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MAJOR ARTICLE

Cost-effectiveness of WHO-Recommended Algorithms for TB Case Finding at Ethiopian HIV Clinics

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Background: The World Health Organization (WHO) recommends active tuberculosis (TB) case finding and a rapid molecular diagnostic test (Xpert MTB/RIF) to detect TB among people living with HIV (PLHIV) in high-burden settings. Information on the cost-effectiveness of these recommended strategies is crucial for their implementation.

Methods: We conducted a model-based cost-effectiveness analysis comparing 2 algorithms for TB screening and diagnosis at Ethiopian HIV clinics: (1) WHO-recommended symptom screen combined with Xpert for PLHIV with a positive symptom screen and (2) current recommended practice algorithm (CRPA; based on symptom screening, smear microscopy, and clinical TB diagnosis). Our primary outcome was US$ per disability-adjusted life-year (DALY) averted. Secondary outcomes were additional true-positive diagnoses, and false-negative and false-positive diagnoses averted.

Results: Compared with CRPA, combining a WHO-recommended symptom screen with Xpert was highly cost-effective (incremental cost of $5 per DALY averted). Among a cohort of 15 000 PLHIV with a TB prevalence of 6% (900 TB cases), this algorithm detected 8 more true-positive cases than CRPA, and averted 2045 false-positive and 8 false-negative diagnoses compared with CRPA. The WHO-recommended algorithm was marginally costlier ($240 000) than CRPA ($239 000). In sensitivity analysis, the symptom screen/Xpert algorithm was dominated at low Xpert sensitivity (66%).

Conclusions: In this model-based analysis, combining a WHO-recommended symptom screen with Xpert for TB diagnosis among PLHIV was highly cost-effective ($5 per DALY averted) and more sensitive than CRPA in a high-burden, resource-limited setting.

Keywords. cost-effectiveness; developing countries; Ethiopia; modeling; TB/HIV co-infection.

Tuberculosis (TB) is the leading cause of death among people living with HIV (PLHIV) globally [1]. In 2015, there were an estimated 1.2 million new TB cases and 400 000 TB-related deaths among PLHIV worldwide [2]. Although the global burden of TB is enormous, TB control efforts are substantially underfunded. The World Health Organization (WHO) estimates that of the $4.8 billion per year required to combat TB disease, there is a $1.6 billion (33%) funding gap [3]. Any attempt to inform TB health policy must consider the economic impact of policy changes given limited resources and health-related budgets in many TB high-burden countries [4, 5].

Ethiopia is one of 30 "high–TB burden" countries that account for nearly 90% of global TB cases [2]. There were an estimated 191 000 new cases of TB in Ethiopia in 2015, and about 10% of new TB cases are co-infected with HIV [2]. In Addis Ababa, the prevalence of active TB disease among PLHIV is estimated to be as high as 17% [6–10]. Ethiopia is one of the world's lowest-income countries (2013 GDP per capita of US$505) and had a government health care budget of $73 per person in 2014 [11, 12].

Because of the impact of HIV co-infection on TB incidence, morbidity, and mortality, the WHO recommends "intensified case finding" of TB among all PLHIV in high–TB burden areas [1]. A 2011 meta-analysis determined that absence of current cough, fever, night sweats, and weight loss in PLHIV identified persons with a very low probability of active TB (negative predictive value of 98% at 5% TB prevalence) [13]. WHO recommends this "symptom-based screen" for PLHIV, followed by a diagnostic work-up for TB in those with a positive symptom screen (ie, at least 1 of the 4 symptoms) [1, 14]. However, the diagnostic test currently most commonly available in resource-limited areas, acid-fast bacillus (AFB) smear, has several limitations, including very poor sensitivity (≤30%) for TB among PLHIV [15].

The Xpert MTB/RIF assay ("Xpert," Cepheid, Sunnyvale, CA) is a rapid molecular diagnostic test that can detect

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M. tuberculosis (*MTB*) and rifampin resistance in less than 2 hours [16]. A multicenter study conducted among HIV+ and HIV– patients in 5 high–TB incidence countries found Xpert to be 98% sensitive for smear microscopy–positive, culture-positive specimens and 73% for smear microscopy–negative TB compared with AFB culture [17]. Specifically, among PLHIV in a high–TB prevalence area in South Africa, Xpert had a sensitivity of 100% for smear-positive TB and 62% for smear-negative TB, compared with smear microscopy sensitivity of 28% [15]. In 2013, the WHO recommended Xpert as the initial diagnostic test for TB in adult PLHIV [14].

Although Xpert improves TB diagnosis compared with the current standard of care (ie, smear microscopy) in most resource-limited countries [16–18], its cost remains an issue. In developing countries, the Xpert platform costs US$17 000 (for a 4-channel instrument) and each test cartridge costs approximately US$10, prices substantially discounted from those in high-income countries [19]. Even with this discount, cost may restrict its availability [20]. We conducted a model-based cohort study to determine the cost-effectiveness of combining a WHO-recommended symptom-based screen with a molecular diagnostic test, Xpert, at an HIV clinic in Ethiopia, a resource-limited, high–TB burden country.

