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Programmatic Evaluation of an Algorithm for Intensified Tuberculosis Case Finding and Isoniazid Preventive Therapy for People Living With HIV in Thailand and Vietnam

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Abstract

Background: Tuberculosis (TB) screening affords clinicians the opportunity to diagnose or exclude TB disease and initiate isoniazid preventive therapy (IPT) for people living with HIV (PLHIV).

Methods: We implemented an algorithm to diagnose or rule out TB among PLHIV in 11 HIV clinics in Thailand and Vietnam. We assessed algorithm yield and uptake of IPT and factors associated with TB disease among PLHIV.

Results: A total of 1448 PLHIV not yet on antiretroviral therapy (ART) were enrolled and screened for TB. Overall, 634 (44%) screened positive and 119 (8%) were diagnosed with TB;

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of these, 40% (48/119) were diagnosed by a positive culture following a negative sputum smear microscopy. In total, 55% of those eligible (263/477) started on IPT and of those, 75% (196/263) completed therapy. The prevalence of TB disease we observed in this study was 8.2% (8218 per 100,000 persons): 46 and 25 times the prevalence of TB in the general population in Thailand and Vietnam, respectively. Several factors were independently associated with TB disease including being underweight [aOR (95% CI): 2.3 (1.2 to 2.6)] and using injection drugs [aOR (95% CI): 2.9 (1.3 to 6.3)].

Conclusions: The high yield of TB disease diagnosed among PLHIV screened with the algorithm, and higher burden among PLHIV who inject drugs, underscores the need for innovative, tailored approaches to TB screening and prevention. As countries adopt test-and-start for antiretroviral therapy, TB screening, sensitive TB diagnostics, and IPT should be included in differentiated-care models for HIV to improve diagnosis and prevention of TB among PLHIV.

Keywords

tuberculosis; isoniazid preventive therapy; intensified case finding; Southeast Asia; implementation science; TB/HIV

INTRODUCTION

An estimated 1.2 million persons living with HIV (PLHIV) developed Tuberculosis (TB) disease in 2015, representing 11% of all new TB cases globally.[1] Tuberculosis remains the leading preventable cause of death and accounts for more than a quarter of deaths among PLHIV.[1–4] In Southeast Asia, between 20% and 30% of PLHIV with TB disease die during TB treatment.[5–9] Most TB-associated deaths among PLHIV occur within 2 months of TB diagnosis and delayed TB diagnosis contributes to high TB/HIV mortality.[5–9] Among PLHIV, TB screening and prompt initiation of TB treatment can reduce morbidity and mortality and interrupt disease transmission.[4,10–12]

Tuberculosis screening also affords clinicians the opportunity to rule out TB disease and initiate preventive therapy.[3,12] The World Health Organization (WHO) recommends isoniazid preventive therapy (IPT) be offered to all PLHIV for whom TB disease has been ruled out through screening.[2] Isoniazid preventive therapy provides additional protection from TB disease above what is conferred by antiretroviral therapy (ART) alone, even among those who initiate ART at CD4 counts >500 cells/mm^3, making IPT an important tool to reduce TB incidence and mortality among PLHIV.[13] However, in 2015, only 38% of PLHIV newly enrolled into HIV care received IPT globally.[14] Clinical presentation of TB disease among PLHIV can often be nonspecific and tools used to screen for TB disease in resource-limited settings such as sputum smear microscopy have poor sensitivity among PLHIV.[15–17] Clinicians may be hesitant to provide IPT given the challenges in accurately and efficiently excluding TB disease and fear of inadvertently prescribing isoniazid monotherapy to persons with TB disease and thereby promoting selection of resistant bacteria.[18]

The improving diagnosis of TB among people living with HIV (ID-TB/HIV) study, conducted in Cambodia, Thailand, and Vietnam from 2006 to 2008, developed an algorithm to better diagnose and exclude TB disease among PLHIV.[19] The ID-TB/HIV algorithm

exhibited 93% sensitivity and a 97% negative predictive value when used with PLHIV at enrollment into HIV care, making it useful for intensified case finding and for ruling out TB to initiate IPT. After this study, Ministries of Health in these 3 countries sought to implement symptom-based screening algorithms for PLHIV to screen for and diagnose TB or rule out TB disease and identify persons eligible for IPT.[19]

This study aimed to implement and evaluate the utility of this evidence-based algorithm in (1) diagnosing TB disease and (2) ruling out TB disease and prescribing IPT of under routine programmatic settings in Thailand and Vietnam. Specifically, we aimed to describe participant flow through the screening and diagnostic cascade, evaluate the diagnostic yield of each screening step or test in the algorithm, and describe uptake and outcomes for both persons diagnosed with TB disease and those started on IPT. We also aimed to characterize factors associated with screening positive and TB diagnosis among PLHIV.

METHODS

Setting and Study Design

In Thailand in 2010, the incidence of TB was 137 per 100,000 persons and the HIV prevalence was 1.3% overall and 16% among persons with TB.[20,21] In Vietnam in 2010, the incidence of TB was 199 per 100,000 persons and the HIV prevalence was 0.5% overall and 8% among persons with TB disease.[20,21]

We enrolled PLHIV presenting to 11 HIV outpatient clinics (OPCs) in Bangkok, Thailand (n = 7) and Ho Chi Minh City (HCMC), Vietnam (n = 3) and Hanoi, Vietnam (n = 1) between January 2010 and November 2011. Study sites were selected based on patient enrollment and perceived ability to implement the study algorithm. Written informed consent was obtained in Vietnamese and Thai, and study staff were trained to administer consent and avoid coercive practices; no incentives or payments were offered as part of this study. We enrolled all consenting PLHIV aged ≥18 years not yet receiving ART, both newly and previously registered for HIV care. Persons living with HIV were ineligible for the study if they were <18 years, currently receiving ART or treatment for TB disease, treated for TB in the previous year, or took medications with anti-mycobacterial activity within the past month. Those who were not eligible or declined participation received routine care per local guidelines. Outcomes of TB treatment or IPT were recorded at 1 year after enrollment. The protocol was approved by Institutional Review Boards in Thailand, Vietnam, and at the U.S. Centers for Disease Control and Prevention (CDC).

