to individuals with TB who were promptly treated. Clinical evaluation of urine LAM detection in outpatient settings might provide additional insights. Rapid initiation of HIV treatment is also essential if the benefit of urine LAM testing is to be optimized. In our sensitivity analysis, we found that the cost of LAM testing per DALY averted rose threefold when life expectancy after TB cure was decreased from 5 years to 1.45 years, as might be expected if antiretroviral coverage were incomplete.[22,23]

As with any modeling analysis, there are limitations to this study. We did not model reductions in transmission, though effects on TB transmission are likely to be small in this setting of high background mortality. Our data (e.g., TB prevalence, assay specificity, willingness-to-pay thresholds) may not generalize to countries with fewer resources or to the outpatient setting. For the sake of simplicity, we focused only on the costs and effectiveness associated with the lateral-flow urine LAM assay; the cost of HIV treatment was therefore not included. Inclusion of these costs might lower the cost-utility of urine LAM, as antiretroviral therapy – which would be recommended for all survivors in this analysis – is generally less cost-effective than TB diagnosis and treatment.[24] Our determination of LAM specificity was based on the population with CD4>50 cells/μL, as false-negative TB culture results (the “gold standard”) were felt to be less likely in this subgroup; additional adjudication of all results has confirmed this specificity estimate (data not shown). Nevertheless, we did conduct sensitivity analysis for a specificity estimate as low as 70%, under which the LAM assay remained cost-effective. We also assumed that a negative LAM result would not affect clinical decision-making in this seriously ill population. To the extent that physicians would be less likely to treat TB cases with negative LAM results (i.e., false-negatives), our analysis may overestimate effectiveness; however, to the extent that true-negatives would also not be treated, we may also overestimate incremental costs. Finally, we assume that survival will improve for TB patients who are appropriately treated on the basis of a positive LAM test. Preliminary data suggest that patients testing positive with urine LAM may have higher background mortality, such that the survival benefit associated with an accurate diagnosis may be lower than expected.[25]

In conclusion, we found that lateral-flow detection of LAM in urine among HIV-infected, severely immunocompromised, hospitalized African adults is likely to be both an effective and cost-effective strategy for diagnosis of TB in high-burden settings, whether low income (Uganda) or upper-middle income (South Africa). Urine LAM represents the first true point-of-care diagnostic test for TB and likely provides an important and cost-effective benefit to this narrowly selected patient population, although this cannot be confirmed unless further studies demonstrate a survival benefit. Due to the narrow indication of this assay, broader control of the TB epidemic will depend will depend on our ability to develop novel develop novel technologies that that improve TB diagnosis in more general more general populations as well.

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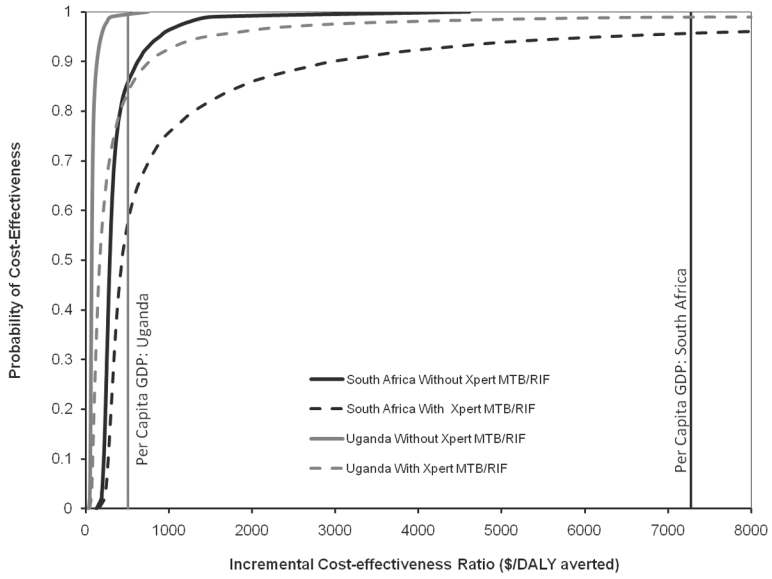

Figure 1. Cost-effectiveness Acceptability Curves for Lateral-Flow Urine LAM Detection

Curves show the probability of cost-effectiveness (cost per DALY averted lower than the value on the x-axis) of urine LAM, over 10,000 Monte Carlo simulations. Black lines show cost-effectiveness in South Africa (where TB treatment is more expensive); grey lines represent Uganda (where TB treatment is cheaper). Solid lines utilize a baseline in which smear and other non-bacteriological diagnostics (e.g., chest X-ray) are available, but not Xpert MTB/RIF; dotted lines assume that Xpert MTB/RIF is also available.

