Symptom Screen for Identification of Highly Infectious Tuberculosis in People Living with HIV in Southeast Asia

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Background: Tuberculosis (TB) is the leading cause of death among people living with HIV and frequently transmitted among this susceptible group. Transmission can be reduced by infection control practices. Simple evidence-based methods to identify patients who should be isolated are not well described in the literature. We sought to identify a simple, sensitive symptom or symptom combination that healthcare providers in resource-limited settings can use to identify and isolate persons living with HIV with highly infectious TB.

Methods: Participants from 8 outpatient facilities in Cambodia, Thailand, and Vietnam underwent an extensive evaluation for TB. Patients with ≥1 positive sputum smear and *Mycobacterium tuberculosis* culture growth from a pulmonary site were defined as having highly infectious TB. We calculated sensitivity and prevalence of individual symptoms and >1000 symptom combinations.

Results: Of 1980 participants, 272 (14%) had TB. Forty percent (n = 109) were highly infectious. Sensitivity for detecting highly infectious TB was highest for having the following symptoms in the past month as follows: weight loss (84%), cough (83%), fever (81%), and fatigue (78%); however, these symptoms were found in 46%–54% of all participants. Having 2 or 3 of 4 symptoms (prevalence, 26%–47%)—weight loss, fever, current cough, and night sweats—was 72%–90% sensitive for highly infectious TB.

Conclusions: The 2 or 3 of 4 symptom combinations of weight loss, fever, current cough, and night sweats, which are the same symptoms comprising the current World Health Organization–recommended TB diagnostic screen, are sensitive for detecting highly infectious TB in people living with HIV.

Key Words: *Mycobacterium tuberculosis*, HIV, screening, infectiousness, infection control

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INTRODUCTION

Healthcare facilities are widely recognized as high-risk settings for tuberculosis (TB) transmission.[1] With the emergence of HIV, outbreaks of multidrug-resistant TB began occurring among people living with HIV (PLHIV) in healthcare facilities, causing high mortality. In several outbreak investigations, healthcare–associated TB among PLHIV was transmitted by only a few people with highly infectious TB.[1–6] These findings demonstrate the importance of identifying and separating persons with highly infectious TB from susceptible patients to prevent spread of TB among PLHIV.

TB transmission among PLHIV can be reduced by good infection control practices.[7,8] Practices recommended by the World Health Organization (WHO) include prompt identification of persons suspected of having TB when they first present to any inpatient or outpatient setting, separation of infectious patients from others, use of cough etiquette and respiratory hygiene strategies, rapid TB diagnosis and treatment initiation, and reduction in the time spent in healthcare facilities.[9] In resource-rich settings, patients with TB risk factors and symptoms are isolated until they are found to be noninfectious; however, in resource-limited settings, these practices are rarely feasible because of the large volume of suspected TB cases that present regularly, the absence of appropriate respiratory isolation areas, and limited diagnostic capacity.[7] Given that transmission is most intense and frequent among persons who are highly infectious,[10] infection control efforts in resource-limited settings should focus on identifying these persons.

Crowded waiting rooms, which are common in resource-limited settings, are conducive to rapid TB transmission, placing PLHIV at high risk for healthcare–associated TB.[11] The current WHO recommendation for HIV care settings, published in 1999, is to identify persons at risk for TB by asking about prolonged cough (defined as cough for

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2 weeks or more) and then separating them from others in an indoor or outdoor isolation area.[12] This approach, however, has not been formally evaluated and validated. Previous studies have evaluated the best approach to identifying TB patients that should be rapidly isolated,[13–16] but few have focused exclusively on PLHIV or used microbiologic criteria to evaluate TB infectiousness.

We sought to develop a simple, evidence-based method for identifying highly infectious TB that can be used by healthcare providers in resource-limited settings that predominantly care for PLHIV. We analyzed data from a large Southeast Asia study of TB screening and diagnosis in PLHIV presenting to healthcare facilities and analyzed symptom combinations predictive of highly infectious TB.[17]

STUDY POPULATION AND METHODS

Study Population and Laboratory Methods

PLHIV were consecutively enrolled from 8 outpatient facilities that provide HIV care in Cambodia, Thailand, and Vietnam from September 2006 through July 2008, as previously described[17]; however, unlike the parent study, patients were eligible regardless of antiretroviral therapy treatment status. Eligible patients were older than 6 years, had not been screened for TB with the use of chest radiography or sputum smears in the previous 3 months, had not received isoniazid preventive therapy in the previous year, and had not taken TB medications in the previous month. Patients were recruited regardless of the presence of clinical symptoms or clinical suspicion for TB.

