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The Effect of Immune Status on the Performance of a WHO-recommended Screening Tool for Tuberculosis in HIV-infected Patients in South-East Asia

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Abstract

The Effect of Immune Status on the Performance of a WHO-recommended Screening Tool for Tuberculosis in HIV-infected Patients in South-East Asia
By William Ford

Background: Tuberculosis and HIV are major causes of morbidity and mortality worldwide, and TB/HIV co-infection is a major barrier to global TB and HIV control efforts. Successful interventions exist to control TB and HIV individually, but they are less effective in areas where TB/HIV co-infection is prevalent partly because TB is difficult to diagnose in immunosuppressed persons. The World Health Organization recommends a symptom-based clinical screening tool to help clinicians rule out TB in HIV-infected patients and initiate appropriate treatment. To date, the performance of this screening tool has not been evaluated across a range of immune status.

Methods: We conducted a secondary analysis of data from a cross-sectional study of HIV-infected patients seeking care in Cambodia, Thailand, and Viet Nam to evaluate the performance of the WHO screening tool using a reference standard approach and mycobacterial culture status as the referent. Logistic regression modeling with piecewise linear splines was used to estimate the sensitivity and specificity of the screening rule compared to mycobacterial culture across a continuous range of CD4+ cell counts, comparing the effect of immune status on the tool's performance in persons with CD4+ cell counts above and below 400.

Results: Of 1,988 participants who underwent TB evaluation, 276 (13.8%) had TB and 1,514 (76.2%) had at least one of the 4 symptoms comprising the WHO screening tool. Among patients with CD4 counts below 400, the sensitivity (AOR 0.41) and (1-specificity) (AOR 0.765) decreased with increasing immune status. There is no evidence of a statistically significant effect of immune status above 400 cells on the sensitivity or specificity of the screening tool.

Conclusions: Our results indicate that among persons infected with HIV in South-East Asia, the WHO screening tool for TB is more sensitive with falling immune status. The screening rule is most effective among those with more severe immunosuppression, so it may improve TB case-finding and treatment initiation among those most susceptible to infection and adverse health outcomes.

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Contents

Tables

1. Introduction

Tuberculosis and HIV are leading infectious causes of morbidity and mortality worldwide. Roughly ⅓ of the world's population (> 2 billion people) is estimated to be latently infected (LTBI) with *Mycobacterium tuberculosis* (MTB); and 34 million suffered from HIV infection as of 2011 [1, 2]. In addition to 2 billion persons with LTBI, an estimated 8.9 million people progressed to active tuberculosis disease (TB) in 2011 [3]. The confluence of the two epidemics – the TB/HIV "syndemic" – is a major public health concern because the two diseases exacerbate each other at both individual and population levels. HIV infection often delays the diagnosis of active TB, leaving patients undiagnosed with TB until they progress to severe disease and become more likely to suffer disability or death [4]. Diagnostic delays resulting from HIV infection represent a significant barrier to global TB control. There is a need to intensify case-finding and enhance early treatment to prevent transmission and mortality.

TB is a leading cause of death in persons with HIV because a compromised immune system is less able to control the spread of MTB through the body and HIV viral replication may be accelerated at the site of MTB infection. HIV-associated TB accounts for a disproportionate number of deaths worldwide, affecting 15% of TB-infected persons yet representing 29% of TB-related mortality [3]. The interaction of the two epidemics requires special focus to control and prevent further transmission and mortality.

Effective interventions exist to reduce morbidity and mortality individually, but collaborative TB/HIV activities are complicated by the clinical interactions of TB and HIV requiring specific, evidence-based guidelines [5]. Persons with LTBI are non-infectious and asymptomatic, but are at increased risk of progressing to infectious,

symptomatic TB when co-infected with HIV [6, 7]. Isoniazid preventive therapy (IPT) can be used in people living with HIV (PLHIV) and LTBI to prevent progression to TB, but initiation of IPT in a patient with undiagnosed active TB may result in treatment failure. Initiating IPT in people with TB may result in isoniazid mono-resistance, so a multi-drug treatment regimen (TB treatment) is needed to effectively treat TB [8].

Anti-retroviral therapy (ART) is recommended in PLHIV because it can reduce TB and HIV transmission and mortality; however initiating ART in PLHIV with undiagnosed TB can lead to unintended, negative health outcomes. Global TB/HIV control strategies therefore rely heavily on the ability to accurately diagnose or exclude TB in PLHIV [9, 10]. A number of diagnostic and screening tools currently exist, but their availability and performance varies, especially in under-developed and under-served countries with large or concentrated HIV burdens.

Current World Health Organization (WHO) guidelines for collaborative TB/HIV activities recommend evaluating all newly infected HIV patients for TB, but TB can be difficult to diagnose using widely available diagnostic tools in immuno-compromised patients [11-13]. Existing TB diagnostics are either too expensive and require too much training to be widely available in low-resource settings most affected by TB/HIV, or they are too insensitive in the PLHIV to be very useful to prevention and control efforts [14]. New point-of-care diagnostic technologies that are cheap, simple, and effective in immuno-compromised patients are needed to continue progress toward preventing and controlling TB worldwide. Such technologies are being developed, but in the meantime screening tools can help clinicians in low-resource settings improve case management by allowing them to separate HIV-infected patients into two groups: those unlikely to have

active TB who may begin IPT, and those who need further evaluation for TB before diagnosis and TB treatment initiation [15]. Separating patients this way offers several benefits to case management and TB/HIV control. Ruling out TB in HIV-infected patients can save costs associated with further evaluation using more expensive technologies like mycobacterial culture and improve health outcomes by preventing the development of active TB.

Preventing progression to TB in patients with LTBI can also reduce TB incidence at the population level because persons with LTBI are non-infectious. Identifying TB suspects for evaluation before IPT and ART are initiated can prevent the development and spread of isoniazid resistance and immune-reconstitution inflammatory syndrome (IRIS), both of which can complicate treatment and lead to adverse health outcomes.

The utility of screening tools for improving patient management and control efforts in communities with large HIV burdens depends heavily on their performance at different levels of immune status because more severely immunosuppressed patients often have different presentation of disease from more immune-competent ones [16]. High performing screening tools should be cheap and simple to implement to maximize their availability in low-resource settings. Using the presence or absence of symptoms as a screening tool is a common approach in under-resourced settings, but many currently rely on prolonged cough, which was recently found to be highly insensitive in PLHIV . The WHO now recommends asking about a combination of symptoms when screening for TB in PLHIV [5]. The current recommendation is based on the absence of any one of current **c**ough, **f**ever, night **s**weats, or **w**eight loss (i.e., the CFSW tool). Patients with none of the four symptoms are considered safe for initiation of IPT, and those with any

one of the four are recommended for continued TB evaluation before IPT or TB treatment is initiated. The performance of the WHO screening tool across a range of immune status has yet to be evaluated.

