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Enhancing Tuberculosis Case Finding among HIV-Infected Patients in Ethiopia

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Abstract

Enhancing Tuberculosis Case Finding among HIV-Infected Patients in Ethiopia
By Max W. Adelman

Introduction: Tuberculosis (TB) is the leading cause of death among people living with HIV (PLHIV) worldwide. For PLHIV, the World Health Organization (WHO) recommends both active TB case finding in high-burden settings and a rapid molecular diagnostic test for TB case detection. There are limited data on the utility of combining these two recommendations. We evaluated the clinical utility and cost-effectiveness of combining a WHO-recommended symptom screen and rapid molecular diagnostic test (Xpert MTB/RIF) to enhance TB case finding among PLHIV.

Methods: This study was implemented at a large HIV Clinic in Addis Ababa, Ethiopia in two phases: (1) A cross-sectional implementation science study in which PLHIV were screened for TB with a symptom-based algorithm (cough, fever, night sweats, weight loss). Those with a positive symptom screen (PSS) (≥1 symptom) underwent diagnostic testing with sputum smear microscopy, AFB culture, and Xpert. (2) A model-based cost-effectiveness analysis comparing 15,000 PLHIV progressing through either a WHO-recommended TB diagnostic algorithm or current practice for TB diagnosis. Clinical and cost inputs were determined. Our primary outcome was US$ per disability-adjusted life year (DALY) averted.

Results: Among 828 PLHIV, 321 (39%) had a PSS. In multivariate analysis, an unscheduled clinic visit (aOR=3.8, 95% CI 2.7-5.3), CD4 count <100 (aOR=2.6, 95% CI 1.2-5.6) and prior history of TB (aOR=1.6, 95% CI 1.1-2.3) were predictors of a PSS. Among those with a PSS, 6% had active pulmonary TB. Smear microscopy sensitivity was 30% compared to culture and Xpert. Combining a symptom screen with Xpert for TB diagnosis at Ethiopian HIV clinics had an incremental cost of US$36/DALY averted. In a model of 15,000 patients, this algorithm would avert 2059 false positive and 54 false negative cases, but at higher cost (US$251,000) than current practice (US$206,000).

Conclusions: A high proportion of PLHIV had a PSS. Xpert enhanced TB case finding among PLHIV compared to smear microscopy, and a WHO-recommended algorithm for TB diagnosis among PLHIV would be highly cost-effective. However, its incremental cost (US$45,000 per 15,000 patients) may limit its feasibility. Additional resources will be needed to implement the WHO recommended TB screening algorithm in combination with Xpert.

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INTRODUCTION

Tuberculosis (TB) is an enormous global public health problem. The World Health Organization (WHO) estimates that there were approximately 9 million new cases of TB in 2013 and 1.5 million deaths due to TB disease (1). Additionally, HIV is an important risk factor for progression to active TB disease, and TB is the leading cause of death worldwide among people living with HIV (PLHIV) (2-4). TB/HIV co-infection is an especially prevalent problem in sub-Saharan Africa, where both diseases remain endemic and epidemic. Ethiopia, the second most populous country in Africa, is one of 22 "high-burden" TB countries which together account for >80% of global TB cases (1). Additionally, Ethiopia has nearly 1 million PLHIV, and HIV prevalence is highest in urban areas in Ethiopia, especially in the capital, Addis Ababa (5).

Given the high burden of TB disease among PLHIV and the associated high morbidity and mortality, WHO recommends active TB case finding among PLHIV in high TB-burden settings such as Ethiopia (2). Specifically, the WHO recommends that all PLHIV presenting for health care be screened for TB using a symptom-based screen of cough, fever, night sweats, and weight loss (2). A 2011 meta-analysis determined that absence of all of these four symptoms has a 98% negative predictive value (NPV) for TB among PLHIV in settings with a 5% TB prevalence (6). Those with a negative symptom screen are assumed to not have pulmonary TB; those who have a positive symptom screen (at least one symptom) are recommended to undergo further diagnostic work-up to determine if they have active TB disease (2).

There are limited data on the utility and effectiveness of combining the WHO-recommended symptom screen with Xpert MTB/RIF, a novel molecular TB diagnostic test that was recommended as initial TB diagnostic testing for PLHIV by the WHO in 2013 (7). To evaluate the feasibility and effectiveness of implementing these two WHO recommendations (symptom screen and Xpert) at an Ethiopian HIV clinic, we conducted an implementation science/operational research project (8, 9) to evaluate the utility of combining two WHO recommendations. In addition, using clinical data derived from this study, we conducted a cost-effectiveness analysis to determine if implementing the WHO-recommended TB diagnostic algorithm is cost-effective at Ethiopian HIV clinics. We hypothesized that the WHO-recommended algorithm would be cost-effective compared to current practice (less than 3x current Ethiopian GDP per capita per WHO cost-effectiveness thresholds) (10).

BACKGROUND

Tuberculosis (TB) is the leading cause of death among people living with HIV (PLHIV) globally (2, 3). In 2013, there were 1.1 million new TB cases among PLHIV and 360,000 TB-related deaths among PLHIV worldwide (1). Due to the high burden of TB/HIV co-infection, the World Health Organization (WHO) recommends "intensified case finding" for active TB among PLHIV in high-burden areas, including screening for TB at every health care encounter (2). A 2011 meta-analysis determined that the absence of four symptoms—current cough, fever, night sweats, and weight loss—has a 98% NPV for pulmonary TB among PLHIV in settings with a 5% prevalence of active TB disease (6). The WHO recommends that PLHIV with a positive symptom screen (i.e., having at least one of four symptoms) undergo further TB diagnostic testing (2). However, TB diagnosis is limited by the poor sensitivity of the most commonly available diagnostic tests in resource-limited settings. Smear microscopy has a very low sensitivity for TB diagnosis among PLHIV; acid-fast bacilli (AFB) culture, the gold standard for TB diagnosis, is not widely available in resource-limited areas and requires substantial laboratory infrastructure (11-16).

The Xpert MTB/RIF ("Xpert") assay (Cepheid, Sunnyvale, CA, USA) is a rapid TB molecular diagnostic test that can be performed in less than two hours and was endorsed by the WHO in 2010 for use in resource-limited settings (16, 17). In 2013, WHO expanded its recommendation to include Xpert as the initial diagnostic test for PLHIV with signs and symptoms compatible with TB in low- and middle-income countries (7).

A study conducted in five high TB-incidence countries among patients with and without HIV found the Xpert assay to have a sensitivity of 98% for smear-positive TB and 73% for smear-negative TB compared to AFB culture (18). Among PLHIV in a high TB prevalence area in South Africa, the Xpert had a sensitivity of 73% when performed at a national reference laboratory (including both AFB smear positive and smear negative specimens) compared to 28% for smear microscopy (16). Despite promising results when performed in centralized facilities, the role of Xpert in enhancing active TB case finding among PLHIV has not been well defined in most resource-limited health care facilities, especially outside of South Africa (19). Additionally, there are very limited data on the utility of combining the WHO-recommended symptom screen in combination with Xpert in resource-limited settings (19).