Screening, Diagnosis and IPT Eligibility

Participants were screened and evaluated according to the algorithm (Fig. 1). Screening was based on the presence of any of the following symptoms within the 4 weeks preceding the clinic visit: (1) cough of any duration; (2) fever of any duration; or (3) drenching night sweats ≥3 weeks. Further diagnostic evaluation was required for individuals reporting one or more of the 3 screening symptoms (ie, screening positive). Unique to this algorithm was that PLHIV with a positive symptom screen, negative sputum smear, and a normal chest radiograph were then stratified by their CD4 count. Persons living with HIV with

CD4 counts <350 cells/μL had liquid culture of sputum. Individuals with CD4 counts ≥350 cells/μL were re-evaluated for TB using the algorithm at their next clinical encounter.

Participants not reporting any of the 3 symptoms could be initiated on IPT or have chest radiography per the clinician's discretion to increase the negative predictive value of the algorithm (Fig. 1). Both persons with a negative symptom screen and a positive symptom screen were eligible for IPT after TB disease was sufficiently ruled out. In Thailand, only PLHIV with a positive tuberculin skin test (TST) were eligible for IPT per national guidelines. Based on consensus between the Ministries of Health and investigators, participants were considered ineligible for IPT if they had any of the following characteristics: (1) current TB diagnosis; (2) any chest radiography abnormalities; (3) a record of previous or current treatment for TB; (4) reported alcohol dependency; (5) were pregnant, (6) had advanced HIV disease (WHO clinical stage III or IV); (7) a history of hepatitis or liver disease; or (8) any abnormal liver function test (alanine aminotransferase test or aspartate aminotransferase test ≥120 units/L).

Data Collection and Analysis

Site staff used standardized study forms during clinical encounters to collect data on demographic indicators, including self-reported use of injection drugs and smoking. Site staff also used standardized forms to abstract the results of TB screening and laboratory tests, and clinical interventions including TB treatment or prescription of IPT from participants' HIV medical records.

We described demographic and clinical characteristics of participants. We documented how participants moved through the steps of the diagnostic algorithm, the results of diagnostic tests, and proportion of PLHIV diagnosed at each step of the algorithm. We also quantified eligibility, prescription and outcome of IPT, and number and types of deviations from the diagnostic algorithm (ie, missing or extra diagnostic tests). We examined bivariable and multivariable associations between demographic and clinical characteristics and country of enrollment, screening result, and TB diagnosis using generalized estimating equations (GEE) to account for clustering within study sites. All measured variables and their pairwise interaction terms were considered for inclusion in final models, which were constructed using backwards elimination at a significance value of $\alpha = 0.05$. Known predictors of TB disease were identified a priori and remained in the final adjusted models regardless of statistical significance (ie, country, gender, age, previous TB diagnosis, smoking, and adherence history to HIV care visits).

RESULTS

Demographic and Clinical Characteristics of Study Participants

A total of 1448 PLHIV not yet on ART were enrolled and screened for TB between January 2010 and November 2011; 659 (46%) from Thailand and 789 (54%) from Vietnam (Table 1). Fifty-two percent (n = 749) of participants were men and 30% (n = 435) were underweight. Current smoking was common among participants (n = 562, 39%); however, more men reported smoking than did women (63% vs. 14%, respectively). Seventy-three

participants (5%) reported having a previous TB diagnosis and 3% (n = 41) reported injecting drugs.

Overall, 39% (n = 569) of participants had been diagnosed with HIV in the past 6 months; however, 31% of participants (n = 442) had been diagnosed with HIV more than 3 years before study enrollment. Participants had a median CD4 count of 327 cells/μL (IQR 168, 478), with no difference in baseline CD4 between Thailand and Vietnam. Participants from Vietnam tended to be younger, underweight at enrollment, were more likely to report a previous TB diagnosis, have a history of missing HIV care visits, and were more likely to report regular smoking and using injection drugs than participants in Thailand (Table 1).

Algorithm Performance at Study Enrollment

Overall, 634 (44%) participants had cough, fever or night sweats and thus screened positive for TB. Cough was the most common screening symptom reported, with 538 (37%) of participants reporting having cough; 369 (25%) reported having fever, and 154 (11%) reported night sweats lasting 3 or more weeks (Table 1). Of the 634 participants with a positive screen, 92 (15%) were diagnosed with TB disease per the diagnostic algorithm (Fig. 2)—26 through a positive sputum smear, 13 based on CXR abnormalities, 39 through sputum culture, and 14 empirically treated for TB, including 9 with extrapulmonary TB (EPTB) disease. For participants with a negative symptom screen (n = 814), 505 (62%) underwent optional CXR and of these, 467 (92%) had no abnormalities noted (Fig. 2).