A detailed understanding of the effect of immune status on the CFSW screening tool's performance in HIV-infected patients may recommend further applications in a variety of settings. To date, no study has examined a screening tool's performance across a continuous range of immune status. The analysis of this study aims to fill that gap. It stems from the **I**mproving **D**iagnosis of **TB** in **HIV**-infected persons (ID-TB/HIV) study conducted by the U.S. Centers for Disease Control and Prevention (CDC) in Cambodia, Thailand, and Viet Nam from 2006 to 2008 [15]. Results from this cross-sectional study informed the original development of the WHO-recommended CFSW screening tool [5]. We used the same data and multivariate regression analysis to evaluate that tool's effectiveness across a range of immune status by predicting its sensitivity and specificity across a continuous range of CD4 counts (the most commonly used measure of immune status).

The results of this analysis can inform further recommendations for the tool's use in specific sub-populations of PLHIV. We hope that by refining the tool's use, we can improve the confidence with which clinicians manage their HIV-infected patients and improve the uptake of IPT, thereby contributing to worldwide TB control and eventual elimination.

2. Literature Review

2.1 Introduction and TB/HIV Epidemiology

An extensive body of literature exists describing TB and HIV, their respective threats to human health, and their sinteractions at the cellular, individual, and population levels [4]. Significant overlap exists between the global TB and HIV pandemics and every year millions are affected by this TB/HIV "syndemic."

Two billion people are estimated to be latently infected with MTB worldwide [1]. In 2008 nearly 30% of the estimated 33.4 million people infected with HIV were also infected with TB, and 13% of 8.9 million incident TB cases in 2011 were also infected with HIV [3, 4]. TB is a leading cause of death in PLHIV worldwide, and HIV infection is the strongest known risk factor for progressing from latent infection to active TB disease [3, 4]. There are some data that TB may facilitate HIV replication and accelerate progression to AIDS – Increased viral loads are often found at the site of MTB infection in co-infected patients – but it remains uncertain whether the cause of increased replication is MTB itself or the inflammatory response it engenders at the site of infection [4, 17].

Persons with LTBI are asymptomatic and non-infectious, but the risk of progressing to active TB makes such a large pool of persons with latent infection a threat to public health. A competent immune system is normally able to contain tubercle bacilli following infection with MTB, keeping the infection from progressing to active TB and preventing serious illness and further transmission [18]. Persons with compromised immune systems are less able to contain MTB after infection, making progression from LTBI to active TB more common among PLHIV. The average lifetime risk of progressing from LTBI to active TB is higher in HIV-infected patients than HIV-

uninfected ones due to a compromised immune system's diminished ability to sequester the tubercle bacilli before they multiply and spread [6].

In addition to increased susceptibility, TB tends to be more severe and cause higher mortality among those infected with HIV [19]. HIV-associated TB accounts for a disproportionate share of total TB mortality worldwide. It accounted for 29% of total TB-related deaths in 2008 despite only 15% of incident TB cases being HIV-related [20]. There were an estimated 8.7 million incident TB cases and 1.4 million deaths from TB in 2011, including 430,000 (30%) among PLHIV [3]. Over 1.1 million incident cases of TB were recorded among PLHIV in 2010 [21].

Part of each country's efforts to control TB and HIV is expanding access to effective treatment. Active TB can be effectively treated with TB treatment, and LTBI can be treated with IPT to prevent progression to active TB [6, 22, 23]. Access to TB treatment and IPT is expanding, but it remains below target levels in many countries and should not be initiated until active TB is confirmed [3]. Accurately diagnosing TB in PLHIV can improve treatment uptake but remains challenging, especially in under-resourced settings where laboratory capacity and access to most effective diagnostic tools (like the ability to grow cultures) may be limited [13]. In the absence of improved diagnostic tools, screening tools that can help distinguish those with latent infection who need IPT from those with active TB who need TB treatment can improve patient management and health outcomes.

ART can significantly reduce mortality in HIV-infected persons including those co-infected with TB, and initiating ART earlier appears to improve treatment outcomes at the population level [21, 24, 25]. ART can also reduce TB incidence at the population

level – a prospective cohort study in South Africa found a strong, independent relationship between updated CD4 counts (resulting from ART) and reduced TB incidence [26]. WHO recommends offering ART to all HIV-infected persons, however initiation of ART in people with active TB can result in IRIS [5, 27]. This is a potentially fatal condition that can occur when there is undiagnosed TB infection in the setting of a newly reconstituted immune system dysregulated by HIV, and it can complicate treatment initiation in co-infected patients [28]. IRIS is most common in people with advanced immunosuppression, low initial CD4 cell counts, high initial antigen or viral load, and more rapid immune reconstitution following ART initiation [29]. As these risk factors suggest, persons whose health is poor and who need ART the most are those at highest risk of dangerous complications following ART initiation if active TB is not diagnosed or ruled out first. Screening tools can be help rule out active TB, and if used before ART initiation can prevent IRIS and improve treatment outcomes.

The risk of IRIS makes it important to rule out active TB in HIV patients before initiating ART, so accurate screening tools are of special importance in patients with HIV [30]. The threat of IRIS makes the question of when to initiate ART in patients with active TB a difficult one, but recent studies in Africa and Asia have shown earlier initiation tends to result in increased survival [31, 32]. These studies were mainly limited to patients with pulmonary TB, so the optimal timing in those with extra-pulmonary TB remains uncertain [9]. Initiating IPT in people with undetected active TB may also result in treatment failure. This may put patients at risk of developing isoniazid (INH, one of the main frontline anti-TB drugs) resistance, though current evidence of the latter is inconclusive [8].

WHO publishes guidelines for collaborative TB and HIV activities for national TB programs [5]. Among recommended activities are: intensify TB case-finding among PLHIV; use IPT in HIV-infected patients without TB; provide TB treatment, co-trimoxazole preventive therapy (CPT), and ART to TB patients with HIV; and provide HIV testing and counseling to persons with confirmed or presumptive TB [5]. Case-finding and initiation of effective therapies depend on high-quality TB diagnostics; the lack thereof in many low-resource settings has impeded progress toward national and global TB control efforts [33].

Operational research into the effectiveness and affordability of TB control guidelines is important to continue because it may help improve their uptake among countries with high TB burdens, especially when evidence exists that some WHO-recommended tools and policies could perform better [34, 35]. Progress toward understanding and controlling the TB/HIV syndemic is slow, and improving each national program's ability to accurately diagnose TB in PLHIV with new diagnostic and screening tools is critical to achieving control objectives. Investigating the performance of screening tools that can avoid IRIS and improve the effectiveness of ART and IPT should be a priority for future research [5].

2.2 TB Diagnostics and the HIV Context

A range of effective TB diagnostics has existed for years; the most effective has limited use in many settings due to high cost, training requirements, and long delays in producing results. Cheaper, simpler, and faster technologies are available and widely used in under-resourced settings, but they are less accurate and unreliable [14]. The choice of a diagnostic tool becomes more complicated in areas affected by HIV because the clinical presentation of TB can be unusual in patients co-infected with HIV. Newer

diagnostics are being developed to address this and other issues, including the challenge of detecting multi-drug resistant TB (MDR-TB). However until they are more widely available it remains important to explore ways of improving currently available diagnostics.

Mycobacterial culture is the gold standard for diagnosing TB, but it takes several weeks for results and requires sophisticated laboratory capacity [13, 36]. Lymph node aspirate, blood, urine, or stool can be cultured to detect extra-pulmonary TB [6]. The time to receive culture results limits its usefulness in clinical settings; many under-resourced settings lack the laboratory capacity necessary to perform culture testing.