Although the global burden of TB is enormous, TB control efforts are substantially underfunded; the WHO estimates that of $4.8 billion per year required to fight TB disease, there is a $1.6 billion (33%) funding gap yearly (20). Any attempt to inform TB health policy must take into account the economic impact of policy changes given the cost of TB control and care as well as limited budgets in most high-burden countries (21, 22). Although Xpert has a much higher sensitivity for TB diagnosis compared to smear microscopy (the most available diagnostic test in most resource limited areas), it is much more costly: In developing countries, the Xpert platform costs US$17,000 and each test cartridge costs approximately US$10 (16, 18, 19, 23). Cost-effectiveness analyses of Xpert are needed to determine its financial impact and in resource-limited settings.

Ethiopia is one of the WHO-designated 22 "high burden" countries which account for over 80% of global TB cases (1). There were an estimated 210,000 new cases of TB in Ethiopia in 2013, and HIV co-infection is estimated to occur in ≥10% of TB cases (1). Furthermore, there are an estimated 790,000 PLHIV in Ethiopia (24). In Addis Ababa, the capital, the prevalence of active TB disease among PLHIV is incompletely defined but has been estimated to range between 4-17% (13, 25-27). Many PLHIV in Ethiopia are treated empirically for TB, without microbiological confirmation or a definitive diagnosis, because of the lack of laboratory infrastructure and infrequent availability of sensitive diagnostic tests (11, 12, 26, 28). Ethiopia is also one of the world's poorest countries (2013 GDP per capita of US$505) and is combating these dual epidemics on a limited healthcare budget (29, 30). Due to limited resources, laboratory capacity and infrastructure is limited; there is only one clinical microbiology laboratory in Ethiopia that meets international accreditation standards (31). To inform clinical decisions regarding intensified case finding including active TB screening among PLHIV as well as scale-up of Xpert in Ethiopia and other developing countries, we performed an implementation science/operational research study and cost-effectiveness analysis to assess the utility and feasibility of implementing the WHO-recommended symptom-based screen for TB in combination with Xpert, a molecular diagnostic test, at a large HIV clinic in Addis Ababa, Ethiopia (8, 9).

METHODS

Study Setting and Population

This study was conducted to determine the feasibility, clinical utility, and cost-effectiveness of implementing two WHO-recommended guidelines (symptom screening and Xpert for PLHIV with TB symptoms) for TB diagnosis among PLHIV in resource-limited settings. This study took place from July-October 2013 in Addis Ababa, Ethiopia, at the ALERT Hospital HIV Clinic, which provides care for approximately 15,000 PLHIV. During clinic visits, clinicians asked adult patients (≥18 years of age) to participate; those who agreed and provided verbal consent were enrolled. PLHIV currently being treated for active TB disease were excluded. These patients either presented for routine (scheduled) visits or walk-in (unscheduled) visits. Patients who were enrolled were asked about the presence of current cough, fever, night sweats, and weight loss per the WHO-recommend TB screening algorithm for PLHIV (2). Patients with a positive symptom screen (i.e., one or more of the four symptoms) were asked to provide sputum samples. Because of limited laboratory capacity, only the first five patients with a positive symptom screen were enrolled into the study each day. Additionally, we conducted a 20-day sub-study where all PLHIV who presented to the clinic were screened for TB during clinic registration. Our study was approved by the Armauer Hansen Research Institute (AHRI)/ALERT Hospital and Emory University Institutional Review Boards.

Laboratory Methods

PLHIV with a positive symptom screen were asked to provide three sputum specimens for diagnostic testing: (1) A "spot" sputum specimen at the time of enrollment, (2) a "morning" sputum specimen, and (3) an additional "spot" sputum specimen when the morning specimen was returned. Once consented and enrolled in the study, the patients were given a laboratory request form for diagnostic TB testing, and were instructed to bring this form to the laboratory where they were given sputum collection cups and instructed on sputum production techniques per laboratory guidelines. Demographic information, prior history of TB, HIV treatment and anti-retroviral medication use, and laboratory results (including CD4 count) were abstracted from medical records.

AFB sputum smear microscopy was performed on all sputum samples at the ALERT Hospital microbiology laboratory using a direct Ziehl-Neelson stain as previously described (32). In addition to smear microscopy, the morning sputum sample was used for AFB culture, performed at the AHRI TB Laboratory (located on the ALERT Hospital campus) using Löwenstein-Jensen (LJ) solid media and standard diagnostic methods as previously described (26). A morning sputum specimen was also used for Xpert MTB/RIF, performed at the Addis Ababa Regional Health Research Laboratory twice weekly as previously described (16). Xpert results were reported as positive, negative, or indeterminate for *M. tuberculosis*, and for presence or absence of rifampin resistance if *M. tuberculosis* was present. Laboratory results were communicated verbally to the patient's primary clinician and recorded in the medical record; all management and treatment decisions were at the discretion of the patient's clinician.

Data Management and Analysis

Data were entered into a password-protected electronic database (REDCap) and analyzed with SAS v9.4 (SAS Institute, Cary, NC, USA) (33). Descriptive statistics were used to report the proportion of patients with a positive WHO-recommended symptom screen, sputum microscopy, Xpert, and AFB culture, and with TB disease. Active TB disease was defined as having a positive Xpert result and/or positive AFB culture for *M. tuberculosis*. χ^2, two sample t-tests, and Fisher's exact test were used to compare baseline characteristics between PLHIV with a positive versus negative WHO-recommended symptom screen and to compare those PLHIV with and without active TB disease. Univariable and multivariable logistic regression were performed to assess risk factors for a positive symptom screen as well as TB disease. Risk factors with statistical significance ($p \leq 0.05$) on univariable analysis as well as variables with biologic plausibility were included in the final multivariable models.

Cost-Effectiveness Analysis Inputs

Clinical inputs were determined from the above described implementation science study when available. When such inputs were not available, they were determined from relevant literature regarding either Ethiopian PLHIV or PLHIV in sub-Saharan Africa if Ethiopia-specific inputs were not available (**Table 1**). Base-case cost inputs were determined directly from the ALERT Hospital, Ethiopian Public Health Institute (EPHI), or Ethiopian Federal Ministry of Health (EFMOH). Costs in Ethiopian birr were converted to US dollars ($) based on the September 30, 2014, exchange rate (US$1=20 Ethiopian birr) and all prices were converted to 2014 US dollars with the U.S. Bureau of

Labor Statistics Consumer Price Index Inflation Calculator (1, 34). We took the position of cost to the Ethiopian health care system and considered costs related to TB diagnosis and treatment. We did not consider costs for maintenance of a laboratory facility where AFB cultures were performed because this is consumed equally under both algorithms.