METHODS

Parent Study and Clinical Inputs

Clinical inputs were derived in large part from an operational research project we conducted on implementation of the WHO-recommended TB symptom screen for PLHIV (cough, fever, night sweats, weight loss) followed by diagnostic testing with Xpert among sputum specimens collected from PLHIV with a positive symptom screen [1, 9, 13]. Methods of the parent study are described in detail elsewhere [9]. That study took place from July to October 2013 at the ALERT Hospital HIV Clinic, which cares for approximately 15 000 PLHIV in Addis Ababa, Ethiopia. The Armauer Hansen Research Institute (AHRI)/ALERT and Emory University Institutional Review Boards approved the parent study. Results from the parent study [9] were used to estimate base case clinical characteristics (Table 1). Where these were not available, inputs were determined from relevant literature on PLHIV in Ethiopia or in sub-Saharan Africa when Ethiopia-specific inputs were not available. Xpert MTB/RIF sensitivity and specificity were determined from a meta-analysis on test characteristics in PLHIV [21]. For sensitivity analysis, we used lower and upper estimates from relevant literature; input references are listed in Table 1. In our parent study, 89% of PLHIV at the clinic were on antiretroviral therapy (ART), and the mean CD4 count was 420 cells/μL [9]. We did not assume differential test characteristics of any of the diagnostic tests based on CD4 count or whether the patient was on ART. Further details on cost and disability-adjusted life-year inputs are described in the Supplementary Appendix.

Modeling Strategies

We modeled 2 strategies for intensified TB case finding among PLHIV (Figure 1) and compared hypothetical cohorts of 15 000 PLHIV (equivalent to the ALERT HIV Clinic cohort) progressing through each diagnostic strategy. We assumed that each of the 15 000 PLHIV in each cohort would progress through the model only once, thus not accounting for repeat visits. Models were constructed with TreeAge (TreeAge Software, Inc., Williamstown, MA, USA), and additional calculations were performed using SAS v9.4 (SAS Institute, Cary, NC, USA). The 2 diagnostic algorithms compared were:

1. WHO-recommended TB symptom screen plus WHO-recommended Xpert diagnostic algorithm ("SSX"). PLHIV were screened for TB using the WHO-recommended symptom screening algorithm (cough, fever, night sweats, or weight loss) [1, 13]. If the symptom screen was negative (ie, absence of all 4 symptoms), the patient was considered to not have active TB disease and was prescribed isoniazid preventive therapy (IPT) for presumed latent TB infection, per WHO guidelines [1]. However, a proportion of these PLHIV were assumed to have active TB (ie, false-negative diagnoses) based on symptom screen test characteristics.

   If a patient had a positive symptom screen (ie, at least 1 of the 4 symptoms), sputum samples would be collected and tested initially for *MTB* with Xpert, per WHO guidelines for diagnostic tests for PLHIV, and would not be tested with smear microscopy [14]. Sputum samples obtained from patients with a positive symptom screen were either positive or negative for *MTB* (and rifampin resistance) based on Xpert results. Of those PLHIV with active TB, some had drug-susceptible TB (DS-TB) and others had multidrug-resistant TB (MDR-TB). PLHIV with presumptive MDR-TB based on a positive Xpert test for rifampin resistance had their sputum specimens tested with AFB culture and drug susceptibility testing (DST) and received treatment for MDR-TB. Patients with negative Xpert results were prescribed IPT.

   This algorithm also considers the cost of an Xpert MTB/RIF platform (a 1-year payment based on machine cost of $17 000 amortized over 10 years at a 3% interest rate) and cost of laboratory maintenance (Table 1). The number of Xpert instruments needed was based on clinic volume (patients per day) and proportion of patients with a positive WHO-recommended symptom screen (ie, patients who would require TB diagnostic testing with Xpert). We assumed the laboratory would utilize 4-channel Xpert machines operating at maximum capacity of 4 simultaneous tests and running for 8 hours per day. For calculating incremental cost of the SSX algorithm, the total cost of the Xpert platform and

Table 1. Model Parameters for Cost-effectiveness Analysis, Base Case, and Ranges for Sensitivity Analyses