Recent developments in TB diagnosis like the GeneXpert nucleic amplification assay (Xpert MTB/RIF) may make important contributions to TB diagnosis, care, and control [37, 38]. This new technology is much faster than mycobacterial culture, has demonstrated high sensitivity to TB, is easy to use, and can simultaneously detect MTB and resistance to rifampicin (RIF), a critical drug in TB treatment regimens [20]. However, the roll out of Xpert MTB/RIF is still ongoing, and it is not readily available in all under-resourced settings [39].

In the absence of the capacity to perform mycobacterial culture, some rely on other tools like sputum smear microscopy, chest radiography, or clinical presentation to diagnose TB [40]. Sputum smear microscopy for acid-fast bacilli (AFB) is a common diagnostic tool but lacks sensitivity, especially in PLHIV who may present with abnormal pulmonary or extra-pulmonary TB [12, 16, 41-43]. Many HIV-infected patients have sputum smear-negative TB, and smear-negative TB is more likely in those with greater immunosuppression. New methods are also being developed to improve the performance

of direct sputum microscopy, but like Xpert MTB/RIF their availability in low-resource settings remains limited [44, 45].

Chest radiography (CXR) also has low sensitivity and is of limited use for detecting active TB in PLHIV because immunosuppression can cause unusual, non-specific, or even normal (i.e., not indicative of any pulmonary disease) radiographic results [46-48]. The performance of CXR as a diagnostic tool also depends on interpretation of radiographic results by healthcare professionals, which can be difficult and result in poor inter-reader agreement [34]. Although adding CXR to screening algorithms is often found to increase their sensitivity, not all settings have reliable access to CXR due to unreliable electricity supplies, shortages in radiography film, or not enough staff trained to interpret CXR results [49]. Screening algorithms should therefore be effective without CXR results. Furthermore CXR and screening tools (especially those based on prolonged cough) are mainly useful for detecting pulmonary TB, but they may miss cases in high HIV-burden areas because extra-pulmonary TB is common in HIV-infected patients [6, 50].

Diagnosing LTBI is also more difficult in HIV-infected than uninfected persons. The tuberculin skin test (TST) and interferon gamma release assay (IGRA) are tools commonly used to detect LTBI (IGRA can also detect active disease) and can facilitate the safe initiation of IPT or TB treatment [6]. Use of TST is complicated in countries where the Bacille Calmette Guerin (BCG) vaccine is used because the immunity stimulus it provides can interfere with the accuracy of TST readings. IGRA offer several advantages over the TST in general, including improved sensitivity in immune-competent patients and not requiring multiple visits to a healthcare center. There is currently no

evidence that they offer improved sensitivity over the TST in settings with high HIV prevalence [11]. Many patients still require further evaluation because positive TST and IGRA results are not specific to LTBI or TB. Therefore their usefulness is limited in settings with high HIV prevalence because they detect a TB-specific immune response found lacking in many immunosuppressed individuals.

Given the caveats and limitations of classic TB diagnostic tools in under-resourced, HIV-prevalent settings, simple, rapid, and inexpensive screening tools are needed to reduce delays in TB diagnosis and increase the uptake of IPT [51]. Many settings rely on presence of prolonged cough (i.e., cough > 3 weeks), but this is not sensitive enough in PLHIV in most settings as severely immunosuppressed patients often have fewer respiratory symptoms than immune competent ones [14]. The WHO recently recommended a clinical screening algorithm that could be used to rule out those unlikely to have active TB (and in whom IPT could be initiated) and those who need further evaluation for TB before IPT or ART initiation [5]. The new screening algorithm, and others like it, is based on combinations of symptoms and has generally been found to have improved sensitivity for detecting TB in people with compromised immune systems and unusual clinical manifestations [15, 51].

2.3 TB/HIV Epidemiology and Control in S.E. Asia

Most of the TB/HIV syndemic is concentrated in sub-Saharan Africa (sSA) – South Africa alone is home to 80% of the global TB/HIV cases – and there is significant regional variation in TB incidence, prevalence, and mortality as well as a range of other characteristics like male:female mortality ratio and temporal trends in TB incidence [3, 40]. Broad trends like poverty, population mobility, and poor infection control practices

in congregate settings have fueled both epidemics, and access to services including HIV testing and counseling, TB evaluations, and therapy for TB and HIV is still uneven [4].

In addition to sSA, a substantial portion of the global TB/HIV burden is shared by South-East Asia (S.E. Asia) [40]. Cambodia, Thailand, and Viet Nam are among the 22 high-TB-burden countries listed by the STOP TB partnership, an international body linked to WHO. Other S.E. Asian countries on the list include China, Indonesia, Myanmar, and the Philippines, indicating a dire need for improved control efforts in the region [52]. While incidence rates of TB are falling in all six WHO regions, the rate of decline between 2010 and 2011 in S.E. Asia was 2%, the second lowest of all regions [3]. The high death rate from TB in PLHIV in S.E. Asia (ranging from 20 to 50%) could be the result of delayed TB diagnosis and treatment initiation, a notion suggested by the fact that patients tend to be severely immunosuppressed at the time of TB diagnosis [53]. Common causes of death in co-infected persons in sSA include TB, pneumonia, bacteremia, cerebral toxoplasmosis, and *Pneumocystis jirovecii* pneumonia (PCP). Causes in S.E. Asia are not as well understood because autopsies are less commonly performed there than in Africa [53]. Understanding the sources of HIV-related mortality in S.E. Asia can help correctly identify TB when clinical manifestations of disease are often ambiguous, so continued epidemiologic study in these countries will be important to successfully controlling the syndemic. Different clinical presentations between countries make it important to study and understand country-specific interactions between TB and HIV and to develop diagnostic, screening, and treatment guidelines appropriate for each country.

Cambodia is ranked 4th among the countries with the highest TB burdens in the world with a prevalence of 817 and incidence of 424 cases per 100,000, despite experiencing a 45% reduction in the prevalence of TB since 2002 [3]. HIV prevalence in incident TB cases is 5.1% in 2011, lower than Thailand and Viet Nam [3]. A cross-sectional study in rural Cambodia found that HIV prevalence in TB patients was 38% and TB prevalence in HIV patients was 24% [54]. Such a substantial overlap means cooperative control activities, including integrated diagnostic and service-delivery models, are needed to adequately address TB and HIV. The same study found nearly 25% of those with TB/HIV co-infection died during TB treatment. This death rate and that reported from a study in Ho-Chi-Minh city is higher than in some sSA [55, 56]. A study of risk factors of AFB-negative TB in PLHIV found risk factors differed between patients in Cambodia and Africa. Concurrent bacterial, parasitic, or fungal infections and abnormal CXR findings were associated with higher risk of AFB-negative TB in both setting [57]. AFB-negative TB is important because many settings rely on direct sputum examination for AFB to diagnose TB and will miss most AFB-negative cases, and HIV-infected persons are more likely to have AFB-negative TB [43]. Understanding the epidemiology of AFB-negative TB in HIV-prevalent settings is important to improving case-finding. The presence of other infections in persons with AFB-negative TB also suggests the symptoms included in the WHO screening tool are not specific to TB, so screening should be followed by evaluation with more specific diagnostic tools before TB is diagnosed and treatment initiated.