Cost-Effectiveness Analysis Modeling Strategies

We modeled two different 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. 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 two diagnostic algorithms compared included:

(1) **WHO-recommended TB symptom screen plus Xpert diagnostic algorithm.** Under this algorithm, all PLHIV are screened for TB using the WHO-recommended symptom-screening algorithm (cough, fever, night sweats, and weight loss) (2, 6). If the symptom screen is negative (absence of all four symptoms), the patient was considered to not have active TB disease and prescribed isoniazid preventive therapy (IPT) for presumed latent TB infection per WHO guidelines (2). However, a certain proportion of these patients have active TB (i.e. false negative diagnoses).

If a patient had a positive symptom screen (presence of at least one of four symptoms), sputum samples would be tested for TB with Xpert as per WHO

guidelines for diagnostic tests for PLHIV (7). Sputum samples obtained from patients with a positive symptom screen are either positive or negative for active TB disease based on Xpert results, and a certain proportion of these are false negative or false positive diagnoses. Of those with active TB, some have drug-susceptible TB (DS-TB) and others have multi-drug resistant (MDR)-TB (MDR-TB). Patients with presumptive MDR-TB based on a positive Xpert test for rifampin resistance have sputum specimens sent for culture and drug susceptibility testing (DST) and receive treatment for MDR-TB.

This algorithm also considers cost of an Xpert MTB/RIF platform instrument (a 1-year payment based on instrument cost of US$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 (i.e., 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. The total number of machines included in the model was dependent on clinic volume (patients per day) and percent with positive symptom screens (**Table 1**).

(2) **Current practice algorithm ("CP").** As in the symptom screen and Xpert algorithm, all PLHIV are initially screened with the WHO-recommended symptom screen. Those who have a negative symptom screen are assumed to not

have active TB disease and are prescribed isoniazid preventive therapy (IPT). Those who have a positive symptom screen provide sputum samples, which are tested for active TB with two separate smear microscopy tests. PLHIV with smear microscopy results negative for TB are clinically diagnosed to be TB positive or negative. Based on an operational research study carried out at the ALERT HIV Clinic, we estimated that 64% of the patients suspected to have active TB disease although negative smear microscopy results have sputum obtained for testing via AFB culture and 92.8% of those suspected to have TB had a chest radiograph performed (26).

Cost-Effectiveness Analysis Outcomes

Our primary outcome was the incremental cost-effectiveness ratio (ICER) of the symptom screen and Xpert algorithm, calculated as 2014 U.S. dollars per disability-adjusted life year (DALY) averted. The symptom screen and Xpert algorithm was considered to be cost effective if the ICER was less than 3x Ethiopian gross domestic product (GDP) per capita and highly cost effective if less than 1x Ethiopian GDP per capita (10). Ethiopian GDP per capita was $505 (USD) in 2013 as reported by the World Bank (4). Secondary outcomes were false positive and false negative TB diagnoses, and additional ICERs of 2014 US dollars per false positive and false negative TB diagnoses averted, respectively.

DALYs were calculated as previously described with inputs shown in **Table 2** (35). For DALY calculations, we assumed that each patient was the same age (38 years, mean age

in parent study cohort). In the parent study, mean ages did not differ between those with positive and negative WHO-recommended symptom screens (38.0 vs. 38.2 years, p=0.74) or between those with and without active TB (33.8 vs. 39.2 years, p=0.08). Additionally, we assumed that proportions equivalent to the cohort proportion of women and men (65% and 35%, respectively) would end up in each arm. Similar to age, there was no gender difference between those with positive and negative WHO-recommended symptom screens (32% men vs. 36% men, p=0.21) or between those with and without active TB (38% men vs. 33% male, p=0.70). The discount rate was 3% per year (36).

Cost-Effectiveness Sensitivity Analyses

We conducted one-way sensitivity analyses by varying model inputs over reasonable ranges of parameters determined from the literature (**Table 1**). Where possible, we included ranges from Ethiopian HIV clinics; when these were unavailable, we used ranges from other studies of PLHIV in sub-Saharan Africa. References for model ranges are included in **Table 1.**

RESULTS

Patients

A total of 850 PLHIV were assessed for study eligibility (**Figure 2**); 22 were excluded due to current treatment for active TB disease. The remaining 828 PLHIV were screened for TB with the WHO-recommended symptom screen. The mean age of those who had a symptom screen performed was 38.2 years (standard deviation [SD] ±10.0); 535 (65%) were female and 293 (35%) were male (these demographics reflect the age and gender distribution in the clinic). The mean CD4 count was 420 cells/µl (SD ±219), and 730 (89%) were currently on anti-retroviral therapy (ART). A total of 272 (33%) who underwent the symptom screen had been treated for TB in the past, and 265 (33%) presented for an unscheduled visit (**Table 3**).

WHO-Recommended TB Symptom Screen

Among the 828 PLHIV screened for TB using the WHO-recommended symptom screen, 321 (39%) had a positive symptom screen (one or more of the four symptoms): 280 (34%) reported cough, 172 (21%) night sweats, 159 (19%) fever, and 103 (13%) weight loss (**Table 3**). PLHIV with a positive symptom screen were more likely to have an unscheduled visit (57%) than those who had no symptoms (24%) (odds ratio [OR]=4.11, 95% confidence interval [CI] 2.97-5.67), be screened by a physician (56% vs. 19%, OR=4.89, 95% CI 3.15-7.60), have a CD4 count <100 cells/µl (8% vs. 3%, OR=3.17, 95% CI 1.62-6.18), and not be receiving ART (16% vs. 8%, OR=2.32, 95% CI 1.48-3.64) (**Table 4**). In multivariable analysis, independent risk factors for having a positive

symptom screen included an unscheduled visit (adjusted odds ratio [aOR]=3.78, 95% CI 2.69-5.32), CD4 count <100 cells/µl (aOR=2.62, 95% CI 1.23-5.59), and past treatment for active TB (aOR=1.62, 95% CI 1.12-2.31 (**Table 5**).

TB Diagnostic Testing Results

Among the 321 PLHIV with a positive symptom-based screen, 256 were asked to provide sputum specimens for diagnostic testing (52 [16%] declined collection and 13 [4%] were not referred by their clinician for sputum collection) (**Figure 2**). There was no difference between those who accepted and declined sputum collection with respect to female gender (66% vs. 78%, p=0.09), current ART (84% vs. 82%, p=0.74), or mean CD4 count (407 cells/µl vs. 474 cells/µl, p=0.06). Among the 256 patients, 39 (15%) did not provide a sputum sample for diagnostic testing. There was no difference between those who provided sputum samples for diagnostic testing and those who did not with respect to female gender (65% vs. 67%, p=0.84), current ART (84% vs. 85%, p=0.91), or mean CD4 count (419 cells/µl vs. 367 cells/µl, p=0.13). The remaining 217 patients provided sputum samples, had AFB smear microscopy performed on these sputum specimens, and had Xpert and AFB cultures ordered on sputum samples. A total of 13 (6.0%, 95% CI 3.5-10.0%) of the 217 PLHIV had a positive Xpert and/or positive culture for *M. tuberculosis* and had active TB disease based on these positive TB diagnostic test result (**Figure 2**). None of eight patients with a positive Xpert result had rifampin-resistant TB. Compared to the gold standard of a positive Xpert test and/or positive culture for *M. tuberculosis*, the sensitivity of smear microscopy was 30%, the specificity was 100%, the positive predictive value (PPV) was 100% and the NPV was 96%.