In total, 119 PLHIV were diagnosed with TB disease; 29 (24%) were diagnosed based on smear, 48 (40%) based on culture, 15 (13%) based on CXR, and 27 (23%) based on clinical judgment. Of 48 participants with TB diagnosed through culture, all 48 were diagnosed following a negative sputum smear and 58% (28/48) following a normal chest radiograph. Overall, 92 of 634 (15%) PLHIV with positive symptom screens were diagnosed with TB per the diagnostic algorithm and 5 of 814 (1%) participants with negative symptoms screens were diagnosed through algorithm-permitted tests following abnormal CXR for a total of 97 TB diagnoses made through the algorithm. There were 253 laboratory tests (167 sputum smear examinations and 86 cultures) performed outside of the screening and diagnostic algorithm among 16% (238 of 1448) of participants. Tests ordered outside of the diagnostic algorithm resulted in 9 (7 culture, 2 smear) additional laboratory-confirmed TB diagnoses; 5 among PLHIV that screened positive and 4 that screened negative (Fig. 2). An additional 13 PLHIV (7 with positive symptom screens and 6 with negative symptom screens) were empirically treated for TB outside of what was indicated by the algorithm and without laboratory confirmation. Approximately half (13/27) of TB diagnoses made based on clinical judgment were extrapulmonary diagnoses (Fig. 2).

TB Prevalence and Screening, TB Treatment, and IPT Initiation

Overall, 16% of PLHIV with a positive symptom screen (104 of 634) and 2% of PLHIV with a negative symptom screen (15 of 814) were diagnosed with TB disease through their enrollment screening. The overall prevalence of TB among PLHIV at enrollment was 8218 per 100,000 persons, substantially higher than among the general populations in Vietnam (334 per 100,000 persons) and Thailand (182 per 100,000 persons) during

our study period.[20] Seventy-eight percent of diagnoses were pulmonary disease (n = 93); however, 15% (n = 18) of all TB diagnoses were extrapulmonary TB, and 7% (n = 8) had both pulmonary and extrapulmonary involvement.

Several factors were significantly associated with a positive symptom screen and TB diagnosis in bivariable and multivariable analysis (Table 2). In adjusted models, being underweight, low CD4 count, previous TB diagnosis, injection drug use, smoking, and more recent HIV diagnosis were independently associated with a positive screening (Table 2). Similarly, being underweight, male sex, low CD4 count, and injection drug use were independently associated with TB diagnosis (Table 2). The highest prevalence of positive symptom screening and TB disease was observed among persons who inject drugs (PWID), of whom 73% (30 of 41) screened positive and 24% (10 of 41) were diagnosed with TB disease. In adjusted models, the odds of being diagnosed with TB disease were 2.9 times higher (95% CI aOR: 1.3 to 6.3) among PLHIV reporting injection drug use than among PLHIV who did not report injecting drugs.

Of the 119 PLHIV diagnosed with TB, 115 (97%) initiated TB treatment and of these, 77 (67%) were cured, completed treatment or were still receiving treatment 1 year after enrollment. Fifteen (13%) PLHIV died while receiving treatment (Table 3). The median time from TB screening to TB treatment initiation was 13 days (IQR: 7, 43); however, time to treatment was longer for participants diagnosed by culture [median: 42.5 days (IQR: 22, 59)] compared with those diagnosed by all other methods [median: 8 days (IQR: 6, 19)].

Overall, 53 of 659 (8%) of participants in Thailand and 424 of 789 (54%) of participants in Vietnam were eligible for IPT (Table 3). In Thailand, only participants with a positive TST were eligible for IPT, and 53% (346 of 659) were ineligible because of negative TST results (n = 278) or because no TST was conducted (n = 68). Among the PLHIV eligible, 87% (46 of 53) in Thailand and 51% (217 of 424) in Vietnam initiated IPT. One year after enrollment, 83% (38 of 46) and 77% (168 of 217) of participants who began IPT in Thailand and Vietnam, respectively, either completed 9 months of IPT or were still taking IPT. Overall, 3 PLHIV started on IPT (1%) developed TB disease during IPT compared with 5% (10 of 214) of those eligible but not prescribed IPT. All 3 participants diagnosed with TB disease while on IPT initially screened negative (asymptomatic) and had normal CXR results. Among 346 participants in Thailand otherwise eligible for IPT but excluded from IPT eligibility because of TST criteria, 6 (2%) developed TB disease during 1-year follow-up—1% (4 of 278) of those with a negative TST and 3% (2 of 68) with TST not done.

DISCUSSION

Performance of the Screening Algorithm

In years before this study, Ministries of Health in Thailand and Vietnam recommended screening PLHIV for chronic cough greater than 2 weeks; however, this approach was not sensitive to detect TB in PLHIV. In this study, use of the algorithm enabled clinicians to systematically screen and focus diagnostic evaluations on the less than half of PLHIV screening positive for TB (44%), where we noted a very high prevalence of TB disease

among PLHIV enrolled in our study—more than 25 times the prevalence of TB in the general populations in Thailand and Vietnam. For PLHIV diagnosed with TB disease, less than one quarter were diagnosed by smear microscopy, which remains the primary diagnostic test for TB in many parts of the world. Sputum culture was the most common method of diagnosis (48 of 119), and nearly 60% of those with a positive culture had negative smear and normal CXR; these individuals likely would have a missed or delayed diagnosis if culture was not included in this algorithm. Additionally, those diagnosed through culture experienced substantial delays in TB treatment initiation—5 times longer than those diagnosed through other methods (median of 43 days compared with 8 days, respectively). Although this study was implemented before the recommendation, routine availability, and use Xpert MTB/Rif (Xpert) as the initial test for diagnosing TB among PLHIV, our results underscore the importance of rapid diagnostic tests to improve sensitivity and reduce time to TB treatment for PLHIV. Current diagnostic algorithms in Vietnam and Thailand should be revisited to reflect these recommendations and GeneXpert instrument availability PLHIV to alleviate the need for culture and improve sensitivity over smear microscopy (eg, current diagnostic algorithm in Vietnam recommends Xpert MTB/Rif for PLHIV in Vietnam only after a negative smear).