Thailand has a smaller TB burden relative to Cambodia and Viet Nam, but its HIV burden is substantially higher at 1.2% prevalence among adults aged 15-49 years

[2]. The TB prevalence is 164 and the incidence 124 cases per 100,000. In 2011 15% of incident TB cases in Thailand were HIV-related, compared with 5.1% in Cambodia and 8% in Viet Nam [3]. In addition to a heavy TB/HIV burden, the prognosis for co-infected patients – especially those with extra-pulmonary TB (i.e., MTB infections in sites outside the lungs) – is generally poor. Forty percent of HIV-associated TB cases in Thailand have extra-pulmonary TB; 25% of which also have pulmonary TB. In a prospective cohort study of 769 co-infected patients, 19% of patients with any extra-pulmonary TB died during treatment [58]. The risk of death was especially high for those with CD4 counts <200, but CPT, fluconazole, and ART all significantly reduced the risk of death [58]. Those with MDR-TB and gastrointestinal TB were at higher risk of mortality than those with other manifestations in another study, and ART was again found to significantly reduce the risk of mortality [53, 59]. Earlier TB detection and ART initiation are therefore crucial to preventing TB/HIV-related mortality. Elevated mortality among persons with gastrointestinal TB is further evidence that using prolonged cough for screening is insufficient and risks missing cases at high risk of mortality.

Another prospective observational study found 39% of deaths in co-infected patients in Thailand were TB-related [53]. Another 45% were HIV-related, and only 16% of deaths were not associated with either TB or HIV [53]. It was also found that some patients turned out not to have TB at all and were originally misclassified, highlighting the importance of modern, accurate TB diagnostics becoming more widely available in HIV-prevalent areas. Finally, hospitalization at the time of enrollment was found to be strongly associated with death during treatment. The link between

hospitalization and death could be spurious and simply indicate a relationship between more severe disease and death, but it could also indicate poor quality of care or hospital-acquired TB infections. Regular HIV testing, ART for all people with HIV and CD4 counts <250, and CPT are all recommended by Thailand's national TB program [53]. Persistently high mortality demonstrates the need to improve adherence to these recommendations.

Viet Nam was estimated to have a prevalence of 323 and incidence of 199 TB cases per 100,000 in 2011, and an estimated 8% of incident TB cases in were HIV-associated [3]. An estimated 0.5% of the population aged 15 – 49 was infected with HIV in 2011, and Khue *et* al. found a high (14.2%) rate of HIV co-infection in a survey of TB patients in Viet Nam's third-largest city [2, 60]. HIV in Viet Nam is mainly concentrated in urban areas and among high-risk populations like injection drug users, commercial sex workers and their clients, and spouses of HIV-infected men [61, 62]. TB patients co-infected with HIV have a 34% mortality rate compared to 3% in HIV-uninfected patients [62]. The high prevalence and mortality of TB/HIV co-infection in Viet Nam indicates a need for improved diagnosis and access to TB and HIV care, especially in urban areas.

2.4 The Need for Screening Tests and How to Evaluate Their Effectiveness

Given the needs in low-resource settings, screening tools that are simple, resource-sparing, and effective are urgently needed to improve individual patient outcomes and control the spread of infectious disease [14, 35]. The health workforce in some developing countries is too small and not educated enough, so screening tools should not require too much training to be applied. Many areas lack reliable electricity or disposable materials for equipment like radiograph machines, so screening tools should rely on clinical presentation that does not require things like chest radiography or other

imaging procedures (i.e., they should be resource-sparing). In addition to technological resources, time and effort of healthcare workers (HCWs), in the form of number of TB suspects who need to be evaluated for every case detected, should be kept to a minimum. Finally, a good test should be effective. Low cost must be balanced against the risk of returning false negative results because false negatives can result in poor health outcomes and continued transmission. Sensitivity and predictive values should be high so only patients with a high likelihood of having a disease undergo further evaluation or treatment and only those with a very low likelihood are not evaluated further.

It is important to understand the effect of immune status on the performance of symptom screens because HIV is prevalent in many of the same settings in which TB is prevalent and HIV changes the clinical presentation of TB, making TB more difficult to diagnose in immunosuppressed patients [16, 63]. Immune status is also an important prognostic indicator in HIV-infected patients, as evidenced by the reduction in mortality from ART [25, 64]. Patients with more severely compromised immune systems are more likely to experience poor health outcomes, so a symptom screen that effectively rules out TB (or any other opportunistic infection) and reduces the time until treatment initiation could improve such patients' chances of living and avert substantial morbidity and mortality in high-burden populations. If negative screening results are more common among more immunocompromised patients, then recommendations to initiate IPT in patients who screen negative may need to be revised because initiating IPT in immunosuppressed patients who may have active TB increases the risk of IRIS, treatment failure, or both.

Like any diagnostic test, the effectiveness of TB screening tools can be judged based on a number of characteristics. Sensitivity, specificity, predictive value positive and negative, and likelihood ratios are all commonly used measures of a diagnostic accuracy and represent different conditional probabilities related to test results and true disease status [65]. Other qualities like cost, time, and ease of use are also important both clinically and programmatically. There are often tradeoffs associated with these values, so choosing which to prioritize is an important task.

A common approach to evaluating new diagnostic tools is the reference standard approach, wherein the results of an untested tool are compared to those of an accepted gold-standard tool [15, 51, 65]. A number of studies including meta-analysis and prospective cohort designs used such an approach (with mycobacterial culture as the referent) and mathematical modeling to calculate the sensitivity and specificity for thousands of symptom combinations to develop the WHO-recommended screening tool [5, 15, 51]. Other methods like those in Davis *et* al. can also be used to evaluate screening tools [63].

Modeling sensitivity and specificity in population sub-groups can identify additional uses for screening tools. For example an analysis of the WHO-recommended screening tool shows it may have applications for infection control in congregate settings because it can distinguish highly infectious TB cases from less infectious ones [66]. Further scrutiny of the screening tool's performance across a continuous range of immune status using a reference standard approach and mathematical modeling may suggest more applications still.

3. Methods and Results

3.1 Methods

3.1.1 Study population and specimen collection

Data were collected during a prospective, cross-sectional study of those living with HIV conducted by the CDC to assess the sensitivity and specificity of symptom combinations related to mycobacterial culture. Patients with HIV receiving care in outpatient settings in Cambodia, Thailand, and Vietnam were enrolled between September 2006 and July 2008. Eight facilities were included: four in Cambodia (two in Banteay Meanchey province, one in Battambang, and one in Phnom Penh); one in Thailand (Bangkok); and three in Ho Chi Minh City, Vietnam.

All persons with HIV visiting these sites during the enrollment period were assessed for eligibility. Eligible participants were >6 years of age, had not received IPT or TB treatment in the previous year, had not taken any drugs with anti-TB properties in the previous month, and had not been screened for TB by chest radiography or sputum smears in the previous three months. After receiving their informed consent, each participant underwent a standardized clinical history and physical examination in which 73 signs and symptoms were evaluated. Three sputum samples and one sample each of urine, stool, blood, and lymph node aspirate (if indicated) were collected from each patient for diagnostic evaluation [15].