In univariable analysis, patients with active TB were younger (OR=0.94 per year, 95% CI 0.88-1.01, p=0.08), more recently diagnosed with HIV (OR=0.98 per month since diagnosis, 95% CI 0.97-1.00, p=0.09), and had CD4 counts <100 cells/µl (OR=3.29, 95% CI 0.61-17.68, p=0.16), and were not be on current ART (OR=2.67, 95% CI 0.77-9.23, p=0.12) compared to those without TB, but the differences were not statistically significant. Prior active TB treatment was not a risk factor for current TB disease (OR=1.02, 95% CI 0.32-3.24, p=0.97). No risk factor routinely assessed at clinic visits differed significantly between those with and without active TB, including symptom screen results (**Table 6**).

Sub-Study: Symptom Screening of All HIV Clinic Patients

PLHIV enrolled into our study represented a subset of patients seen at the ALERT HIV Clinic. Therefore, over a 20-day period the WHO-recommended symptom screen was performed on all PLHIV seen at the ALERT Hospital HIV Clinic to assess the full impact of implementation of the WHO-recommend symptom screen. During this 20-day time period, 2687 PLHIV were seen in the clinic and had a symptom screen performed, and 1410 had a positive symptom screen (52.5%, 95% CI 50.6%-54.5%). On average, 134 patients visited the clinic per day, and 71 had a positive symptom screen.

Cost-Effectiveness Analysis, Base Case

We assessed the use of a WHO-recommended TB symptom screen in combination with Xpert, a molecular diagnostic test for TB, among a simulated cohort of 15,000 PLHIV in

Addis Ababa, Ethiopia. We found that the use of these two recommended WHO protocols for enhanced TB case finding among PLHIV would be highly cost-effective at an ICER of $36 per DALY averted (less than current Ethiopian GDP per capita of $505). The symptom screen/Xpert algorithm would avert 1300 DALYs compared to current practice (29,200 DALYs with symptom screen and Xpert algorithm compared to 30,500 DALYs with current practice) (**Table 7**). The symptom screen and Xpert algorithm was estimated to be more costly than current practice. With base case inputs (**Tables 1 and 2**), the symptom screen and Xpert algorithm would cost $251,000, compared to $206,000 under the current practice algorithm, an incremental cost of $45,000.

Compared to current practice, the symptom screen and Xpert algorithm would avert both false negative and false positive TB diagnoses. There would be an estimated 388 false negative cases with symptom screen and Xpert compared to 442 with current practice (54 false negative cases averted, ICER=$853 per false negative case averted). There would be 141 false positive cases with the symptom screen and Xpert algorithm compared to 2200 with current practice (2060 false positive cases averted, ICER=$22 per false positive case averted). The symptom screen and Xpert algorithm would be more cost-effective at averting false positive TB cases than at averting false negative TB cases.

Cost-Effectiveness Analysis, Sensitivity Analyses

The symptom screen and Xpert algorithm would be highly cost effective under a range of parameter estimates (**Figure 3**). It would be least cost-effective with a high Xpert cartridge cost of $73, the current price in developed countries (7). With this high

estimate, the ICER was $417 per DALY averted, still less than Ethiopian GDP per capita ($505). With a high MDR-TB treatment cost of $9712, the ICER was $91 per DALY averted. Similarly, the symptom screen and Xpert algorithm would be less cost-effective than base case with high clinical TB diagnosis sensitivity of 67% (ICER = $66 per DALY averted) and high TB prevalence of 17% (ICER = $54 per DALY averted), although still highly cost-effective in both cases. The symptom screen and Xpert algorithm would be most costly at TB prevalence of 17% ($407,000), due to the large number of PLHIV requiring TB diagnostic tests and treatment. The symptom screen and Xpert algorithm would be least costly at a low MDR-TB prevalence of 0% ($182,000), due to fewer patients requiring costly MDR-TB treatment (over 100x more costly than treatment for drug-susceptible TB).

Under two scenarios the symptom screen and Xpert algorithm would be less costly than current practice. With a high DS-TB treatment cost of $66, total cost of the symptom screen and Xpert algorithm would be US$271,000, versus $293,000 for current practice (cost savings of $22,000). Additionally, with low MDR prevalence of 0%, total cost of the symptom screen and Xpert algorithm would be $182,000, versus $206,000 for current practice (cost saving of US$24,000). In all other scenarios the symptom screen and Xpert algorithm would be more costly than current practice.

The difference in DALYs between the symptom screen and Xpert and current practice algorithms was not robust to changes in Xpert sensitivity. At a low Xpert sensitivity of 70% (13), there would be 30,600 DALYs in the symptom screen and Xpert cohort

compared to 30500 in the current practice cohort. With Xpert sensitivity of 70%, the symptom screen and Xpert algorithm would be both more costly and less effective than current practice. In no other sensitivity analysis was the symptom screen and Xpert algorithm less effective than current practice. Changing the sensitivity of smear microscopy (the primary diagnostic test in current practice) did not affect the cost-effectiveness of the symptom screen and Xpert algorithm. With a high estimate for smear microscopy sensitivity (33%) (27), incremental cost of the symptom screen and Xpert algorithm would be $41 per DALY averted. When sensitivity of clinical diagnosis improved to 67% (37), incremental cost of the symptom screen and Xpert algorithm would be $66 per DALY averted.

DISCUSSION

TB remains the leading cause of death among PLHIV in sub-Saharan Africa and globally (3, 5). Therefore, WHO recommends enhanced TB case finding among PLHIV in high-TB burden countries (2). In this implementation science pilot project, we evaluated the feasibility, efficacy, and cost-effectiveness of intensified TB case finding among PLHIV at a large HIV Clinic in Addis Ababa, Ethiopia by implementing the WHO-recommended TB symptom screen in combination with a rapid molecular diagnostic test, Xpert MTB/RIF (2, 6). While both the symptom screen and Xpert are recommended by WHO, there are limited data on the utility of combining these two interventions to enhance TB case finding among PLHIV, especially outside of South Africa. A high proportion of PLHIV (39%) in our primary study had a positive symptom screen (at least one of cough, fever, weight loss, night sweats). Among those with a positive symptom screen who provided a sputum sample, 6% (6000 per 100,000) had laboratory-confirmed pulmonary TB. Thus active pulmonary TB was common among our cohort despite high ART coverage (89%) and a relatively high mean CD4 count (420 cells/μl). Smear microscopy, the standard of care diagnostic test in many resource-limited settings including the ALERT HIV clinic, had a low sensitivity (30%) compared to Xpert and/or culture. This suggests that Xpert can enhance TB case finding among PLHIV when used in combination with the WHO-recommended symptom screen. The prevalence of TB disease in our study was similar to that reported in prior studies in Ethiopia although our cohort had a higher median CD4 count and more ART coverage (26, 27, 38). A study by Balcha et al. reported a higher TB prevalence (17%), but median CD4 count in this study

was substantially lower (172 cells/μl for PLHIV with active TB and 220 cells/μl for those without active TB) (13).