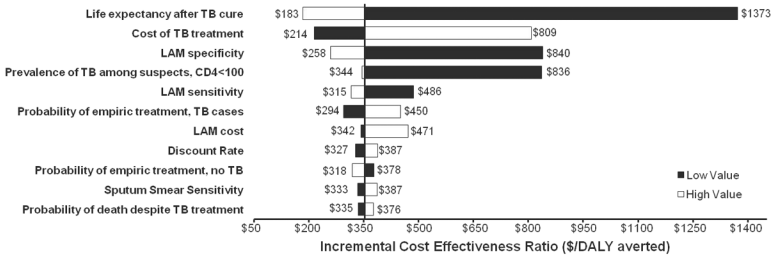

Figure 2. Sensitivity Analysis: Cost-Utility of Lateral-Flow Urine LAM Detection in South Africa

The vertical line represents the base-case scenario ($353 per DALY averted, see also Table 2). The black bars represent the incremental cost-effectiveness ratio at the low value of the sensitivity range for each parameter (Table 1), and the white bars represent the same ratio at the high value of the range.

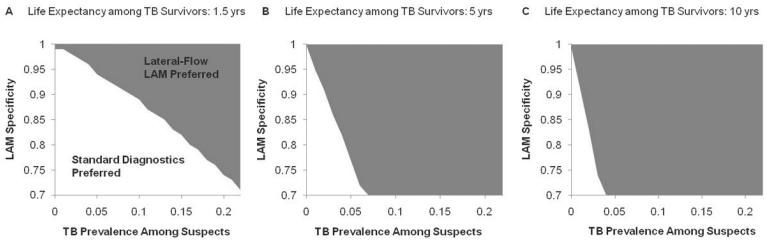

Figure 3. Three-way Sensitivity Analysis: Effect of Assay Specificity, TB prevalence, and Life Expectancy after TB cure in South Africa

Cost-utility of lateral-flow urine LAM, according to specificity, TB prevalence, and life expectancy after TB cure in South Africa. Grey shading indicates that the existing diagnostic strategy (without Xpert MTB/RIF) would be preferred at a willingness to pay (WTP) of $7,275, while white shading indicates that addition of lateral-flow urine LAM would be preferred at this WTP threshold. Thus, for example, assuming a life expectancy of 1.5 years and assay specificity of 95%, lateral-flow urine LAM would be the preferred testing strategy in South Africa if deployed in populations with a probability of finding active TB that is greater than 5% (panel A, transition from white to grey).

Table 1

Parameter values.

Name	Value	Sensitivity Range	Reference
TB Dynamics			
TB Prevalence among suspects with HIV and $CD4^+$ <100 cells/μL	0.38	0.12–0.5	Study data
Probability of death in those with TB and given TB treatment	0.2	0.10–0.30	16
Probability of dying from TB treatment toxicities	5×10^{-5}	8.5×10^{-6}–1×10^{-2}	26
Characteristics of TB Diagnosis			
Probability of empiric treatment among smear-negative TB cases	0.53	0–0.75	27
Probability of empiric treatment among patients without TB	0.21	0–0.5	28
LAM Sensitivity	0.66	0.3–1	Study data,[13]
LAM Specificity	0.95	0.7–1	Study data,[13]
Standard TB Diagnostics Sensitivity	0.345	0.2–0.5	29
Standard TB Diagnostics Specificity	0.998	0.848–1	29
Disability Weights			
HIV+, on ART	0.167	0.142–0.192	30
TB	0.264	0.224–0.304	30
HIV+, not on ART	0.505	0.429–0.581	30
TB treatment	0.10	0.085–0.115	30
Life Expectancy (years)			
HIV on ART (WHO Clinical Stage IV)	5	1.5–10	22,31–34
HIV acutely ill with TB	0.0833	0.071–0.25	Assumption
Unit Cost (2010 USD)			
TB Treatment, South Africa	$850	$500–$2000	17
TB Treatment, Uganda	$178	$100–$500	35
LAM	$3.50	$1.00–$30	29
Standard TB Diagnostics	$1.58	$1.34–$1.82	8
Discount rate	0.03	0–0.07	18

Table 2

Cost-Utility of Lateral-Flow Urine LAM Detection

Country and Diagnostic Strategy	Cohort Size[a]	TB Cases	TB Cases Treated	False-Positives Treated	DALYs	DALYs averted	Cost (2010 US$)	Incremental Cost	Incremental Cost-Effectiveness ($/DALY)
South Africa									
Existing Diagnostics	1000	380	262	130	1491	(ref)	$299,000	(ref)	(ref)
Existing Diagnostics + Urine LAM	1000	380	342	155	1267	224	$378,000	$79,000	$353
Uganda									
Existing Diagnostics	1000	380	262	130	1491	(ref)	$64,000	(ref)	(ref)
Existing Diagnostics + Urine LAM	1000	380	342	155	1267	224	$83,000	$19,000	$208

DALY, disability-adjusted life year; LAM, lipoarabinomannan; TB, tuberculosis