Laboratory assessments were conducted in one reference laboratory in each country using standardized methods. All specimens except blood were examined by Ziehl-Neelsen microscopy and cultured for MTB using Lowenstein-Jensen medium. Laboratories in Thailand and Vietnam also used Mycobacterial Growth Indicator Tube (Becton Dickinson, Franklin Lakes, NJ) and processed samples with BACTEC

Mycobacterial Growth Indicator Tube 960 (Becton Dickinson, Cockeysville, MD). Positive cultures were identified as MTB by biochemical tests or the Accuprobe *M. tuberculosis* complex assay (GenProbe; San Diego, CA) [67]. Quality control measures were implemented to prevent misclassification of disease and ensure data quality. Positive sputum results were confirmed by two separate readers; smears with 1 to 9 acid-fast bacilli per 100 fields were re-read by independent, on-site microbiologists; and positive culture results were evaluated for cross-contamination using a standard approach involving genotyping via spoligotyping and 24-loci mycobacterial interspersed repetitive unit-variable number tandem repeat analysis [15]. The study was approved by institutional review boards or human subjects research ethics committees at the CDC and in each participating country.

Participants were classified as MTB positive if at least one biological specimen from any site grew *M. tuberculosis* during mycobacterial culture. Having symptoms consistent with TB was defined as having at least one of the following: current **c**ough of any duration; **f**ever; night **s**weats; or **w**eight loss in the previous four weeks (i.e., CFSW positive). A Karnofsky performance score was used as an indicator of functional status. It ranged from 0 to 100 in increments of 10, with 100 indicating a patient with no complaints or evidence of disease and zero being death [68]. While it is a common prognostic indicator with generally high validity and reliability in cancer patients, it is also used for other types of illness including HIV [42]. Lower Karnofsky scores indicate generally poorer health and more severe disability.

3.1.2 Statistical analyses

Statistical comparisons were made between patients with and without TB and between patients with positive and negative CFSW screening results to identify differences in characteristics between groups. All analyses were performed using SAS version 9.3 (Cary, N.C., USA). Univariate and bivariate analyses of categorical data were performed using Pearson's chi-squared or Fisher's exact tests as appropriate, and analyses of continuous data were performed using Wilcoxon Mann-Whitney or Kruskal-Wallis tests as appropriate. Cochran-Armitage tests for trend were performed for the presence of symptoms across strata of CD4 count. Relationships with p-values < 0.05 were considered statistically significant.

Multivariate logistic regression models were developed to estimate the effect of immune status (represented by CD4 count) on the log-odds of having symptoms consistent with TB, controlling for significant confounders and effect modifiers. Two models were fit, one for patients with culture-confirmed TB (MTB+), and one for patients without culture-confirmed TB (MTB-). The sensitivity of the CFSW symptom screen was given by the MTB positive model as the log-odds (which can be transformed to the probability) of a positive CFSW result given that a patient is truly MTB+. Specificity can be derived from the MTB negative model by taking the inverse of the modeled log-odds of a positive CFSW, given a patient who is truly MTB- [65]. Developing two models effectively assesses the possibility of interaction between MTB status and the covariates of interest by reporting the effect of covariates on the immune status coefficient estimate at both levels of MTB status separately.

Piecewise linear splines were used to represent CD4 count in the logistic models. This method has several advantages over competing approaches like categorizing CD4 count or using polynomial representations of it. First, it allows us to show a non-linear relationship between immune status and the probability of positive symptom screen results. Second, it represents the relationship in more detail than would be possible by categorizing CD4 count because it preserves the continuous nature of the exposure variable [69]. Using linear splines is a more visually intuitive way to characterize continuous data than categorization or low degree polynomials, and it may avoid highly variable estimates near extreme points of the data (which are exactly the data in which we are most interested for this study) that can result from using high degree polynomials. Finally, it fits easily into standard modeling approaches because it simply involves the addition of extra variables. One knot was chosen at 400 cells per microliter because prior exploratory analyses of these data suggest it is an appropriate cut-point. A knot is a point along the curve at which the slope of the linear spline is allowed to change. Allowing the slope to change at 400 cells allowed us to test the hypothesis that immune status may have different effects on the presence of symptoms above and below a certain level of immune competency.

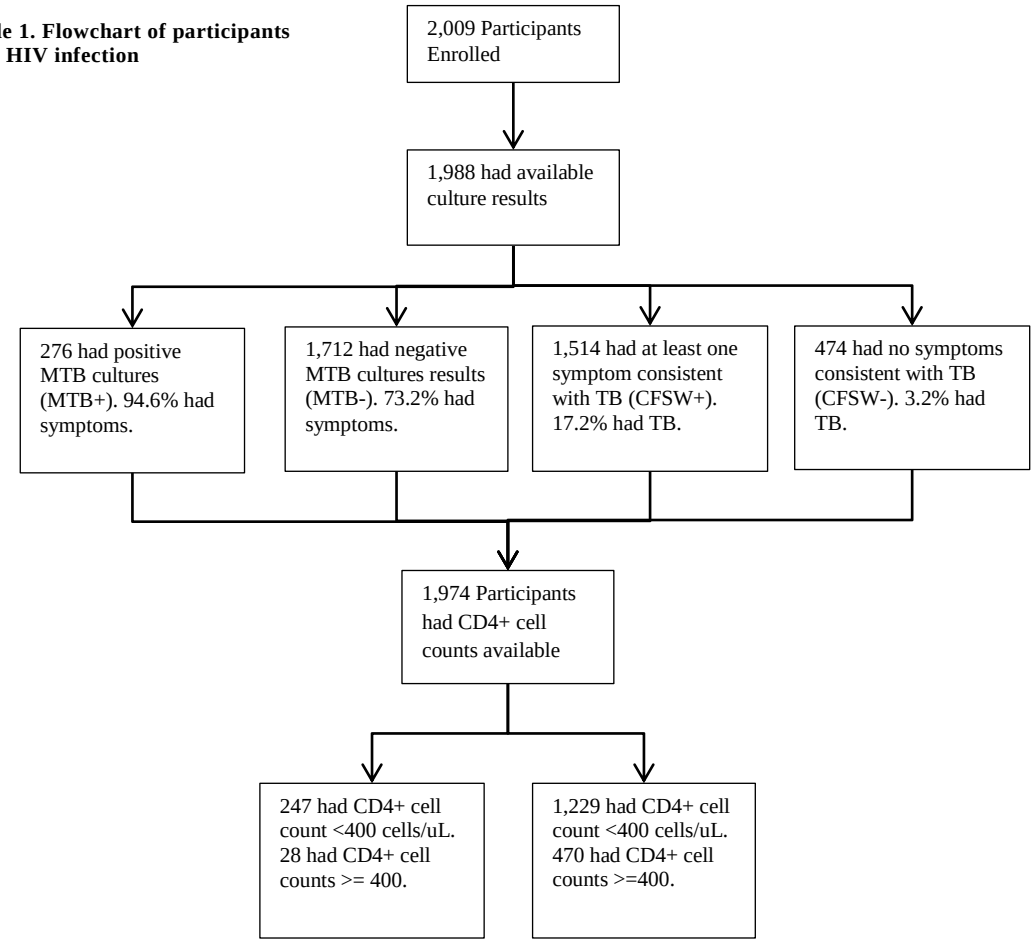
A list of covariates was developed based on review of relevant literature, previous investigator experience, and univariate analysis. Covariates for the final version of each model were selected using a manual hierarchical backward elimination approach. Co-linearity was assessed by comparing condition indices and variance decomposition proportions. Wald chi-squared tests were used to evaluate potential effect modifiers. Interaction terms with p-values not significant at the 0.05 level were excluded from the

final models. Potential confounders were assessed using a backward elimination approach and *a priori* criteria for exclusion in the final model. If removing a covariate from the model resulted in more than a 2% change from the estimated coefficient for the CD4 count term from a "gold standard" model (i.e., one including all covariates after removing non-significant interaction terms) it was considered a potential confounder and included in the final model. Models with all possible covariate patters after interaction assessment were fitted and compared to assess which covariates were potential confounders and which could be removed from the final model.