After providing written informed consent, each study participant underwent a standardized clinical history and physical examination that assessed 73 clinical signs and symptoms, which were performed by research staff, including physicians, nurses, and study coordinators. An extensive diagnostic evaluation was also completed, including the collection of sputum, urine, stool, blood, and lymph node aspirates, if indicated. Sputum samples were concentrated using centrifugation. All samples were examined by Ziehl–Neelsen microscopy and cultured for *Mycobacterium tuberculosis* on Lowenstein–Jensen medium at a country-specific reference laboratory. In Thailand and Vietnam, specimens were also cultured using Mycobacterial Growth Indicator Tube (Becton Dickinson, Franklin Lakes, NJ) and processed with BACTEC Mycobacterial Growth Indicator Tube 960 (Becton Dickinson, Cockeysville, MD).[18] Positive cultures were determined by biochemical tests or the Accuprobe *M. tuberculosis* complex assay (GenProbe; San Diego, CA).[18]

To ensure data quality and minimize misclassification of TB diagnosis, extensive quality control measures were implemented. For example, microbiologists were not blinded to previous test results; however, a positive sputum result was confirmed by 2 different readers. For sputum smears with 1–9 acid-fast bacilli per 100 fields, an independent on-site microbiologist re-read these smears. Also, all patients with at least 1 culture positive for *M. tuberculosis* had their specimens evaluated for cross-contamination using a standard approach, which included genotyping via spoligotyping and 24-loci mycobacterial interspersed repetitive unit-variable number tandem repeat analysis.[19]

The study was approved by institutional review boards or human subjects research ethics committees at the US Centers for Disease Control and Prevention and each collaborating institution. Procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Definitions

Study participants were defined as having TB if at least 1 specimen from any site grew *M. tuberculosis* when cultured. After determination of TB diagnosis, sputum smear results were used as a surrogate marker for infectiousness among those diagnosed with TB because smear-positive TB cases are highly infectious and likely to transmit to others.[20] We defined PLHIV with highly infectious TB as having at least 1 positive sputum smear with a cultured pulmonary specimen that grew *M. tuberculosis*. PLHIV with negative sputum smears, but at least 1 positive culture from any site, were considered to be less infectious. Patients with all negative cultures for *M. tuberculosis* were classified as not having TB. There were no PLHIV with positive sputum smears and only positive extrapulmonary cultures for *M. tuberculosis.*

Statistical Analysis

Statistical comparisons were made between those with highly infectious TB, less infectious TB, and no TB using the Kruskal–Wallis test for continuous variables and the Fisher's exact test or the Pearson χ^2 test for categorical variables, as indicated. Odds ratios and 95% confidence intervals for the presence of a symptom and its association with infectiousness categories were calculated. The Cochran–Armitage test for trend evaluated whether a trend existed between the odds ratio for presence of a symptom and increasing infectiousness. All tests of significance were 2-sided. A P value <0.05 was considered statistically significant.

To develop a symptom or symptom combination that identifies highly infectious TB, we calculated prevalence and performance characteristics relative to culture-confirmed TB, including sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios, of 73 individual symptoms and 1105 symptom combinations. We also evaluated the current WHO diagnostic screening symptoms, which include weight loss, fever, current cough, and night sweats, to see if these also identify patients with highly infectious TB. To choose an ideal symptom or symptom combination, we prioritized high sensitivity, but also looked for low prevalence to insure that infection control resources could be allocated efficiently. Data analysis was conducted using SAS 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Among the entire study population (n = 1980), 272 (14%) were diagnosed with TB. Of PLHIV with TB, 40% (n = 109) were classified with highly infectious TB, and 60%

(n = 163) were classified with less infectious TB. Those with highly infectious TB were predominantly male, had a lower CD4 cell count, and reported a known contact undergoing current TB treatment more frequently than those with less infectious TB or no TB ($P < 0.05$) (Table 1). The odds of having symptoms classically associated with TB, including fever, night sweats, weight loss, and cough in the previous month, were higher in PLHIV with highly infectious TB compared with those with less infectious TB (Table 2). Notably, this trend was not statistically significant for hemoptysis in the previous month or hemoptysis in the last 24 hours (Table 2).

Sensitivity, or the proportion of those with highly infectious TB who are correctly identified, was highest for having the following symptoms in the past month: weight loss (84%), cough (83%), fever (81%), and fatigue (78%); however, the prevalence of these symptoms among the entire study population was 46%–54%, indicating that about half of all PLHIV would be classified as infectious TB suspects (Table 3).