Parameter	Base Case	Range, References	Reference (Base Case)
Cost inputs, laboratory, US$			
Smear microscopy	1.20	0.60[a]–2.40[a]	ALERT
Labor cost per AFB smear	0.63	0.31–0.94 (AHRI)	AHRI
AFB culture	4.80	2.40[a]–8.75 (EPHI)	EPHI
DST	1.8	0.90[a]–12[a]	AHRI
Xpert MTB/RIF, machine[b]	1480	740[a]–2960[a]	[19]
Xpert MTB/RIF, cartridge	9.98	9.98–72.87 [23]	[19]
Xpert MTB/RIF, yearly maintenance	1088.86	544.43[a]–2177.72[a]	[23]
Chest x-ray	3.50	1.75[a]–7[a]	ALERT
Cost inputs, medication, US$			
Drug-susceptible TB	33	25.17 [33]–66[a]	EFMOH
MDR-TB	4856	2428[a]–9712[a]	EFMOH
IPT	5	2.50[a]–10[a]	EFMOH
Clinical characteristics			
TB prevalence	6%	4% [6]–17% [10]	Parent study [9]
Clinic volume, patients/d	135	50%–250[c]	Parent study [9]
Proportion with positive WHO symptom screen	53%	25%–75%[c]	Parent study [9]
Proportion of TB cases that are MDR	2.8%	0%–2.8% [2]	[2]
Symptom screen sensitivity	72%	52% [25]–93% [34][c]	[25]
Symptom screen specificity	50%	33%–56% [25]	[25]
Smear microscopy sensitivity	30%	19% [10]–33% [8]	Parent study [9]
Smear microscopy specificity	100%	99.7% [10]–100% [9]	Parent study [9]
Xpert MTB/RIF sensitivity	72%[d]	66% [10]–94% [35]	[21]
Xpert MTB/RIF specificity	98%	95% [36]–99% [37]	[21]
Xpert RIF resistance sensitivity	95%	95% [21]–100% [38]	[21]
Xpert RIF resistance specificity	98%	98% [21]–100% [17]	[21]
Clinical diagnosis sensitivity, AFB negative TB	61%	55%–67% [24]	[24]
Clinical diagnosis specificity, AFB negative TB	69%	66%–72% [24]	[24]

Abbreviations: AFB, acid-fast bacillus; AHRI, Armauer Hansen Research Institute, Addis Ababa, Ethiopia; ALERT, ALERT Hospital, Addis Ababa, Ethiopia; ART, antiretroviral therapy; DST, drug susceptibility testing; EPHI, Ethiopian Public Health Institute, Addis Ababa, Ethiopia; EFMOH, Ethiopian Federal Ministry of Health, Addis Ababa, Ethiopia; MDR, multidrug-resistant; IPT, isoniazid preventive therapy; RIF, rifampin; TB, tuberculosis; US$, 2014 US dollars; WHO, World Health Organization.

[a]Where values could not be found in literature searches, we assumed lower bounds of ½× base case costs and upper bounds of 2× base case costs.

[b]We determined 1-year cost of Xpert MTB/RIF machine based on amortizing a US$17 000 payment for the machine over 10 years (expected useful life of machine) at a 3% interest rate.

[c]In the cited reference, TB screening using a symptom screen of one of cough, fever, or night sweats had 93% sensitivity for active TB among PLHIV. Adding a fourth symptom, as in our study (ie, weight loss), either would not change or would increase sensitivity. We therefore included this reported sensitivity as the upper limit for sensitivity analysis.

[d]In the cited reference, Xpert sensitivity was 61% among PLHIV with smear-negative TB and 97% among PLHIV with smear-positive TB. To calculate the listed sensitivity, we weighted the Xpert sensitivity by proportion of patients who had smear-negative and -positive disease (ie, pooled Xpert sensitivity = ($p_{\text{smear negative}}$ * Xpert $\text{sensitivity}_{\text{smear negative}}$) + ($p_{\text{smear positive}}$ * Xpert $\text{sensitivity}_{\text{smear positive}}$) = (0.7 * 0.61) + (0.3 * 0.97) = 0.72).

maintenance were divided by the number of patients undergoing analysis (modeled as n = 15 000).

2. Current recommended practice algorithm ("CRPA"). As in the SSX strategy, all PLHIV were initially screened for active TB with the WHO-recommended symptom screen. PLHIV with a negative symptom screen were assumed to not have active TB and were prescribed IPT. Those who had a positive symptom screen provided sputum samples, which were tested for *MTB* with 3 separate smear microscopy tests, and not with AFB cultures. PLHIV with negative smear microscopy results were clinically diagnosed to be TB positive or negative. We modeled clinical assessment based on an operational research study carried out at the ALERT HIV clinic [7]. In this study, PLHIV undergoing diagnostic workup for pulmonary TB were initially tested with smear microscopy. Of those with negative smear microscopy, 64% were tested with AFB culture and 92.8% with chest radiography [7]. Further details on this assessment, including case definitions, have been previously described [7]. All patients not diagnosed with active TB were prescribed IPT.

Further details of the modeling structure are provided in the Appendix.