3.2 Results

Among 1,988 patients with available culture status, 276 (13.8%) were diagnosed with TB and 1,712 (86.2%) were not (Table 1). Using CFSW, 1,514 (76.2%) were positive for TB and 474 (23.8%) were negative. The median age of the study population was 31 years and the median CD4 count was 254 cells per microliter (slightly higher than similar studies conducted in Africa) [16, 59]. Males represented 51% of the population; 11% were receiving HIV treatment at the time of enrollment and 50 (3%) were hospitalized at the time of enrollment.

Table 1. Flowchart of participants with HIV infection



A number of patient characteristics and TB risk factors differed significantly between those with positive and negative results using the CFSW symptom screen (Table 2). The most significant associations were between age (though the difference of 1 year is not clinically meaningful), country of enrollment, current ART, and Karnofsky performance score. Patients who screened CFSW positive were more likely to live in Cambodia, be hospitalized at the time of enrollment, and have Karnofsky scores < 70 (i.e., those unable to work and requiring various levels of assistance to take care of themselves [68]), whereas those who screened CFSW negative were more likely to live in Thailand and be receiving HIV treatment at the time of enrollment.

Table 2. Frequency of selected characteristics by CFSW symptom screen status, Cambodia, Thailand, Viet Nam, 2006-2008 (N=1,988)*

Characteristic	CSFW +	CSFW -	Total	*P*
Median age (IQR)	32 (11)	31(10)	31 (11)	<.001
Male gender, n (%)	782 (51.7)	227 (47.9)	1,009	0.15
Study country, n (%):				
Cambodia	820 (54.2)	108 (22.8)	928	<.001
Thailand	382 (25.2)	248 (52.3)	630	<.001
Viet Nam	312 (20.6)	118 (24.9)	430	0.05
Median cd4 cell count (IQR)	226 (305)	321 (263)	254.5 (308)	0.05
Current HIV treatment, n (%)	118 (7.8)	90 (19.0)	208	<.001
CPT > 14 days, n (%)	79 (5.5)	30 (6.5)	109	0.39
Ever injected drug, n (%)	195 (12.9)	59 (12.5)	254	0.82
Current hospitalization, n (%)	46 (3.04)	4 (0.84)	50	0.01
Karnofsky score < 70, n (%)	79 (5.2)	2 (0.43)	81	<.001

MTB positive participants differed significantly from MTB negative ones in a number of characteristics (Table 3). MTB positive participants were more immuno-compromised, more likely to be male, report having used injection drugs, live in Viet Nam, be hospitalized at the time of enrollment, and have low Karnofsky scores. MTB negative participants were more likely to be on HIV treatment and live in Thailand. Participants with TB generally had more advanced immunosuppression and poorer health than those without it. These associations are consistent with the literature on HIV risk factors in South-East Asia and on the relationship between HIV, immune status, and the likelihood and severity of TB disease.

Table 3. Frequency of selected characteristics by MTB status, Cambodia, Thailand, Viet Nam, 2006-2008 (N=1,988)*

Characteristic	MTB+	MTB-	Total	*P*
Median age (IQR)	31 (11.5)	31.5 (11)	31 (11)	0.48
Male gender, n (%)	177 (64.1)	832 (48.6)	1,009	<.001
Study country, n (%):				
Cambodia	129 (46.7)	799 (46.7)	928	0.98
Thailand	34 (12.3)	596 (34.8)	630	<.001

* Tests for categorical variables were performed using Pearson's chi-square tests on 1 df. The overall test for study country is a Pearson's chi-square test on 2 df. Continuous variables were tested using Wilcoxon Mann-Whitney tests.

Viet Nam	113 (40.9)	317 (18.5)	430	<.001
Median cd4 cell count (IQR)	107 (231)	277 (310)	254.5 (308)	<.001
Current HIV treatment, n (%)	6 (2.2)	202 (11.8)	208	<.001
CPT > 14 days, n (%)	10 (3.9)	99 (6.0)	109	0.17
Ever injected drug, n (%)	79 (28.6)	175 (10.2)	254	<.001
Current hospitalization, n (%)	18 (6.5)	32 (1.9)	50	<.001
Karnofsky score < 70, n (%)	33 (12.0)	48 (2.8)	81	<.001

Patient characteristics and TB risk factors stratified by MTB status and CFSW results revealed MTB positive participants who screened positive (i.e., "true" positives) were more likely to have low Karnofsky scores and tended to be more immunosuppressed relative to the other groups, suggesting more severe HIV disease and disability among true positive cases (Table 4). MTB negative participants who screened negative (i.e., "true" negatives) were more likely to be on HIV treatment and live in Thailand relative to other groups. Patients on HIV treatment were more immune-competent and healthier in general, making them less susceptible to TB.

Discordant groups, or those with conflicting MTB status and CFSW results, show similar differences. Among MTB positives, those with negative CFSW results had higher CD4 counts, were more likely to be on HIV treatment at the time of enrollment, and more likely to report ever using injection drugs than CFSW positives. This raises the question of why injection drug use (IDU) would be associated with lower probability of presenting with symptoms, given positive MTB status. Among MTB negative participants, those with negative CFSW screens had higher CD4 counts and were more likely to receive current HIV treatment and live in Thailand, whereas those with positive CFSW screens were more likely to live in Cambodia, be hospitalized at the time of enrollment, and have low Karnofsky scores.

Table 4. Frequency of potential confounders by MTB and CFSW symptom screen status, Cambodia, Thailand, Viet Nam, 2006-2008 (N=1,988)

Characteristic	MTB+, CFSW-	MTB+, CFSW-	MTB-, CFSW+	MTB-, CFSW-	Total	*P*[†]
Median age (IQR)	31 (12)	28 (11)	32 (11)	31 (10)	31 (11)	0.21
Male gender, n (%)	167 (64.0)	10 (66.7)	615 (49.1)	217 (47.3)	1009	<.001
Study country, n (%):						
Cambodia	128 (49)	1 (6.7)	692 (55.2)	107 (23.3)	928	<.001
Thailand	29 (11.1)	5 (33.3)	353 (28.2)	243 (52.9)	630	<.001
Viet Nam	104 (39.9)	9 (60)	208 (16.6)	109 (23.8)	430	<.001
Median cd4 cell count (IQR)	95.5 (207.5)	322 (282)	252 (313)	321 (266)	254.5 (308)	<.001
Current HIV treatment, n (%)	5 (1.9)	1 (6.7)	113 (9.0)	89 (19.4)	208	<.001
CPT > 14 days, n (%)	9 (3.7)	1 (6.7)	70 (5.8)	29 (6.5)	109	0.49
Ever injected drug, n (%)	72 (27.6)	7 (46.7)	123 (9.8)	52 (11.4)	254	<.001
Current hospitalization, n (%)	18 (6.9)	0	28 (2.2)	4 (0.9)	50	<.001
Karnofsky score < 70, n (%)	33 (12.6)	0	46 (3.7)	2 (0.4)	81	<.001

Trends across categories of CD4 count showed a negative relationship between immune status and presence of symptoms consistent with clinical and epidemiologic literature (Table 5). The drop in the probability of having most symptoms is most dramatic between CD4 counts below 200 and those between 200 and 400 cells. This suggested there might be a threshold of immunosuppression, below which symptoms become far more likely and above which symptoms are relatively rare regardless of further improvements in immune status. Identifying such a threshold may have implications for treatment of TB in PLHIV.