We then investigated the performance characteristics of more than 1000 unique combinations of 1 to 4 clinical symptoms in predicting highly infectious TB, including the WHO diagnostic screen. For example, to screen positive for a 1 of 4 symptom combination, the patient must have reported at least 1 of the symptoms. If the patient reported none of these symptoms, then he or she was considered not to have a positive screen for highly infectious TB. The same logic applied to the other symptom combinations.

Having at least 2 or 3 of the following 4 symptoms in the WHO diagnostic screen—weight loss, fever, current cough, and night sweats—was 90% and 72% sensitive for identifying highly infectious TB in PLHIV, respectively (Table 4). Forty-seven percent and 26% of the entire study population would screen positive as suspects for highly infectious TB using the 2 of 4 and 3 of 4 symptom combinations, respectively (Table 4). We compared the WHO 1999 recommendation to use prolonged cough to the 2 of 4 and 3 of 4 symptom combinations. The sensitivity of prolonged cough was lower (51%) and would fail to identify 49% of those with highly infectious TB (Table 4).

One other combination performed similarly to the 3 of 4 symptom combination. Having cough and any of the other three symptoms (weight loss, fever, or night sweats) had a sensitivity of 73%. Using this symptom combination, 28% of the entire study population would screen positive as suspects for highly infectious TB.

DISCUSSION

Our study found that the 2 and 3 of 4 symptom combinations of weight loss, fever, current cough, and night sweats, currently endorsed by the WHO as part of the

TABLE 1. Study Participant Characteristics by Infectiousness

Characteristic	Highly Infectious TB (n = 109)	Less Infectious TB (n = 163)	No TB (n = 1708)	*P*
Median age (range), yrs	33 (21–65)	30 (19–72)	32 (7–65)	0.02*
Male sex, no. (%)	75 (69)	99 (61)	831 (49)	<0.01†
Country, no. (%)				
Cambodia	63 (58)	66 (40)	797 (47)	<0.01†
Thailand	9 (8)	24 (15)	594 (35)	
Vietnam	37 (34)	73 (45)	317 (18)	
Median CD4 count (IQR)	75 (19–183)	125 (50–286)	277 (116–426)	<0.01*
Sex with same gender, no. (%)	4 (4)	11 (7)	253 (15)	<0.01
Sex with sex worker, no. (%)	32 (29)	52 (32)	419 (25)	0.07†
Traded for sex, no. (%)	2 (2)	8 (5)	102 (6)	0.18
Injected drug use, no. (%)	33 (30)	43 (26)	175 (10)	<0.01*
Blood transfusion, no. (%)	7 (6)	11 (7)	87 (5)	0.58†
Current HIV+ sex partner, no. (%)	17 (16)	44 (27)	593 (35)	<0.01†
Ever treated TB > 4 weeks (not in past year), no. (%)	4 (4)	2 (1)	32 (2)	0.33
Ever TB preventive meds (not in past year), no. (%)	0 (0)	1 (1)	9 (1)	0.77
Anyone at home with TB treatment in past 2 years, no. (%)	15 (14)	23 (14)	190 (11)	0.41†
Person at home with current TB treatment, no. (%)	3 (3)	8 (5)	80 (5)	0.70
Known contact with TB treatment in past 2 years, no. (%)	15 (14)	16 (10)	157 (9)	0.29†
Known contact with current TB treatment, no. (%)	12 (11)	8 (5)	79 (5)	0.01†
Karnofsky score < 70%, no. (%)	21 (19)	11 (7)	48 (3)	<0.01†
Median Karnofsky score (IQR)	80 (70–90)	90 (80–90)	90 (90–90)	<0.01*
Currently hospitalized, no. (%)	13 (12)	5 (3)	32 (2)	<0.01
Mean severity of symptoms (IQR)	6 (5–8)	4.6 (2–7)	4.6 (3–7)	<0.01*

*Kruskal–Wallis test.
†Pearson χ^2 test.
Unless noted, Fisher exact test was used.