Outcomes

Our primary outcome was the incremental cost-effectiveness ratio (ICER) of the SSX algorithm compared with CRPA (US$ per disability-adjusted life-year [DALY] averted). Inputs for DALY calculations are provided in Table 2. SSX was considered cost-effective if the ICER was less than 3 times the Ethiopian gross domestic product (GDP) per capita and highly

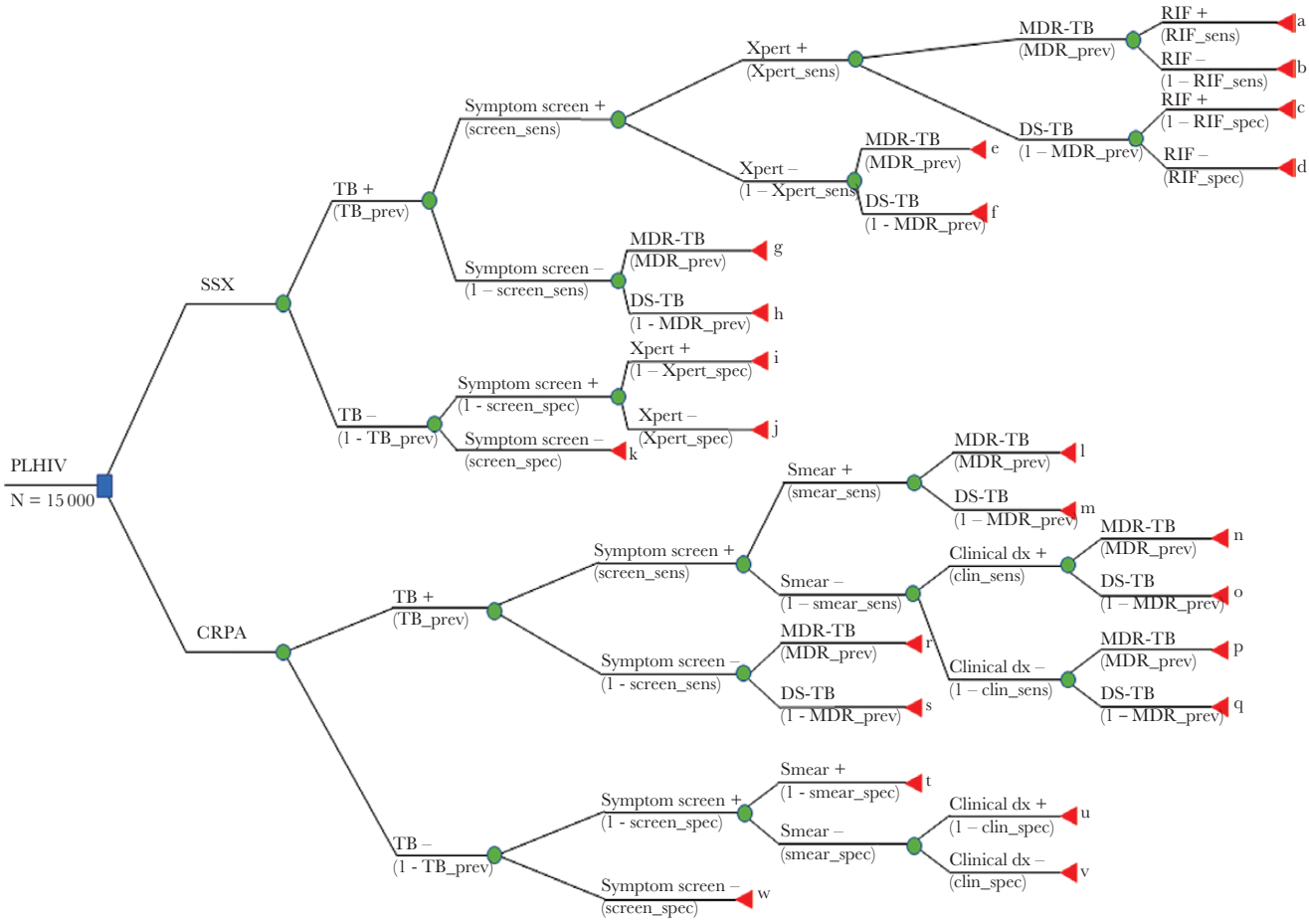

Figure 1. Decision analysis model for tuberculosis screening and diagnosis among patients at Ethiopian HIV clinics. Decision analytic model with 2 different strategies for TB screening and diagnosis among PLHIV: (1) Symptom screen/Xpert ("SSX") combines a World Health Organization–recommended symptom screen (cough, fever, night sweats, weight loss) with Xpert as the initial diagnostic test for PLHIV with a positive symptom screen (ie, having at least 1 symptom) [1, 12]. (2) Current practice screens patients with the symptom screen, and then combines smear microscopy with clinical diagnosis for those with negative smear microscopy results. Squares represent decision nodes, circles represent chance nodes, and triangles represent terminal nodes. The number listed under each arm is the probability of progressing to that arm (from prior node), calculated under base case conditions. Abbreviations: CP, current practice algorithm; DALY, disability-adjusted life-year; DS, drug-susceptible; Dx, diagnosis; HIV, human immunodeficiency virus; MDR, multidrug-resistant; PLHIV, people living with HIV; SSX, symptom screen/Xpert algorithm; RIF, rifampin resistance; TB, tuberculosis.

cost-effective if less than the Ethiopian GDP per capita ($505) [11, 22]. Secondary outcomes were true-positive, false-positive, and false-negative TB diagnoses under each algorithm. We calculated ICERs of US$ per additional true-positive case detected with SSX, and false-positive and false-negative TB diagnoses averted with SSX.