To facilitate TB screening, WHO recommends the four question symptom screen developed by Getahun et al. because of its high NPV (98%); patients who answer no to all four screening questions (cough, fever, weight loss, and/or night sweats) are highly unlikely to have active TB disease (2, 6). Despite the high sensitivity (90% in clinical settings) and NPV of the WHO symptom screen, its low specificity results in a large number of patients who receive follow-up diagnostic testing (6, 39). Our study demonstrates the burden of this low specificity on the clinic's laboratory due to a high proportion of patients with a positive symptom screen. In our sub-study, we assessed the impact of screening and diagnostic testing if all patients visiting the HIV Clinic had a symptom screen performed. During a 20-day period when we screened all patients presenting to the clinic, over half (52.5%) had a positive symptom screen. Based on the high patient volume, 71 patients per day would need to undergo TB diagnostic testing due to a positive symptom screen, a large number for this setting.

In addition to low symptom screen specificity, one of the challenges in diagnosing TB in a resource-limited setting such as Ethiopia is the low sensitivity of smear microscopy (often the only available diagnostic test) among PLHIV. Similar to other studies, we found the sensitivity of smear microscopy was poor (only 30%) (13-16). Given the low sensitivity of smear microscopy, improved diagnostics such as Xpert are needed to ensure higher TB case detection. The limitations of smear microscopy, combined with the poor

specificity of the WHO-recommended symptom screen, make implementing the screen and further diagnostic testing unfeasible without substantial investments in additional resources for laboratory and diagnostic testing. Currently, the ALERT Hospital HIV Clinic and many other clinics in high-burden areas do not have the resources to fully implement intensified TB case finding. Such clinics would need additional funding from either the Federal Ministry of Health or outside donor organizations such as PEPFAR or the Global Fund to scale up enhanced TB case finding through routine WHO-recommended TB screening in combination with improved diagnostics such as Xpert.

Although implementing enhanced TB case finding with symptom screening and Xpert will require additional resources, in our cost-effectiveness analysis our model found the symptom screen and Xpert algorithm to be highly cost-effective (US$36/DALY averted) compared to current practice (CP). This ICER is substantially lower than Ethiopian GDP per capita of US$505, the WHO's threshold for a highly cost-effective intervention (10). Cost-effectiveness of the symptom screen and Xpert algorithm in the model was robust to a wide range of inputs determined from relevant literature. Only when the sensitivity of Xpert dropped to 70% was this algorithm less effective than current practice (30600 DALYs in the symptom screen and Xpert cohort compared to 30500 in the current practice cohort). Cost difference between the symptom screen and Xpert algorithm and current practice was greatest with a high cost of Xpert cartridges (US$73), but symptom screen and Xpert was still highly cost-effective in this scenario (ICER=US$417/DALY averted). Adoption of the symptom screen and Xpert in Ethiopian HIV clinics remains

limited, and our data suggest that this algorithm may be valuable to individual patients and to the Ethiopian public health system as a whole.

Local factors, such as country-level cost inputs and clinic volume, are important in determining cost-effectiveness of various TB diagnostic strategies and therefore the extent to which they will be adopted locally (21). This is the first cost-effectiveness analysis of symptom screening and Xpert at Ethiopian HIV clinics. Although there are no other cost-effectiveness studies using inputs from Ethiopia, our results are similar to model-based cost-effectiveness analyses of Xpert conducted in other countries in sub-Saharan Africa. Among HIV patients in Uganda, a TB diagnostic algorithm using Xpert was shown to be cost-effective compared to smear microscopy (ICER=US$58/DALY averted), although less cost-effective than an algorithm that combined Xpert with a urine lateral flow assay, which our study did not consider (40). Among PLHIV being screened for TB prior to ART initiation in South Africa, a diagnostic algorithm using two Xpert samples was similarly found to be cost-effective (ICER=US$6700 per year of life saved) (41). Our study differs from the South African study because we assumed screening and Xpert testing for all patients regardless of ART status. In the implementation science portion of our study, 89% of HIV patients at the clinic were on ART, and mean CD4 count was 420 cells/μl. That our model found an Xpert algorithm to be cost-effective even in a relatively well-controlled HIV population strengthens the WHO recommendations to test all PLHIV with a positive symptom screen for TB using Xpert (2, 7). More targeted Xpert testing, i.e. more accurately ruling out ART-experienced patients without active TB disease, would both decrease costs of an Xpert algorithm

while decreasing DALYs, by subjecting fewer healthy patients to toxic and burdensome TB treatment. Although we have shown that the recommendation for symptom screening combined with Xpert testing for PLHIV with TB symptoms are cost-effective, further refinement of the symptom screen (i.e., increased specificity) will greatly help Ethiopian HIV clinics, both in terms of cost and feasibility of diagnostic testing for a large number of patients. Additionally, a cheaper point-of-care TB diagnostic test will further enhance cost-effectiveness, while potentially eliminating some of the difficulties involved with Xpert (turn around time, sample transportation, etc.).

Our study is subject to several limitations. First, because of limited laboratory capacity, only sputum samples from the first five patients with a positive symptom-screen could be processed for AFB culture and Xpert each day. This might have biased our findings if more symptomatic patients arrived at the clinic earlier to ensure an appointment; although we did not find a difference in symptom severity between those with and without TB (among those with a positive symptom screen). Secondly, 16% of PLHIV with a positive symptom screen declined to provide a sputum sample and a 15% did not have specimens collected. Although this results in a loss of statistical power, there was no baseline difference between these groups with respect to gender, ART status, or CD4 count, indicating that results are missing at random. In addition, in 5 of 13 active TB cases, either Xpert or culture was not performed. Further interventions with protocol refinement are required to ensure that all patients who have a positive symptom screen have specimens collected. Performing an Xpert test on a single specimen collected at the time of visit and screen would likely improve the rate of diagnostic testing and have a much

higher yield than three specimens for smear microscopy as is the current standard of care at the ALERT HIV Clinic.

As with any cost-effectiveness analysis, it is difficult to capture all costs associated with TB diagnosis and treatment. It is likely that there were costs not captured in our model, but these are not expected to differ greatly between the two algorithms. 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. Additionally, we did not consider transmission data or further downstream effects of TB diagnosis and treatment. However, since the symptom screen/Xpert algorithm is likely to avert more false positive and false negative cases than current practice, if we had considered repeat visits and transmission data, this would likely have caused the Xpert/symptom screen algorithm to be more cost-effective than we showed. Lastly, not all of the inputs were Ethiopia-specific (**Table 1**). While we were able to determine all of the cost inputs from Ethiopian data, there was not Ethiopia-specific data on some clinical inputs (e.g. symptom screen sensitivity and specificity). In these cases, we used data from other PLHIV in sub-Saharan Africa, and we expect these inputs to be similar between these similar populations. Uncertainty in clinical inputs was further reflected in sensitivity analyses.