TABLE 2. Odds of Having Clinical Symptoms in the Previous Month by Infectiousness Per Patient Self-Report*

	Highly Infectious TB (n = 109)		Less Infectious TB (n = 163)		
	OR	95% CI	OR	95% CI	*P*†
Cough	5.6	3.4 to 9.2	2.0	1.4 to 2.7	<0.01
Cough ≥ 14 days	5.3	3.6 to 7.9	1.3	0.9 to 1.9	<0.01
Cough ≥ 20 days	4.5	2.9 to 6.8	1.0	0.6 to 1.7	<0.01
Cough ≥ 28 days	4.0	2.5 to 6.2	0.8	0.5 to 1.5	<0.01
Cough with sputum	2.9	2.0 to 4.3	1.5	1.1 to 2.1	<0.01
Cough causing insomnia	5.2	3.5 to 7.7	1.4	1.0 to 2.1	<0.01
Daily cough	4.1	2.7 to 6.3	1.5	1.1 to 2.0	<0.01
Cough in last 24 hours	6.9	4.4 to 10.8	1.9	1.4 to 2.7	<0.01
Cough worsened in past month	6.8	3.8 to 12.2	0.9	0.3 to 2.5	<0.01
Hemoptysis	2.2	1.0 to 5.0	0.8	0.3 to 2.3	0.13
Hemoptysis in last 24 hours	1.7	0.2 to 13.9	2.3	0.5 to 10.9	0.34
Fever	5.8	3.6 to 9.4	2.7	1.9 to 3.8	<0.01
Fever ≥ 14 days	6.1	4.1 to 9.2	3.5	2.5 to 5.1	<0.01
Fever ≥ 20 days	5.7	3.7 to 8.9	2.8	1.8 to 4.3	<0.01
Fever ≥ 28 days	5.6	3.6 to 8.9	2.4	1.5 to 3.9	<0.01
Fever in last 24 hours	6.1	4.1 to 9.2	2.7	1.9 to 3.8	<0.01
Night sweats	4.4	3.0 to 6.5	2.2	1.6 to 3.1	<0.01
Night sweats ≥ 14 days	3.5	2.2 to 5.7	2.2	1.4 to 3.4	<0.01
Night sweats ≥ 20 days	4.1	2.5 to 6.8	2.2	1.3 to 3.6	<0.01
Night sweats ≥ 28 days	3.2	1.9 to 5.7	1.6	0.9 to 3.0	<0.01
Night sweats in last 24 hours	4.9	3.2 to 7.3	2.6	1.8 to 3.7	<0.01
Weight loss	6.7	4.0 to 11.2	2.3	1.6 to 3.2	<0.01
Difficulty breathing	4.5	3.0 to 6.8	1.7	1.2 to 2.4	<0.01
Difficulty breathing in last 24 hours	4.9	3.3 to 7.3	1.8	1.3 to 2.6	<0.01
Chest pain	3.7	2.5 to 5.5	1.3	0.9 to 1.8	<0.01
Chest pain in last 24 hours	4.9	3.3 to 7.3	1.5	1.0 to 2.1	<0.01
Loss of appetite	3.6	2.4 to 5.4	3.6	2.6 to 5.0	<0.01
Loss of appetite in last 24 hours	4.8	3.2 to 7.1	3.9	2.8 to 5.5	<0.01
Fatigue	3.5	2.2 to 5.5	2.5	1.8 to 3.6	<0.01
Fatigue in last 24 hours	5.0	3.2 to 7.9	3.0	2.1 to 4.2	<0.01
Shaking chills	4.7	3.2 to 7.0	3.0	2.1 to 4.1	<0.01
Shaking chills in last 24 hours	4.3	2.7 to 6.8	2.7	1.7 to 4.1	<0.01

*Reference group = no TB.
†Cochran–Armitage test for trend.

diagnostic screen for TB in PLHIV,[21,22] are sensitive for identifying PLHIV with highly infectious TB. Both symptom combinations are more sensitive than the current WHO recommendation of using prolonged cough. Our study addresses the research gap identified by WHO on the need for specific criteria for identifying and separating TB suspects in clinical settings.[9]

Depending on available resources, either symptom combination may be used to identify and separate PLHIV with highly infectious TB. A setting with few resources may decide to use the 3 of 4 symptom combination due to the lower percentage of PLHIV that would screen positive as highly infectious TB suspects; thus, less space and infection control resources would be needed for separation and isolation of these patients. By choosing to use this symptom combination, however, 28% of highly infectious TB suspects will be missed. In contrast, a setting with more resources may choose to use the 2 of 4 symptom combination, as that setting may have the space to isolate almost half of all its patients who screen positive as highly infectious TB suspects. Ultimately, both symptom combinations may lead to prompt identification and separation of the majority of those with highly infectious TB, thereby, reducing TB transmission among PLHIV.