Table 2. Inputs for Disability-Adjusted Life-Year Calculations

Condition	Mortality (Range)	Disability Weight (Range)
HIV, TB negative	0.05 (0–0.3) [30]	0.053 (0.034–0.079) [39]
HIV, untreated TB	1 (0.5–1) [30, 40]	0.399 (0.267–0.547) [39]
HIV, treated drug-susceptible TB	0.105 (0.04–0.3) [40, 41]	0.1 (0.085–0.115) [30]
HIV, treated MDR-TB	0.2 (0.04–0.37) [40–42]	0.2 [30]

Inputs were used to calculate disability-adjusted life-years, as previously described [43].

Abbreviations: HIV, human immunodeficiency virus; MDR, multidrug-resistant; TB, tuberculosis.

Sensitivity Analyses

We conducted 1-way sensitivity analyses by varying model inputs over ranges determined from the literature (Table 1).

RESULTS

Cost-effectiveness

In a simulated cohort of 15 000 PLHIV attending an HIV Clinic in Ethiopia, an algorithm combining the WHO-recommended symptom screen and Xpert (SSX) was highly cost-effective. The ICER comparing the SSX algorithm with the current recommended practice algorithm (CRPA) was $5 per DALY averted (less than current Ethiopian GDP per capita of $505), highly cost-effective per WHO thresholds for cost-effectiveness [22]. The SSX algorithm averted 243 DALYs compared with CRPA (Table 3). The SSX algorithm was estimated to be marginally costlier than CRPA. With base case inputs (Tables 1 and 2), SSX costs $240 300, compared with

$239 000 under the CRPA algorithm, an incremental cost of $1300 per 15 000 PLHIV.

SSX had a higher case detection rate than CRPA (Table 3). In the SSX cohort, there were 466 true-positive TB cases compared with 458 in the CRPA cohort (8 additional true-positive diagnoses, ICER = $157 per true-positive diagnosis). Additionally, SSX averted both false-negative and false-positive TB diagnoses. There were 434 false-negative cases with SSX compared with 442 with CRPA (8 false-negative cases averted, ICER = $157 per false-negative case averted). There were 141 false-positive cases with SSX compared with 2186 with CRPA (2045 false-positive cases averted, ICER = $1 per false-positive case averted).

Sensitivity Analyses

The SSX algorithm was highly cost-effective under a range of parameter estimates (Figure 2). It was least cost-effective with a high Xpert cartridge cost of $73 (ICER = $1995), the current price in developed countries (although we used $73 as the high end of the range for sensitivity analysis, the current price in developing countries is $9.98) [23].

Under several conditions, the SSX algorithm was less cost-effective than it was in base case conditions. With a high MDR-TB treatment cost of $9712 (cost data provided by the Ethiopian Federal Ministry of Health), the ICER was $253 per DALY averted. Similarly, SSX was less cost-effective than base case with a high TB prevalence of 17% (ICER = $236 per DALY averted) [10], low sputum smear cost of $0.60 (ICER = $62), and high sputum microscopy sensitivity of 33% (ICER = $15) [8]. The full results of the primary sensitivity analysis are shown in Figure 2.

SSX was most costly, at a high Xpert cost of $73 ($724 000 per 15 000 PLHIV). SSX was least costly, at a low MDR-TB prevalence of 0% ($180 000 per 15 000 PLHIV) [2] due to fewer patients requiring costly MDR-TB treatment than the base case MDR-TB rate of 2.8% of TB cases. MDR-TB treatment was more than 100 times costlier than DS-TB treatment.

Under several scenarios, SSX was less costly than CRPA. With a high DS-TB treatment cost of $66, the total cost of the SSX algorithm was $260 000, vs $327 000 for CRPA (cost savings of $67 000 per 15 000 PLHIV). When care is more expensive (eg when DS-TB treatment cost is expensive), SSX becomes more valuable due to its reduction in false-positive cases, which prevents patients from receiving more expensive treatment. Additionally, with a low MDR prevalence of 0% [2], the total cost of the SSX algorithm was $180 000, vs $239 000 for CRPA (cost savings of $59 000 per 15 000 PLHIV). Similarly, with a low MDR-TB treatment cost of $2428, the cost of SSX was $210 000, compared with $239 000 for CRPA (cost savings of $29 000 per 15 000 PLHIV).