For PLHIV with negative symptom screens, Thailand and Vietnam used CXR to increase the negative predictive value of the algorithm; 15 participants were diagnosed with TB following a negative symptom screen. Five of these 15 participants were diagnosed following abnormal CXR; however, the remaining 10 participants were diagnosed without CXR (n = 2) or with normal results on CXR (n = 8). Clinicians in this setting also occasionally ordered diagnostic tests outside of the algorithm's indications. Yield of these microbiological tests was low (2%) when ordered in asymptomatic persons with normal CXR, suggesting that the algorithm is relatively efficient in excluding TB disease for IPT eligibility.

Persons living with HIV enrolled in Vietnam were younger and had a higher prevalence of self-reported injection drug use and smoking than PLHIV enrolled in Thailand, reflecting differences in the HIV epidemics in the respective countries. In Thailand, an estimated 90% of new infections between 2012 and 2013 occurred through sexual transmission, with 41% of new infections among specific vulnerable populations including men who have sex with men (MSM), male sex workers (MSW), and transgender persons (TG).[22,23] In contrast, injection drug use is the predominant transmission route for HIV in Vietnam, where models suggest that 45% of new infections occurred among male PWID (surveys of persons who inject drugs only included men) in 2013.[24,25] Different TB and HIV prevention, care, and treatment strategies are therefore needed to address these specific differences in TB and HIV epidemiology in the two countries.

Among enrolled PLHIV, certain subgroups were especially vulnerable to TB disease, including PWID. Nearly three quarters of enrolled PWID screened positive and more than one quarter were diagnosed with TB disease. Even after adjusting for other factors including CD4 count, the odds of being diagnosed with TB disease were almost 3 times higher among PWID than among PLHIV who did not report injecting drugs. The higher prevalence of TB noted among PWID may be due to both physiological effects of drug use including impaired

immunity, and environmental and behavioral factors that confer greater risk for TB including homelessness and incarceration.[26,27] Based on our data, TB screening and provision of IPT once TB disease is excluded are especially important and high yield for PWID, and programs should consider integrating TB services into existing services designed to reach this population (ie, methadone management programs, harm reduction services, etc.).[28,29]

IPT Prescription and Eligibility

The proportion of eligible PLHIV starting IPT after enrollment (55%) exceeded what has been reported to WHO. Only one percent of those prescribed IPT developed TB disease compared with 5% of participants eligible but not prescribed IPT during the 1-year follow-up. However, the gap between those eligible and those prescribed IPT represents a missed opportunity to treat latent TB infection (LTBI) and provide PLHIV with protection from TB disease while reestablishing immune functioning during the initiation of ART. Before and during our study period, even after training, study staff reported that some clinicians expressed hesitancy to prescribe IPT because of fears of prescribing monotherapy for active TB disease, and study sites reported limited isoniazid stock because of nationwide shortages. These factors may explain some of the gap between those eligible and those prescribed IPT although we did not systematically collect this information.

Although we enrolled only participants not yet on ART, IPT provides additional protection from TB disease above what is conferred by ART alone, even among those who initiate ART at CD4 counts >500 cells/mm^3.[13] Therefore, IPT remains an important tool to prevent TB disease among PLHIV, even for those immediately starting ART when diagnosed with HIV (test-and-start). For this study, we adopted the IPT exclusion criteria from the ID-TB/HIV study which are slightly more exclusive than current recommendations in Thailand and Vietnam which limits our ability to draw conclusions about impact of IPT in excluded groups (eg, pregnant women were excluded from consideration from IPT in the study, but would be eligible per national guidelines).[3] In Thailand, only participants with a positive TST were eligible for IPT per national guidelines; this restriction excluded 346 (>50%) who would have otherwise been eligible for IPT, of whom 2% developed TB during 1-year follow-up. WHO does not require TST for initiation of IPT because of the logistical challenges it may introduce.[3] Although the benefits of IPT may be more pronounced in persons with a positive TST, requiring TST may exclude participants who may otherwise benefit from IPT; TST has poor sensitivity for PLHIV who are immunosuppressed and requires adequate supply of test materials, staff trained to administer and interpret results, and repeated visits by the patient.[30–34]

Limitations

After this study was initiated, WHO added unexplained weight loss as part of the recommended symptom screening for PLHIV.[3] We were unable to evaluate how the addition this symptom to the screening may have impacted our results because we did not collect these data. We recruited only PLHIV not yet on ART, including newly and previously enrolled into HIV care, and therefore excluded individuals already on ART. During study implementation, ART initiation was based on CD4 count and therefore, it is likely that the individuals already on ART and not enrolled into our study had more advanced HIV disease

than enrolled participants, which may limit the generalizability of our results to all PLHIV. Information on ART initiation and CD4 count after enrollment was not collected as part of this protocol. Therefore, we are unable to assess how screening and IPT may have impacted mortality or how ART may have impacted TB treatment outcomes for enrolled PLHIV. A smaller proportion of persons diagnosed with TB during follow-up were prescribed IPT compared with those eligible who did not initiate IPT (1% vs. 5%, respectively), these differences may be due to inherent differences between groups that limit the utility of this comparison and warrants further study. Data on smoking, alcohol use and use of injection drugs were self-reported, introducing potential for under-reporting. Only 4% of PLHIV enrolled in Vietnam reported injecting drugs, which is likely an underestimate, because of sensitivities regarding reporting these behaviors, which are illegal in Thailand and Vietnam.