Because the highly infectious TB symptom combination uses the same symptoms as the WHO TB diagnostic symptom screen, healthcare facilities can screen for TB, highly infectious and less infectious, with one set of questions. Using this one set of questions, healthcare facilities can determine both which patients should have a diagnostic evaluation for TB (ie, which are TB suspects) and which subset of patients that need a TB diagnostic evaluation are highly infectious and should be separated from other patients. Implementation of this screening process will require more

TABLE 3. Performance Characteristics of Individual Clinical Symptoms in Predicting Highly Infectious Tuberculosis (n = 109)

Clinical Symptom	Sensitivity %	Prevalence No. (%)
Weight loss	84	929 (47)
Cough	83	975 (49)
Fever	81	914 (46)
Fatigue	78	1062 (54)
Fatigue in last 24 hours	76	853 (43)
Cough in last 24 hours	75	677 (34)
Daily cough	72	801 (41)
Difficulty breathing	67	676 (34)
Chest pain	64	691 (35)
Cough with sputum	62	745 (38)
Loss of appetite	58	627 (32)
Night sweats	57	522 (26)
Shaking chills	57	509 (26)
Cough causing insomnia	54	414 (21)
Fever in last 24 hours	54	389 (20)
Loss of appetite in last 24 hours	53	463 (23)
Difficulty breathing in last 24 hours	52	416 (21)
Chest pain in last 24 hours	52	409 (21)
Cough ≥ 14 days	51	373 (19)
Fever ≥ 14 days	45	306 (15)
Night sweats in last 24 hours	41	304 (15)
Cough ≥ 20 days	37	255 (13)
Fever ≥ 20 days	33	205 (10)
Cough ≥ 28 days	29	207 (10)
Fever ≥ 28 days	29	169 (9)
Shaking chills in last 24 hours	28	199 (10)
Night sweats ≥ 14 days	25	197 (10)
Night sweats ≥ 20 days	21	147 (7)
Cough worsened in past month	17	70 (4)
Night sweats ≥ 28 days	16	123 (6)
Hemoptysis	6	62 (3)
Hemoptysis in last 24 hours	1	12 (1)

resources. Staff would need to be trained, and the screening would need to be incorporated into the healthcare facility's workflow, potentially increasing the workload of healthcare providers and evaluation time for patients. Also, the use of the screen may highlight the need for improved infection control policies and infrastructure, particularly isolation areas. Depending on the number that screen positive, more masks and respirators may be needed for both patients and healthcare providers.

By completing a comprehensive TB diagnostic evaluation, including testing of extrapulmonary sites, and the use of both solid and liquid cultures, we minimized misclassification of patients across the 3 groups as follows: highly infectious TB, less infectious TB, and no TB. Additionally, our study was conducted in a large study population from multiple urban and rural HIV clinical care sites in 3 Southeast Asian countries; thus, it may be applied widely in this geographic region. Nevertheless, a few limitations to this study deserve mention. The findings of this study may only be generalizable to clinical care settings in which most or all patients have HIV infection. The performance characteristics of this symptom combination may differ in people without HIV. Additionally, children aged 6 years or younger were not enrolled in the study, so the symptom combination cannot be applied to this group; however, young children are generally less infectious and less likely to transmit TB to others.[23] Given the relatively small sample size of PLHIV classified with highly infectious TB, the power of the study may also be limited. Implementation studies are needed to better characterize the performance of our proposed highly infectious TB symptom combination. Last, by focusing on smear-positive TB transmission, the utility of the symptom combination is limited for smear-negative TB transmission; however, smear-positive sputum strongly predicts TB infectiousness, and in turn, transmission among persons.

We recommend that the 4 symptom WHO diagnostic screen of weight loss, fever, current cough, and night sweats, also be used for identifying and separating people at risk of having highly infectious TB in HIV care settings in Southeast Asia. Although a screening tool is relatively simple and inexpensive, continued implementation of recommended infection control measures is still needed to optimally reduce TB transmission in resource-limited settings and, in particular, HIV care facilities.

TABLE 4. Performance Characteristics for Symptom Combinations and WHO-Recommended Screen for Identification and Separation of TB Suspects With Highly Infectious TB in All 1980 Patients

Combination*	Sensitivity (%)	Specificity (%)	Negative Predictive Value (%)	Positive Predictive Value (%)	Prevalence (%)
1 of 4	98	30	100	8	72
2 of 4	90	56	99	11	47
3 of 4	72	77	98	16	26
4 of 4	37	92	96	21	10
WHO 1999 recommendation†					
Prolonged cough (≥2 weeks)	51	83	97	15	19

*Weight loss, fever, current cough, and night sweats.

†World Health Organization. Tuberculosis Infection Control in the Era of Expanding HIV Care and Treatment: addendum to WHO Guidelines for the Prevention of TB in Healthcare Facilities in Resource-Limited Settings. Geneva, Switzerland: WHO Press; 1999.

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