SSX was not more effective than CRPA in all sensitivity analyses. At a low Xpert sensitivity of 66% [10], there were marginally more DALYs in the SSX cohort (31 145) than in the CRPA cohort (30 523). With Xpert sensitivity of 66%, SSX was both costlier and less effective than CRPA. Additionally, with high clinical diagnosis sensitivity of 67% [24], there were more DALYs in the SSX cohort (30 279) than CP (29 931), similar to the low MDR-TB rate of 0% (30 234 DALYs in SSX vs 30 227 in CRPA).

DISCUSSION

In this cost-effectiveness analysis of a WHO-recommended TB case finding algorithm of symptom screening in combination with a molecular diagnostic test, Xpert MTB/RIF, at an Ethiopian HIV clinic (SSX algorithm), we found SSX to be highly cost-effective ($5 per DALY averted) compared with the current recommended practice (CRPA). This ICER is less the than Ethiopian GDP per capita of $505, the WHO's threshold for a highly cost-effective intervention [22]. Additionally, the SSX algorithm detected more TB cases than CRPA (466 vs 458, difference = 8, ICER = $157 per true-positive case) and averted both false-positive (141 vs 2186, difference = 2045, ICER = $1 per false-positive

Table 3. Expected Outcomes and Cost-effectiveness of 2 Strategies for Active Tuberculosis Case Finding at Ethiopian HIV Clinics

	Algorithm (n = 15 000 per Algorithm)		
Outcome	Symptom Screen/ Xpert, No. (Range[b])	Current Practice, No. (range[b])	ICER[a] (Maximum[c])
TB cases, actual	900 (600–2550)	900 (600–2550)	--
Symptom screen positive	7950 (3750–11 250)	7950 (3750–11 250)	--
Cost, 1000 US$	240 (180–724)	239 (208–327)	--
DALYs, thousands	30.3 (12.9–117)	30.5 (13.1–117)	5.2 (1995)
TP TB diagnoses	466 (310–1320)	458 (305–1297)	157 (60 700)
FN TB diagnoses	434 (289–1230)	442 (295–1250)	157 (60 700)
FP TB diagnoses	141 (71–353)	2200 (1920–2930)	1 (240)

Abbreviations: DALY, disability-adjusted life-year; FN, false-negative; FP, false-positive; ICER, incremental cost-effectiveness ratio; TB, tuberculosis; TP, true positive; US$, 2014 US dollars.

[a]ICERs were calculated for each row according to the following formula (eg, for DALY): ICER = [$Cost_{Symptom\ screen/Xpert} - Cost_{Current\ practice}$]/[$DALY_{Current\ practice} - DALY_{Symptom\ screen/Xpert}$]. ICER units are US$ per 1 additional outcome, eg, US$ per DALY averted.

[b]Ranges are minimum and maximum values determined from sensitivity analyses.

[c]We did not report minimum ICERs; under several cases, Xpert was either dominated by or less costly than SSX (please see "Results: Sensitivity Analyses" and Figure 2).