Study sites were not randomly selected, so the results we observed are likely not generalizable to all outpatient HIV care settings in Thailand and Vietnam. We were unable to calculate sensitivity and specificity of the algorithm for TB diagnosis because we do not have a comparative gold standard (ie, culture) for all participants; however, we describe yield of these tests when ordered per the algorithms indications and outside the algorithms indications. Because laboratory testing was performed at multiple sites, it is possible that systematic variability may exist between sites.

CONCLUSIONS

Tuberculosis remains the leading cause of death among PLHIV. Programmatic implementation of TB screening and TB preventive therapy, the core components of this study, remain important tools to reduce TB morbidity and mortality among PLHIV. Systematic screening and use of a diagnostic algorithm yielded a very high prevalence of TB disease among PLHIV enrolled in our study—8218 per 100,000 persons, more than 20 times higher than the prevalence among the general populations in Thailand and Vietnam.[20] Screening for TB disease among PLHIV not only represents an opportunity for early diagnosis and treatment of TB but also a critical opportunity to prevent TB through ruling out TB disease and initiating IPT. Among PLHIV in our study, those underweight or using injection drugs had an especially high burden of TB disease, emphasizing the need for innovative approaches to TB screening and prevention efforts specifically tailored to the address the unique needs of these groups.

The majority of TB diagnoses in this study were made by culture following a negative smear, which underscores the need and potential impact of Xpert MTB/Rif to increase sensitivity and timeliness of TB diagnosis among PLHIV. However, additional evidence is needed to evaluate how best to incorporate Xpert MTB/Rif into TB screening and diagnostic algorithms for PLHIV both already on ART and those initiating ART.[35–37]

Observed gaps between those eligible and those prescribed IPT illustrate a number of missed opportunities to prevent HIV-associated TB morbidity and mortality. Isoniazid preventive therapy independently reduces risk of TB disease even for those already initiated on ART.[13] With the move to test-and-start for all PLHIV, it is critical to ensure that TB screening,

access to sensitive and timely diagnostic tests, and IPT are included in differentiated-care models for HIV care and ART delivery.