In conclusion, we evaluated the utility and cost-effectiveness of combining two WHO-recommended guidelines to enhance TB case finding given limited data on the utility of this approach. We evaluated combining the WHO symptom screen with a molecular diagnostic test, Xpert, to enhance TB case finding among PLHIV. A large proportion of

PLHIV (39%) had a positive WHO-recommended symptom-based TB screen of cough, fever, night sweats, and weight loss. Nearly 90% of our patients were on ART. Of those PLHIV with a positive symptom screen, 6% were diagnosed with laboratory-confirmed active pulmonary TB; the use of Xpert increased the diagnostic yield compared to AFB smear microscopy, the standard of care diagnostic test at the clinic. Combining the WHO-recommended symptom screen and Xpert was shown in our model to be highly cost-effective in Ethiopian clinics compared to current practice (ICER=$36/DALY averted). Screening all PLHIV for TB demonstrated that implementing the WHO-recommended symptom screen in conjunction with Xpert would require substantial additional resources but would greatly enhance TB case finding.

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TABLES

Table 1. Model parameters for cost-effectiveness analysis, base case and ranges for sensitivity analyses.

Parameter	Base case	Range (reference)	Base case reference
Cost inputs, laboratory (US$)			
Smear microscopy	1.20	0.60*-2.40*	ALERT
AFB culture	2.80	1.40*-8.75 (EPHI)	EPHI
DST	1.80	0.90*-12 (EPHI)	EPHI
Xpert MTB/RIF, machine^	1480	740*-2960*	(23)
Xpert MTB/RIF, cartridge	9.98	9.98-72.87 (42)	(23)
Xpert MTB/RIF, yearly maintenance	1088.86	544.43*-2177.72*	(42)
Chest x-ray	3.50	1.75*-7*	ALERT
Cost inputs, medication (US$)			
Drug sensitive-TB	33	25.17 (43)-66*	EFMOH
MDR-TB	4856	2428*-9712*	EFMOH
IPT	5	2.50*-10*	EFMOH
Clinical characteristics			
TB prevalence	6%	4 (25)-17 (13)%	Parent study
Clinic volume (patients per day)	135	50-250†	Parent study
Proportion with positive WHO symptom screen	53%	25-75%†	Parent study

Proportion of TB cases that are MDR	2.8%	0-2.8% (1)	(1)
Symptom screen sensitivity	72%	52-91% (39)	(39)
Symptom screen specificity	50%	33-56% (39)	(39)
Smear microscopy sensitivity	30%	19 (13)-33 (27)%	Parent study
Smear microscopy specificity	100%	99.7 (13)-100%	Parent study
Xpert MTB/RIF sensitivity	79%	70 (13)-86% (44)	(44)
Xpert MTB/RIF specificity	98%	96-99% (44)	(13)
Clinical diagnosis sensitivity, AFB negative TB	61%	55-67% (37)	(37)
Clinical diagnosis specificity, AFB negative TB	69%	66-72% (37)	(37)

Definitions: AFB=acid-fast bacillus; ART=anti-retroviral therapy; DST=drug susceptibility testing; EPHI=Ethiopian Public Health Institute; EFMOH=Ethiopian Federal Ministry of Health; MDR=multi-drug resistant; IPT=isoniazid preventive therapy; TB=tuberculosis; US$=2014 U.S. dollars.

^We determined one year cost of Xpert MTB/RIF machine based on amortizing a US$17000 payment for the machine over 10 years (useful life of machine) at a 3% interest rate.

*Where values could not be found in literature searches we assumed lower bounds of ½x base case costs and upper bounds of 2x base case costs.

†Modeling assumption.

Table 2. Inputs for disability-adjusted life year calculations.

Condition	Mortality (range)	Disability weight (range)
HIV, TB negative	0.05 (0-0.3) (40)	0.053 (0.034-0.079) (45)
HIV, untreated TB	1 (0.5-1) (40, 46)	0.399 (0.267-0.547) (45)
HIV, treated drug-susceptible TB	0.105 (0.04-0.3) (46, 47)	0.1 (0.085-0.115) (40)
HIV, treated MDR-TB	0.2 (0.04-0.37) (46-48)	0.2 (40)

Definitions: HIV=human immunodeficiency virus; MDR=multidrug resistant; TB=tuberculosis.

Inputs were used to calculate disability-adjusted life years as previously described (8). References are listed in parentheses after range.

Table 3. Baseline demographic characteristics of HIV-infected patients screened for tuberculosis at the ALERT Hospital HIV Clinic in Addis Ababa, Ethiopia (N=828).

Characteristic	**N (%)**
Age, years (mean ±SD)	38.2 (±10.0)
Female gender	535 (65%)
Unscheduled visit	265 (33%)
Type of provider at study visit	
Nurse	402 (49%)
Physician	276 (34%)
Health Officer	145 (18%)
HIV History	
Time since HIV diagnosis, months (mean ±SD)	64.8 (±37.1)
CD4 count, cells/µl (mean ±SD)	420.1 (±218.5)
CD4 count (cells/µl)	
<100	40 (5%)
100-200	87 (11%)
>200	683 (84%)
Currently on ART	730 (89%)
Duration of ART, months (mean ±SD)^	57.0 (±32.5)
WHO HIV Stage	
I	430 (55%)
II	150 (19%)
III	148 (19%)
IV	27 (3%)

Unknown	73 (9%)
TB History	
Past active TB treatment	272 (33%)
Type of prior TB*	
Pulmonary	212 (78%)
Extra-pulmonary	35 (13%)
Both	7 (3%)
Unknown	18 (7%)
WHO-Recommended TB Symptom Screen Results[#]	
Any symptom (screen positive)[#]	321 (39%)
Cough	280 (34%)
Night sweats	172 (21%)
Fever	159 (19%)
Weight loss	103 (13%)
≥2 symptoms	222 (27%)
≥3 symptoms	117 (14%)
All 4 symptoms	44 (5%)

Abbreviations: ART=anti-retroviral therapy; HIV=human immunodeficiency virus; µl=microliter; TB=tuberculosis; WHO=World Health Organization

^Only includes patients currently on ART.

*Only includes patients treated for TB in the past.

[#]Per the WHO, HIV patients in high-burden areas with at least one of the four listed symptoms have a positive symptom screen for TB (2, 6).

Table 4. Comparison of baseline characteristics between HIV patients with a positive and negative WHO-recommended TB symptom screen.