Table 5. Presence of symptoms by CD4 cell count, Cambodia, Thailand, Viet Nam, 2006-2008 (N=1,988)[‡]

Symptom	0-200 (N= 811)	201-400 (N= 679)	401-600 (N= 335)	601-800 (N= 114)	801+ (N= 49)	Total	*P*[§]
Cough, n (%)	475 (59)	290 (43)	144 (43)	41 (37)	22 (45)	972	<.001
Fever, n (%)	502 (63)	239 (35)	109 (32)	37 (34)	22 (45)	909	<.001

[†] Tests for significance were performed using Pearson's chi-squared for categorical data (Fisher's Exact was not implicated in any test despite observed cell counts of 0) and Kruskal-Wallis tests for continuous data.

[‡] 14 patients had no recorded CD4 cell count

[§] Tests for significant trend were performed with Cochran-Armitage test for trend on 4 degrees of freedom.

Night sweats, n (%)	292 (37)	140 (21)	61 (18)	18 (16)	8 (16)	519	<.001
Weight loss, n (%)	512 (64)	260 (38)	97 (29)	44 (40)	15 (31)	928	<.001
Symptom screen, n (%)	687 (86)	470 (70)	229 (68)	82 (75)	33 (67)	1,514	<.001

All analyses suggested significant cross-country variation in the prevalence and presentation of TB disease. Patients living in Cambodia were more likely to have MTB and more likely to have positive CFSW symptom screen results than those living in Thailand or Viet Nam, whereas patients living in Thailand were more likely to be MTB and CFSW negative than those in Cambodia and Viet Nam. Prolonged CPT (i.e., CPT for at least two weeks prior to evaluation) was not significantly associated with MTB status or CFSW results, but other characteristics and risk factors were. As expected, patients with TB tended to have more severe disease than those without, and those with more severe disease were generally more likely to have at least one symptom associated with TB.

Results from the initial regression models developed by including the exposure variable (CD4 count) and one covariate from the list of those chosen as potential confounders and effect modifiers showed the estimated coefficient for CD4 count remains essentially constant when controlling for age, sex, country, ART, IDU, hospitalization, performance score, and CPT individually in addition to MTB status (Table 6). The relationship between immune status and the log-odds of screening positive for TB is (very) statistically significant where CD4 count is <400 cells, but there does not appear to be a relationship in patients with CD4 counts >400 cells. In MTB+ patients with CD4 counts <400 cells, the log-odds of having a positive TB screen decrease by 99% for every increase of 100 cells. A patient with a CD4 count of 100 cells could therefore be expected to be 38% as likely to screen positive as someone with a CD4

count of 200 cells. The relationship between immune status and being symptomatic is still significant below 400 cells, but it is not as strong among MTB- patients as it is among MTB+ ones. Among MTB negative patients there were significant but weaker inverse relationships between immune status and the log-odds of positive TB screens. In this group, every increase of 100 CD4 cells is associated with a 31% decrease in the log-likelihood of screening TB positive. An MTB- person with 100 cells would be about 73% as likely as someone with 200 cells to screen positive, given that both patients are MTB negative.

Table 6. Regression models for CFSW Positivity Among Patients with HIV (N=1,988)

	MTB + (N=276)						**MTB - (N=1,712)**					
	CD4 < 400 (N=247)			CD4 >= 400 (N=28)			CD4 < 400 (N=1,229)			CD4 >= 400 (N=470)		
Model	Beta	OR (95% C.I.)	*P***	Beta	OR (95% C.I.)	*P*	Beta	OR (95% C.I.)	*P*	Beta	OR (95% C.I.)	*P*
Crude	-0.99	0.37 (0.22, 0.62)	<.01	0.14	1.15 (0.79, 1.67)	0.46	-0.32	0.73 (0.67, 0.8)	<.01	0.076	1.08 (0.97, 1.2)	0.14
Age	-0.99	0.37 (0.22, 0.62)	<.01	0.15	1.16 (0.79, 1.72)	0.44	-0.31	0.73 (0.67, 0.8)	<.01	0.078	1.08 (0.97, 1.2)	0.14
Male	-0.99	0.37 (0.22, 0.63)	<.01	0.14	1.02 (0.32, 3.24)	0.46	-0.32	0.73 (0.67, 0.8)	<.01	0.076	1.08 (0.97, 1.2)	0.14
Site country	-0.91	0.4 (0.24, 0.67)	<.01	0.12	1.13 (0.77, 1.65)	0.53	-0.31	0.73 (0.67, 0.8)	<.01	0.068	1.07 (0.97, 1.19)	0.2
Current ART	-0.97	0.38 (0.23, 0.63)	<.01	0.13	1.14 (0.79, 1.66)	0.48	-0.30	0.75 (0.68, 0.82)	<.01	0.067	1.07 (0.97, 1.19)	0.2
IDU	-1.00	0.37 (0.22, 0.62)	<.01	0.14	1.15 (0.8, 1.66)	0.45	-0.32	0.73 (0.66, 0.8)	<.01	0.073	1.08 (0.97, 1.19)	0.16
Hospitalized ††	-0.97	0.38 (0.23, 0.64)	<.01	0.13	1.14 (0.79, 1.65)	0.47	-0.31	0.73 (0.67, 0.8)	<.01	0.078	1.08 (0.98, 1.2)	0.14
Karnofsky score < 70**	-0.97	0.38 (0.23, 0.64)	<.01	0.14	1.15 (0.8, 1.66)	0.44	-0.30	0.74 (0.68, 0.82)	<.01	0.08	1.08 (0.98, 1.2)	0.13
CPT > 14 days	-1.05	0.35 (0.2, 0.6)	<.01	0.21	1.23 (0.82, 1.84)	0.32	-0.34	0.72 (0.65, 0.79)	<.01	0.076	1.08 (0.97, 1.2)	0.15

Multivariate regression models developed using the above procedures are shown in Table 7. Among patients with culture confirmed TB, only CD4 count <400 cells was a significant, independent predictor of CFSW positivity when controlling for current HIV

** P-values shown are from Wald chi-squared statistics for each coefficient estimate testing H0: Beta=0. P-values below 0.05 were considered statistically significant.