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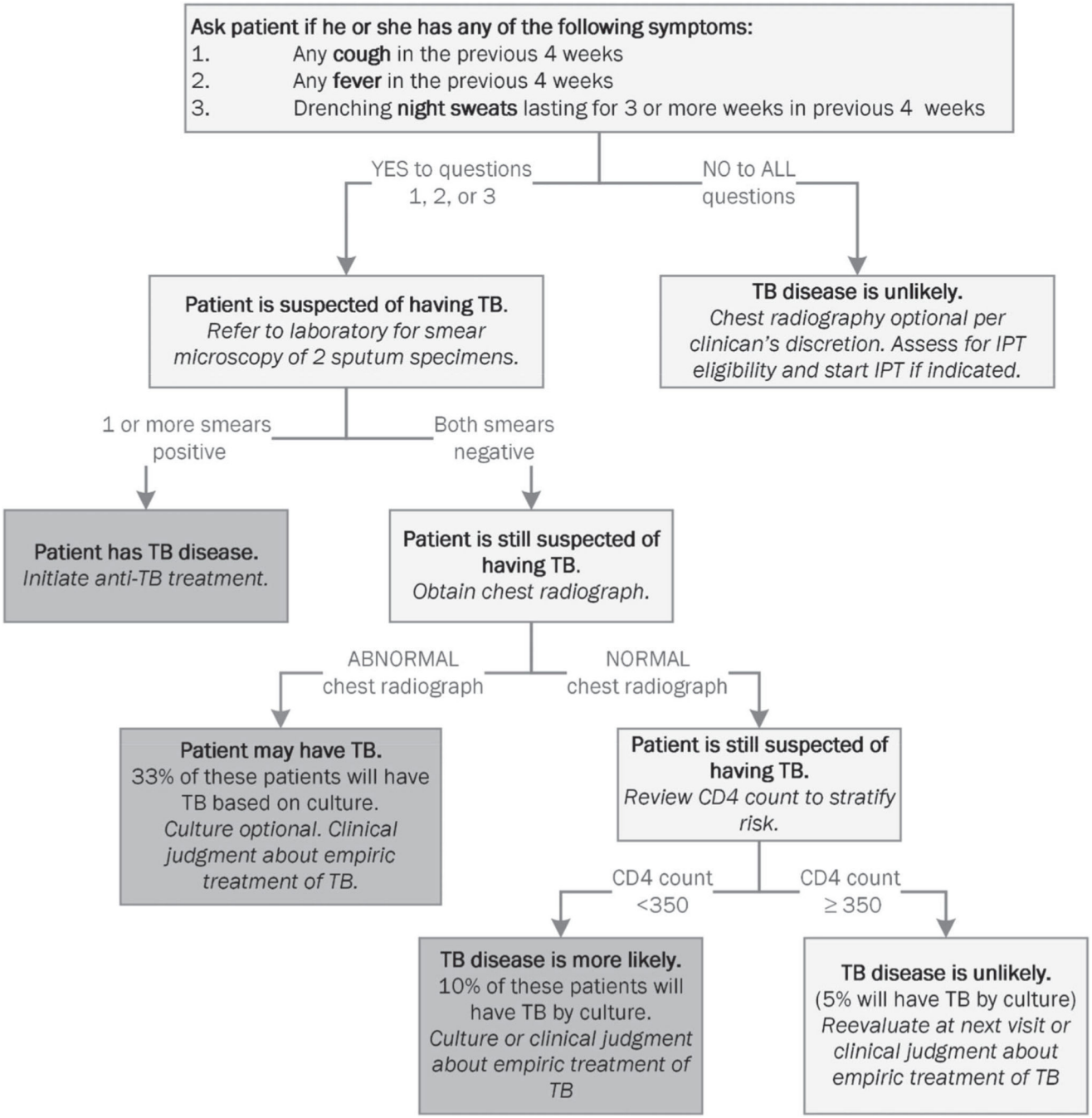
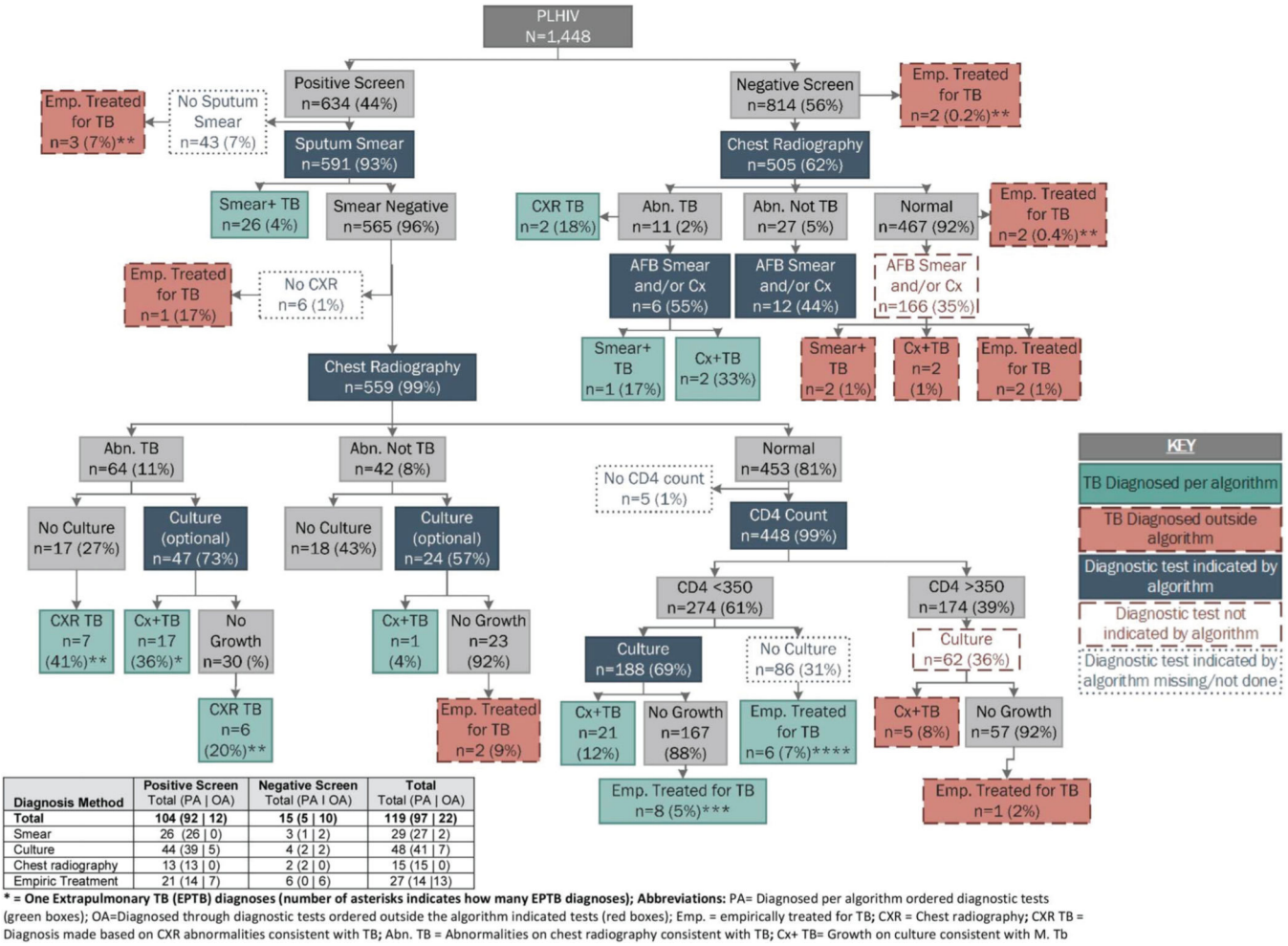


FIGURE 1.
Study algorithm for screening, diagnosis, and prevention of TB among persons living with HIV.



Diagnosis Method	Positive Screen Total (PA | OA)	Negative Screen Total (PA | OA)	Total Total (PA | OA)
Total	**104 (92 | 12)**	**15 (5 | 10)**	**119 (97 | 22)**
Smear	26 (26 | 0)	3 (1 | 2)	29 (27 | 2)
Culture	44 (39 | 5)	4 (2 | 2)	48 (41 | 7)
Chest radiography	13 (13 | 0)	2 (2 | 0)	15 (15 | 0)
Empiric Treatment	21 (14 | 7)	6 (0 | 6)	27 (14 |13)

*** = One Extrapulmonary TB (EPTB) diagnoses (number of asterisks indicates how many EPTB diagnoses); Abbreviations:** PA= Diagnosed per algorithm ordered diagnostic tests (green boxes); OA=Diagnosed through diagnostic tests ordered outside the algorithm indicated tests (red boxes); Emp. = empirically treated for TB; CXR = Chest radiography; CXR TB = Diagnosis made based on CXR abnormalities consistent with TB; Abn. TB = Abnormalities on chest radiography consistent with TB; Cx+ TB= Growth on culture consistent with M. Tb

FIGURE 2.