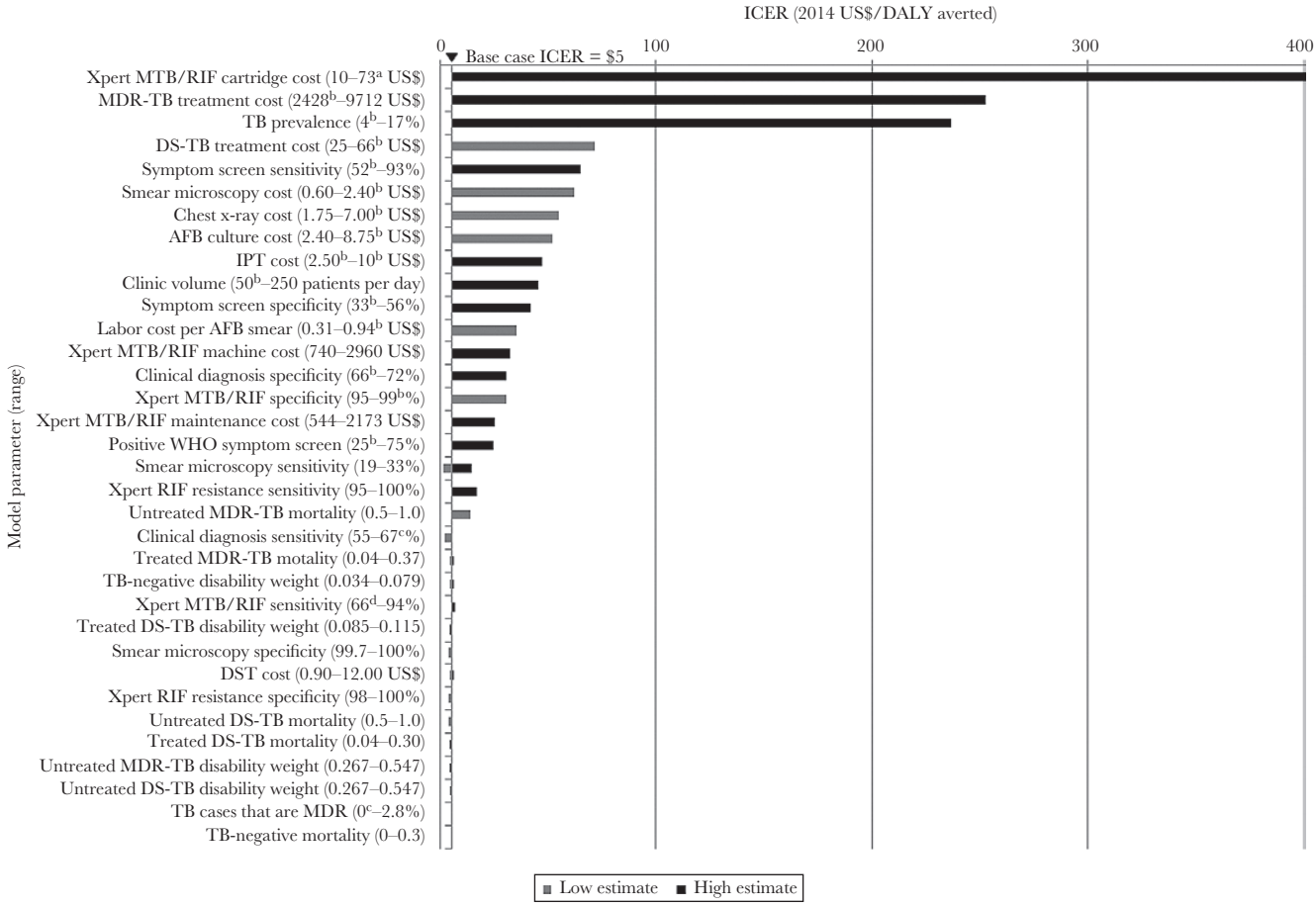

Figure 2. Ranges of incremental cost-effectiveness ratio (US$ per disability-adjusted life-year averted) of a World Health Organization–recommended tuberculosis diagnostic algorithm vs current recommended practice at Ethiopian HIV clinics. [a]Graph truncated for space reasons; in this case, ICER = $1995. [b]Under these conditions, the symptom screen/Xpert algorithm was cost-saving; ICERs are not reported in these cases. [c]Under these conditions, the symptom screen/Xpert algorithm was less effective than current practice; the ICER was not reported in this case. [d]At low Xpert sensitivity of 66% [10], the symptom screen/Xpert algorithm was dominated (more costly and less effective) at current practice; the ICER was not reported in this case. Abbreviations: AFB, acid-fast bacillus; DALY, disability-adjusted life-year; DS, drug-susceptible; DST, drug susceptibility testing; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; IPT, isoniazid preventive therapy; MDR, multidrug-resistant; TB, tuberculosis; WHO, World Health Organization.

diagnosis averted) and false-negative diagnoses (434 vs 442, difference = 8, ICER = $157 per false-negative diagnosis averted) compared with CRPA. Based on our results, the value of SSX comes from increased diagnostic accuracy (given enhanced case finding with the use of the combined WHO algorithms), especially given the poor test characteristics of those tests used in CRPA (ie, smear microscopy and clinical diagnosis), which leads to more false-positive TB cases. Specifically, the value of the SSX algorithm is more related to its ability to avert false-positive diagnoses than to detect additional true-positive cases.

PLHIV in high-burden settings in low- and middle-income countries with a positive WHO-recommended TB symptom screen (at least one of cough, fever, night sweats, or weight loss) are recommended to undergo TB diagnostic testing with Xpert [14]. However, TB diagnosis in resource-limited settings generally relies on smear microscopy, and the poor sensitivity of smear microscopy among PLHIV (≤30%) leads to low rates of microbiologically confirmed disease [15]. As a result, there is a high rate of empiric treatment. In our model-based study, there were 2200 (1920–2930) false-positive TB cases in the CRPA cohort. A large proportion of patients (53%) with a positive WHO-recommended symptom screen were therefore recommended to undergo further testing [9]. Given the low specificity of the symptom screen (50%) [25], many of these patients with a positive symptom screen did not have active TB. When followed by testing with a more specific diagnostic test such as Xpert (98% specificity) [21] in the SSX algorithm, this is able to limit the number of false-positive cases (141 false-positives in SSX algorithm). However, when symptom screening is part of an algorithm followed by diagnostic tests with lower specificity, such as clinical diagnosis (69%) [24], patients are more likely to be diagnosed empirically with TB. Given the high specificity of smear microscopy (100%) [9], this indicates that many of the false-positive cases are related to clinical diagnosis. That clinical diagnosis specificity is not a major driver of the ICER (Figure 1) may be related to the narrow range of specificity in

sensitivity analysis; further data are needed on clinical diagnosis in Ethiopia and other resource-limited settings.