Risk Factor	Symptom screen positive (n=321, 39%) N (%)	Symptom screen negative (n=493, 61%) N (%)	OR* (95% CI)	P
Age, years (mean ±SD)	38.0 (±10.4)	38.2 (±9.7)	1.00 (0.98-1.01)	0.74
Female gender	213 (68%)	312 (64%)	1.21 (0.90-1.63)	0.21
Unscheduled visit	157 (57%)	107 (24%)	4.11 (2.97-5.67)	<0.001
Clinician type				
Physician	179 (56%)	92 (19%)	4.89 (3.15-7.60)	<0.001
Nurse	99 (31%)	295 (60%)	0.84 (0.55-1.29)	0.43
Health officer	41 (13%)	103 (21%)	1	--
Months since HIV diagnosis (mean ±SD)	62.2 (±37.6)	66.3 (±36.9)	1.00# (0.99-1.00)	0.14
Current CD4 count, cells/µl (mean ±SD)	410.9 (±228.4)	423.9 (±211.9)	--	--
CD4 count status (cells/µl)				
<100	26 (8%)	14 (3%)	3.17 (1.62-6.18)	<0.001
100-200	34 (11%)	52 (11%)	1.12 (0.70-1.77)	0.64
>200	248 (81%)	423 (87%)	1	--
Not currently on ART	51 (16%)	39 (8%)	2.32 (1.48-3.64)	<0.001
Duration of ART, months (mean ±SD)^	55.0 (±33.2)	57.3 (32.4)	1.00# (0.99-1.00)	0.38

WHO HIV Stage				
I	152 (50%)	267 (57%)	1	--
II	55 (18%)	93 (20%)	1.04 (0.71-1.53)	0.85
III	75 (25%)	73 (16%)	1.81 (1.24-2.64)	<0.01
IV	13 (4%)	13 (3%)	1.76 (0.79-3.89)	0.16
Past active TB treatment	115 (36%)	150 (31%)	1.31 (0.97-1.76)	0.16

Definitions: ART=anti-retroviral therapy; CI=confidence interval; HIV=human immunodeficiency virus; µl=microliter; OR=odds ratio; SD=standard deviation; TB=tuberculosis; WHO=World Health Organization.

*Odds ratios are results of univariable analysis of risk factors for a positive symptom screen.

#Odds ratios reflect change in odds for one unit increase in time.

^Only includes patients currently on ART.

Table 5. Multivariable analysis of risk factors for a positive WHO-recommended tuberculosis symptom screen among HIV-infected patients.

Characteristic	OR (95% CI)	P
Age (per year)	1.01 (0.99-1.03)	0.41
Female gender	1.33 (0.92-1.92)	0.13
Visit type		
Unscheduled	3.78 (2.69-5.32)	<0.001
Scheduled	1.00	
<100	2.62 (1.23-5.59)	0.01
100-200	1.18 (0.69-2.02)	0.54
>200	1.00	
No current ART	1.56 (0.89-2.74)	0.12
Past active TB treatment	1.62 (1.12-2.31)	<0.01

Definitions: ART=anti-retroviral therapy; CI=confidence interval; HIV=human immunodeficiency virus; µl=microliter; OR=odds ratio; SD=standard deviation; TB=tuberculosis; WHO=World Health Organization.

Table 6. Comparison of baseline characteristics between HIV-infected patients with positive and negative tuberculosis diagnostic tests.

Risk Factor	Positive TB diagnostic test (n=13, 6%) N (%)	Negative TB diagnostic test (n=204, 94%) N (%)	OR* (95% CI)	P
Age, years (mean ± SD)	33.8 (±8.1)	39.2 (±10.8)	0.94[#] (0.88-1.01)	0.08
Male gender	5 (38%)	66 (33%)	1.25 (0.39-3.97)	0.70
Unscheduled visit	8 (62%)	88 (52%)	1.47 (0.46-4.69)	0.51
Clinician type				
Doctor	7 (54%)	101 (50%)	0.83 (0.16-4.26)	0.83
Nurse	4 (31%)	78 (38%)	0.62 (0.11-3.57)	0.59
Health officer	2 (15%)	24 (12%)		
Symptom screen results				
Cough	12 (92%)	169 (84%)	2.27 (0.29-18.09)	0.44
Fever	5 (38%)	95 (48%)	0.69 (0.22-2.19)	0.53
Night sweats	5 (38%)	111 (55%)	0.51 (0.16-1.60)	0.25
Weight loss	6 (46%)	63 (32%)	1.87 (0.60-5.77)	0.28
≥2 symptoms	7 (54%)	144 (71%)	0.48 (0.16-1.51)	0.21
≥3 symptoms	7 (54%)	74 (36%)	2.05 (0.66-6.33)	0.21
4 symptoms	2 (15%)	28 (14%)	1.14 (0.24-5.43)	0.87
Time since HIV diagnosis, months	44.2 (±39.1)	65.3 (±37.7)	0.98[#] (0.97-1.00)	0.09

(mean ±SD)				
Current CD4 count, cells/µl (mean ±SD)	360.1 (±261.3)	412.5 (±224.2)	--	--
CD4 count status (cells/µl)				
<100	2 (20%)	16 (8%)	3.29 (0.61-17.68)	0.16
100-200	2 (20%)	23 (12%)	2.29 (0.44-12.03)	0.33
>200	6 (40%)	158 (80%)	1	--
No current ART	4 (31%)	28 (14%)	2.67 (0.77-9.23)	0.12
Duration of ART, months (mean ±SD)^	62.5 (±27.3)	57.7 (±34.2)	1.00[#] (1.00-1.00)	0.70
Past active TB treatment	5 (38%)	77 (38%)	1.02 (0.32-3.24)	0.97

Definitions: ART=anti-retroviral therapy; CI=confidence interval; HIV=human immunodeficiency virus; OR=odds ratio; SD=standard deviation; TB=tuberculosis; WHO=World Health Organization.

*Odds ratios are results of univariable analysis of risk factors for a positive symptom screen.

[#]Odds ratios reflect change in odds for one unit increase in time.

^Only includes patients currently on ART.

Active TB disease was defined as having a positive Xpert results and/or positive AFB culture for *M. tuberculosis.*

Table 7. Expected outcomes and cost-effectiveness of two WHO-recommended strategies for intensified tuberculosis case finding at Ethiopian HIV clinics.

Outcome	Algorithm		ICER^
	Symptom screen/Xpert, N (range*)	Current practice, N (range*)	
TB cases	900 (600-2550)	900 (600-2550)	--
Cost, 1000 US$	251 (182-735)	206 (175-293)	--
DALYs, thousands	29.2 (11.9-116)	30.5 (13.1-117)	36 (-1100-418)
FN TB cases	388 (253-1100)	442 (295-1250)	853 (-8270-9800)
FP TB cases	141 (71-282)	2200 (1920-2930)	22 (-12-258)