Clinical cascade through the screening and diagnostic algorithm for study participants, Thailand and Vietnam.

TABLE 1.

Selected Demographic and Clinical Characteristics of Study Participants

	Thailand, n = 659		Vietnam, n = 789		Overall, N = 1448		
	n	Col %	n	Col %	n	Col %	*P* *
Gender							
Male	330	50.1	419	53.1	749	51.7	0.2507
Female	329	49.9	370	46.9	699	48.3	
Age category, yrs							
18–24	56	8.5	97	12.3	153	10.6	<0.0001
25–29	81	12.3	313	39.7	394	27.2	
30–34	140	21.2	207	26.2	347	24.0	
35–39	157	23.8	91	11.5	248	17.1	
40+	225	34.1	81	10.3	306	21.1	
BMI category, kg/m^2 †							
Underweight (<18.5 kg/m^2)	160	24.3	275	34.9	435	30.0	<0.0001
Normal (18.5–24.9 kg/m^2)	397	60.2	477	60.5	874	60.4	
Overweight (25.0–29.9 kg/m^2)	90	13.7	30	3.8	120	8.3	
Obese (≥30.0 kg/m^2)	12	1.8	4	0.5	16	1.1	
Baseline CD4 category, cells/μL ‡							
≤100	119	18.1	138	17.5	257	17.7	0.1439
101–200	75	11.4	76	9.6	151	10.4	
201–350	185	28.1	192	24.3	377	26.0	
351–500	136	20.6	202	25.6	338	23.3	
>500	144	21.9	176	22.3	320	22.1	
Previous TB diagnosis §							
Yes	23	3.5	50	6.3	73	5.0	0.0138
No	632	95.9	735	93.2	1367	94.4	
Time since HIV diagnosis							
<6 mo	286	43.4	283	35.9	569	39.3	0.0062
6 mo–11 mo	49	7.4	75	9.5	124	8.6	

	Thailand, n = 659		Vietnam, n = 789		Overall, N = 1448		
	n	Col %	n	Col %	n	Col %	*P* *
1 yr–3 yrs	122	18.5	191	24.2	313	21.6	
>3 yrs	202	30.7	240	30.4	442	30.5	
Injection drug use ‖							
Yes	6	0.9	35	4.4	41	2.8	<0.0001
No	653	99.1	754	95.6	1407	97.2	
Excess alcohol use ‖							
Yes	141	21.4	76	9.6	217	15.0	<0.0001
No	518	78.6	713	90.4	1231	85.0	
Current smoking ‖							
Yes	155	23.5	407	51.6	562	38.8	<0.0001
No	504	76.5	382	48.4	886	61.2	
Poor adherence to HIV care visits ¶							
Yes	7	1.1	83	10.5	90	6.2	<0.0001
No	652	98.9	706	89.5	1358	93.8	
Baseline screen result #							
Screen negative—No symptoms	387	58.7	427	54.1	814	56.2	0.0785
Screen positive	272	41.3	362	45.9	634	43.8	
One symptom only							
Cough	75	11.4	154	19.5	229	15.8	
Fever	38	5.8	32	4.1	70	4.8	
Night sweats	5	0.8	3	0.4	8	0.6	
Two symptoms							
Cough, Fever	73	11.1	108	13.7	181	12.5	
Cough, night sweats	9	1.4	19	2.4	28	1.9	
Fever, night sweats	9	1.4	9	1.1	18	1.2	
Three symptoms—cough, fever, night sweats	63	9.6	37	4.7	100	6.9	

*Thailand vs. Vietnam, χ^2 *P*-value; or Fisher's exact test when expected cell values <5.

†n = 3 missing BMI in Vietnam.

[‡] n = 5 missing baseline CD4 in Vietnam.

[§] n = 8 missing previous TB diagnosis; n = 4 missing from Vietnam and n = 4 from Thailand.

[//] Injection drug use, alcohol use, and current smoking measured by self-report.

[¶] History of missing more than one scheduled HIV care appointment.

[#] Reported having any one of the 3 screening symptoms within the 4 weeks preceding the clinic visit: (1) cough of any duration; (2) fever of any duration; or (3) drenching night sweats ≥3 weeks.

BMI, Body mass index.

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TABLE 2.

Proportion of Study Participants Screening Positive and Diagnosed With TB by Demographic and Clinical Characteristics