There are few data on rate of clinical diagnosis and resultant empiric treatment of TB in PLHIV, largely due to inability to diagnose TB (ie, no good gold standard) in such patients. However, a study in Uganda found that among PLHIV who were suspected of having TB, 33% of smear-negative patients were initiated on empiric TB treatment [26]. In one randomized controlled trial, a large proportion of PLHIV (46%) with CD4 counts <150 cells/μL had a "high suspicion" of TB; there was no mortality benefit when these patients were assigned to a nurse-driven protocol that emphasized early TB treatment, indicating that empiric diagnosis may not be accurate in these patients [27]. Further studies are needed to explore rates of empiric treatment and its potential consequences.

Given the high rates of empiric TB treatment, an accurate diagnostic test such as Xpert would be valuable for HIV clinics in resource-limited areas where TB/HIV co-infection is prevalent. However, for clinics such as the ALERT HIV clinic, with a high volume (135 patients per day) and high rate of symptom screen positivity (53%) [9], the WHO recommendations require a large number of PLHIV to undergo routine TB testing with Xpert. This calls into question the feasibility of routine Xpert rollout in resource-limited settings. Substantial additional resource expenditure from either local governments or outside organizations (eg, PEPFAR, Global Fund) will be required to implement enhanced TB case finding with symptom screening and Xpert. Although nongovernmental organizations currently fund a large proportion of TB control and care in developing countries [28], cheaper, more efficient point-of-care tests are needed to reduce this funding burden.

Local factors, such as country-level cost inputs and clinic volume, are important for determining cost-effectiveness of various TB diagnostic strategies and therefore the extent to which they will be adopted locally [4]. This is one of the first cost-effectiveness analyses of symptom screening and Xpert at Ethiopian HIV clinics, and therefore these data may be valuable for scaling up Xpert in Ethiopia. Although we conducted sensitivity analyses by varying model inputs with data taken from the literature on Ethiopia and sub-Saharan Africa where available (Table 1), characteristics of the local population may vary beyond the ranges we have used in sensitivity analyses. Other specific local factors may affect the cost-effectiveness of a diagnostic algorithm that includes Xpert; local clinicians and policy makers will need to consider these factors when considering optimal diagnostic strategies.

Several studies have examined use of Xpert in other sub-Saharan countries. The only other cost-effectiveness analysis based in Ethiopia similarly found diagnostic algorithms that concluded Xpert to be highly cost-effective; however, this analysis did not specify symptom screening of presumptive TB cases and included both HIV+ and HIV- patients [29]. In a model-based study of PLHIV in Uganda, a TB diagnostic algorithm using Xpert was cost-effective compared with smear microscopy (ICER = $58), which is similar to the results of our current study, indicating that a diagnostic algorithm using Xpert may be cost-effective across a range of model parameters (as this study used different inputs than ours) [30]. In a model-based study of PLHIV being screened for TB prior to ART initiation in South Africa, a diagnostic algorithm using 2 Xpert samples was cost-effective (ICER = $6700 per year of life saved) [31]. Our study differs from the South African study because we assumed screening and Xpert testing for all patients regardless of ART status, as recommended by the WHO [1]. However, a 2017 analysis of Xpert roll-out in South Africa found that using Xpert as the initial diagnostic test was not more expensive than using smear microscopy, but showed that Xpert was unlikely to be cost-effective [32]. Further real-world implementation studies will be important to determine for which populations Xpert is likely to be cost-effective.

Our cost-effectiveness analysis is subject to several limitations. We did not quantify costs associated with scale-up of Xpert; we took the position of a diagnostic system (including Xpert machines) that was already implemented. Additionally, we did not consider Xpert's potential impact on TB transmission, further downstream effects of delays in TB diagnosis and treatment, efficacy of IPT and TB treatment, and issues regarding delivering Xpert results and linkages to care. These considerations will be important for policy makers considering Xpert implementation. We did not consider patients who are unable to provide a sputum sample or otherwise lost to follow-up; these proportions may differ between groups. Similarly, there was no empiric treatment following a negative Xpert test. However, as the CRPA algorithm requires more sputum samples than SSX and did include clinical diagnosis, consideration of these factors would likely make SSX more cost-effective. We additionally did not vary diagnostic test characteristics by CD4 count or ART status; in practice, these clinical characteristics may affect these tests' diagnostic yield. We attempted to reflect uncertainty in clinical inputs in sensitivity analyses. For some sensitivity analyses, small changes in input parameters significantly impacted the results, which would have important consequences for implementation of any diagnostic strategy.

In conclusion, a TB diagnostic algorithm that combines a WHO-recommended symptom screen with Xpert for PLHIV with a positive symptom screen was highly cost-effective in an Ethiopian HIV clinic compared with current recommended practice (ICER = $5 per DALY averted). Adoption of the symptom screen and Xpert in Ethiopian HIV clinics remains limited, and our data suggest that clinicians and policy makers in Ethiopia could consider a similar diagnostic algorithm for TB diagnosis among PLHIV.

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Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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