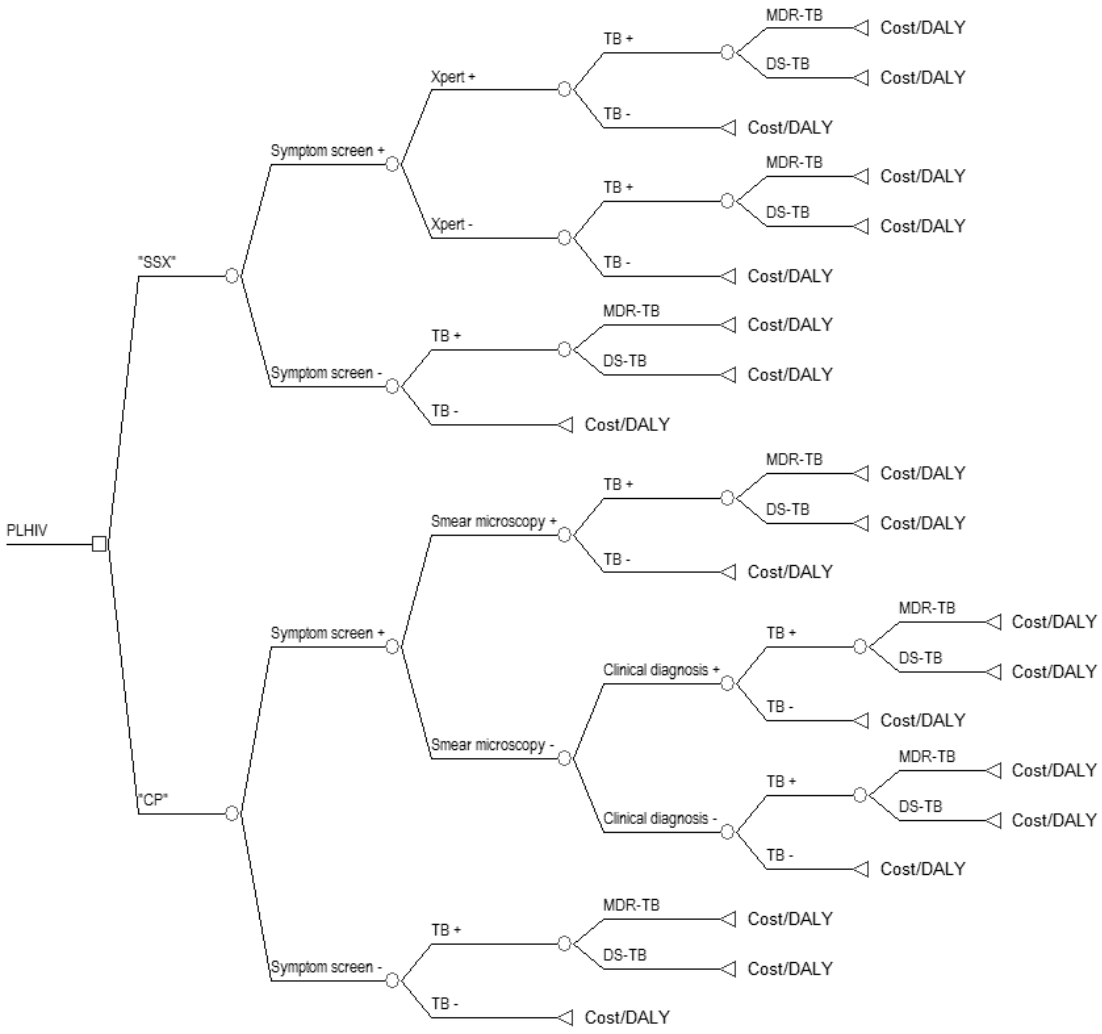
Definitions: DALY=disability-adjusted life year; FN=false negative; FP=false positive; ICER=incremental cost-effectiveness ratio; TB=tuberculosis; US$=2014 US dollars.

^ICERs were calculated for each row according to the following formula (e.g. for DALY): $ICER=[Cost_{Symptom\ screen/Xpert} - Cost_{Current\ practice}]/[DALY_{Current\ practice} - DALY_{Symptom\ screen/Xpert}]$.

*Ranges are minimum and maximum values determined from sensitivity analyses.

FIGURES

Figure 1. Decision analysis model for tuberculosis screening and diagnosis among patients at Ethiopian HIV clinics.

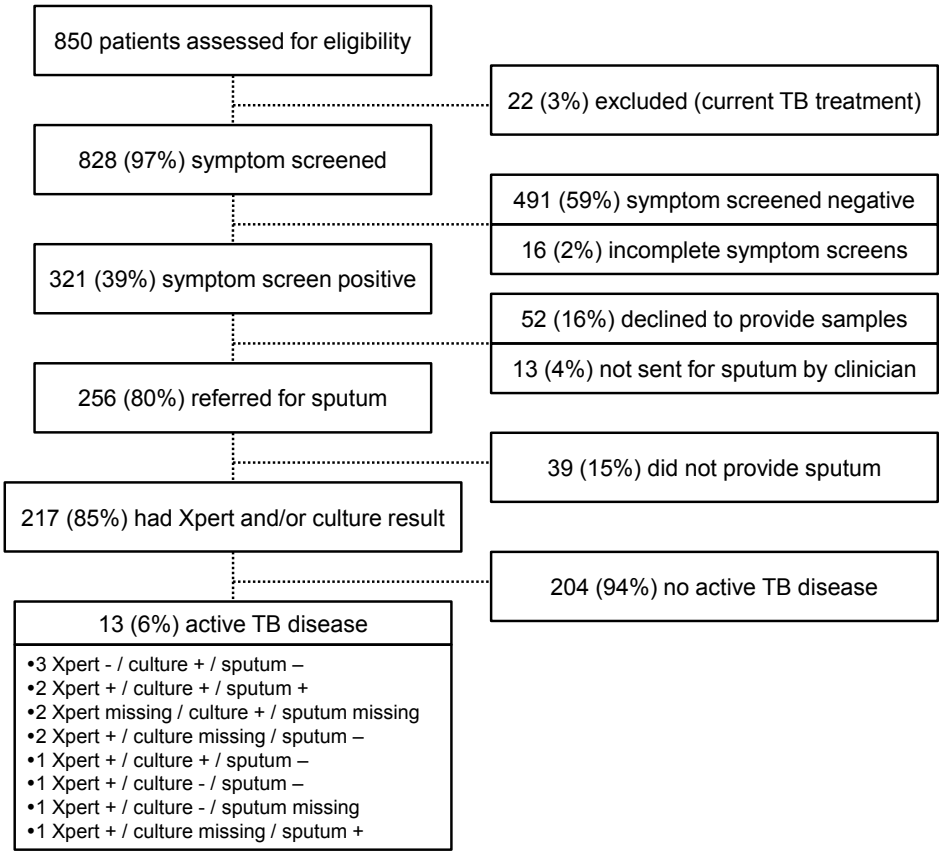


Definitions: CP=current practice algorithm; DALY=disability-adjusted life year; DS=drug sensitive; MDR=multi-drug resistant; PLHIV=people living with HIV; SSX=symptom screen/Xpert algorithm; TB=tuberculosis.

Legend: Decision analytic model with two different strategies for TB screening and diagnosis among PLHIV: (1) Symptom screen/Xpert ("SSX") combines a WHO-recommended symptom screen (cough, fever, night sweats, weight loss) with Xpert as the initial diagnostic test for those who screen positive (have at least one symptom) (2, 6). (2) Current practice ("CP") 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.

Figure 2. Flow diagram of HIV-infected patients screened and tested for tuberculosis at the ALERT Hospital HIV Clinic in Addis Ababa, Ethiopia.



Abbreviations: HIV=human immunodeficiency virus; TB=tuberculosis.

Active TB disease was defined as a positive Xpert MTB/RIF result and/or a positive AFB culture for *M. tuberculosis.*