		Screened Positive for TB*				Diagnosed with TB			
	Total	**n**	**%**	**aOR†**	**95% CI**	**n**	**%**	**aOR†**	**95% CI**
Total	1448	634	43.8			119	8.2		
Country									
Vietnam	789	362	45.9	1.0	0.4 to 2.0	68	8.6	1.2	0.6 to 2.4
Thailand	659	272	41.3	ref.		51	7.7	ref.	
Gender									
Male	749	373	49.8	0.9	0.7 to 1.3	88	11.7	2.3	1.3 to 4.1
Female	699	261	37.3	ref.		31	4.4	ref.	
BMI Category, kg/m^2‡									
Underweight (<18.5 kg/m^2)	435	249	57.2	1.6	1.2 to 2.0	67	15.4	2.3	1.4 to 3.8
Normal (18.5–24.9 kg/m^2)	874	343	39.2	ref.		46	5.3	ref.	
Overweight (25.0–29.9 kg/m^2)	120	39	32.5	1.0	0.7 to 1.3	5	4.2	0.9	0.4 to 2.0
Obese (≥30.0 kg/m^2)	16	3	18.8	0.3	0.1 to 1.4	1	6.3	2.1	0.1 to 35.4
Baseline CD4 Category, cells/μL§									
≤100	257	180	70.0	3.1	1.6 to 6.1	58	22.6	6.6	1.2 to 2.6
101–200	151	79	52.3	1.6	0.9 to 2.8	24	15.9	4.7	2.6 to 8.7
201–350	377	155	41.1	1.2	0.9 to 1.5	16	4.2	1.2	0.6 to 2.6
351–500	338	102	30.2	0.8	0.6 to 1.0	12	3.6	1.3	0.8 to 1.9
>500	320	114	35.6	ref.		9	2.8	ref.	
Previous TB Diagnosis ‖									
Yes	73	49	67.1	2.6	1.7 to 4.1	11	15.1	1.3	0.7 to 2.4
No	1367	581	42.5	ref.		107	7.8	ref.	
Time since HIV Diagnosis									
<6 mo	569	308	54.1	1.6	1.2 to 2.2	68	12.0	1.0	0.7 to 1.6
6 mo–11 mo	124	49	39.5	1.2	0.8 to 1.6	3	2.4	0.4	0.2 to 0.8
1 yr–3 yrs	313	118	37.7	1.2	0.9 to 1.6	17	5.4	1.0	0.5 to 1.9
>3 yrs	442	159	36.0	ref.		31	7.0	ref.	

		Screened Positive for TB*				Diagnosed with TB			
	Total	n	%	aOR†	95% CI	n	%	aOR†	95% CI
Injection drug use¶									
Yes	41	30	73.2	2.3	1.8 to 3.0	10	24.4	2.9	1.3 to 6.3
No	1407	604	42.9	ref.		109	7.7	ref.	
Current Smoking¶									
Yes	562	290	51.6	1.5	1.1 to 1.9	59	10.5	0.8	0.5 to 1.3
No	886	344	38.8	ref.		60	6.8	ref.	

*Reported having any one of the 3 screening symptoms within the 4 weeks preceding the clinic visit: (1) cough of any duration; (2) fever of any duration; or (3) drenching night sweats ≥3 weeks.

†In addition to factors listed in table, models are adjusted for age and adherence history to HIV care visits regardless of statistical significance and accounts for clustering within study sites.

‡n = 3 missing BMI in Vietnam.

§n = 5 missing baseline CD4 in Vietnam.

‖n = 4 missing previous TB diagnosis in Vietnam and n = 4 in Thailand (total n = 8 missing previous TB diagnosis).

¶Injection drug use and current smoking measured by self-report.

BMI, Body mass index.

TABLE 3.

TB Treatment Outcomes and IPT Eligibility, Prescription, and Outcomes by Country

	Thailand, n = 659		Vietnam, n = 789		Total, N = 1448	
	n	Col %	n	Col %	n	Col %
TB Diagnosed	51		68		119	
TB Treatment initiated	47	92.2	68	100.0	115	96.6
Cured	11	21.6	7	10.3	18	15.1
Completed treatment	23	45.1	30	44.1	53	44.5
Still receiving treatment	2	3.9	4	5.9	6	5.0
Defaulted	0	0.0	9	13.2	9	7.6
Died	6	11.8	9	13.2	15	12.6
Outcome missing	5	9.8	5	7.4	10	8.4
Transferred out	0	0.0	4	5.9	4	3.4
IPT Exclusion Criteria	659		789		1448	
TB diagnosis	51	7.7	68	8.6	119	8.2
Previous IPT	28	4.2	2	0.3	30	2.1
Previous TB Treatment	20	3.0	42	5.3	62	4.3
Abnormal CXR	44	6.7	42	5.3	86	5.9
History of Hepatitis or Liver Disease	15	2.3	29	3.7	44	3.0
Abnormal liver function tests	4	0.6	19	2.4	23	1.6
OI or stage 3 or 4 HIV Disease	17	2.6	33	4.2	50	3.5
Other IPT Exclusion Criteria [*]	0	0.0	4	0.5	4	0.3
TB Symptoms, Further evaluation indicated	56	8.5	91	11.5	147	10.2
Culture indicated, but not done	25	3.8	35	4.4	60	4.1
TST indicated, but not done [†]	68	10.3	—	—	68	4.7
TST negative	278	42.2	—	—	278	19.2
Total IPT Eligible	53	8.0	424	53.7	477	32.9
IPT prescribed among eligible	46	86.8	217	51.2	263	55.1
IPT Treatment Outcome						
Still taking IPT	2	4.3	8	3.7	10	3.8
Completed IPT	36	78.3	160	73.7	196	74.5

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	Thailand, n = 659		Vietnam, n = 789		Total, N = 1448	
	n	Col %	n	Col %	n	Col %
Developed TB during IPT	1	2.2	2	0.9	3	1.1
Lost to follow-up	2	4.3	5	2.3	7	2.7
Treatment stopped by patient	1	2.2	14	6.5	15	5.7
Treatment stopped by clinician	3	6.5	25	11.5	28	10.6
Outcome missing	1	2.2	3	1.4	4	1.5

*Other exclusions in Vietnam included pregnancy and history of alcohol abuse.

†Positive TST was only required for IPT initiation in Thailand, not Vietnam.