†† Only partial convergence was achieved in the MTB+ model, making the reliability of the current hospitalization estimates questionable.

treatment, injection drug use, country of evaluation, and prolonged CPT. Increasing CD4 count above 400, HIV treatment at time of enrollment, injection drug use, country of evaluation, and prolonged CPT were all non-significant factors. Among MTB negatives, CD4 counts <400 cells were significantly associated with a decreased odds of CFSW positivity. HIV treatment at the time of enrollment and study site country were also significant independent predictors of CFSW positivity when controlling for immune status, injection drug use, and CPT. CD4 count >400, injection drug use, and CPT were not significantly associated with CFSW positivity among MTB negative patients when controlling for low CD4 count, HIV treatment, and study site country. These results showed a significant association between immune status when CD4 counts were low and the odds of CFSW positivity when controlled for potential clinical and behavioral factors. The relationship was significant regardless of MTB status, though it appeared stronger among patients without culture-confirmed TB.

Table 7. Multivariate Logistic Regression Models for CFSW Positivity Among Patients with HIV (N=1,988)

	MTB + (N=276)			MTB - (N=1,712)		
Characteristic	OR	95% C.I.	*P*‡‡	OR	95% C.I.	*P*
Increasing CD4, < 400§§	0.41	(0.23, 0.71)	0.002	0.77	(0.69, 0.85)	<.01
Increasing CD4, >400	1.18	(0.76, 1.81)	0.46	1.06	(0.95, 1.18)	0.29
Current HIV treatment	0.8	(0.07, 9.13)	0.85	0.54	(0.37, 0.77)	<.01
Ever injected drug, n (%)	0.54	(0.14, 2.13)	0.38	1.19	(0.78, 1.82)	0.42
Study country:						
Cambodia	Referent	-	-	Referent	-	-
Thailand vs. Cambodia	0.12	(0.01, 1.21)	0.07	0.26	(0.2, 0.34)	<.01
Viet Nam vs. Cambodia	0.19	(0.02, 1.91)	0.16	0.25	(0.17, 0.36)	<.01

‡‡ P-values shown are from Wald chi-squared statistics for each coefficient estimate testing H_0: Beta=0. P-values below 0.05 were considered statistically significant.

§§ CD4 parameters represent the continuous effect of CD4 on the odds of CFSW positivity. Odds ratios therefore represent the odds of CFSW positivity for each additional 100 CD4 cells (i.e., relative to an individual with 100 fewer CD4 cells), controlling for covariates. Two CD4 parameters are included because that is how CD4 is represented in a regression model using linear splines.

CPT > 14 days	0.27	(0.02, 3.39)	0.31	0.76	(0.45, 1.27)	0.29

The probability of having at least one TB symptom decreases with increasing CD4 count, up to 400 cells (Table 8, Appendix 4). The relationship is negative and statistically significant regardless of MTB status. The relationship between immune status and the probability of having at least one TB symptom is not statistically significant beyond 400 cells, i.e., the slope in Appendix 4 does not differ significantly from zero. Probability estimates are less precise at higher CD4 counts because there were relatively few participants with such competent immune systems.

Table 8. Estimated Sensitivity and (1-Specificity) at Intervals of CD4 Count in HIV-infected Patients, Cambodia, Thailand, Viet Nam, 2006-2008 (N=1,988)

	MTB +	MTB -
CD4 cell count	Sensitivity (95% C.I.)	1-Specificity (95% C.I.)
100	0.99 (0.95, 0.997)	0.82 (0.79, 0.85)
200	0.97 (0.92, 0.989)	0.78 (0.75, 0.8)
300	0.93 (0.82, 0.97)	0.73 (0.7, 0.76)
400	0.85 (0.6, 0.95)	0.67 (0.63, 0.72)

4. Discussion, Conclusions, and Recommendations

4.1 Review of major findings

In a multivariate regression analysis of the relationship between immune status and the performance of the screening tool recommended by the WHO in HIV-infected patients seeking care in South-East (S.E.) Asia, we found a statistically significant, negative, linear relationship between the log-odds of having TB symptoms and continuous immune status. This relationship is independent of country of evaluation, current ART use, IDU, and prolonged CPT, and culture status. That is, among those with positive (MTB+) and negative (MTB-) cultures, the log-odds for symptoms decrease with increasing CD4 cell count, up to 400 cells. The probability of having TB symptoms remained virtually constant at CD4 counts >400. ART, IDU, prolonged CPT, and country site were not significantly associated with the log-odds of having symptoms among participants with CD4 counts <400 cell when controlling for immune status.

The probability of having TB symptoms among those with CD4 counts <400 was greater for MTB+ than MTB- patients, corresponding to the sensitivity and 1–specificity of the WHO-recommended screening tool. Among those with CD4 counts <400, the sensitivity of the CFSW screening tool was higher among more immuno-compromised patients and increases continuously with falling CD4 count. The inverse of the sensitivity of the screening tool is the probability of a false negative result (i.e., of a MTB+ patient screening negative). The potential negative health outcomes of missing a TB case in the HIV-infected population is substantial given the high mortality rates and risk of IRIS documented in other studies [9, 24, 25]. A high sensitivity can therefore protect the

patient by allowing earlier diagnosis and treatment initiation, and it can protect a population by preventing further transmission and drug resistance. The higher sensitivity we observed among more immunosuppressed patients was a useful characteristic clinically and epidemiologically because it means fewer false negatives among those who need treatment most and are the most likely to transmit TB.

While the changing sensitivity with immune status was main focus of this analysis, an important feature of a screening tool is its absolute sensitivity in a given setting [65]. Our results suggest the sensitivity falls substantially as patients progress from the low end of the immune status spectrum to the center (i.e., around 400 cells). This analysis presented estimated values of sensitivity at different levels of immune function (Table 8), and showed a high sensitivity in people with CD4 counts <400 that declines with increasing immune function.

As a multivariate analysis, these estimates account for different values of covariates like ART, IDU, prolonged CPT, and study site country. The specified values are based on the average frequency in this study population and not the general population, but the sensitivity estimates are likely still representative of the region because the study population was taken from a wide cross-section of people.

Including the estimates in this analysis was meant primarily to provide a statistical basis on which HIV patients undergoing TB screening could be reasonably separated into two groups: those with CD4 counts <400, and those with CD4 counts >400. The separation may be reasonable because the sensitivity falls with increasing immune status to a level that may be of limited value among those with CD4 counts >400. The value of this added nuance to the application of the screening tool should be the subject of further

investigation before becoming a strong recommendation because it is based on the characteristics of a specific population in one geographic region.

Among those with CD4 counts <400 and in general, the specificity of the CFSW screening tool is lower among more immuno-compromised patients. Low specificity is not a major concern for the use of the tool because it is low in all groups: MTB+ and MTB-, and CD4 counts above and below 400. It is also an accepted tradeoff when developing screening tools because the high probability of a false positive result poses little risk beyond the health system expending extra resources unnecessarily on further evaluation. The specificity of any screening tool is therefore not expected to be high. Falling specificity with decreasing immune status is also consistent with the natural history of HIV infection; the increased likelihood of non-specific symptoms among those with more severe immunosuppression is unsurprising and does not change the application or interpretation of the screening tool.

An important function of a screening tool and a consequence of it being highly specific is that excluding people from further evaluation with complex, resource-intensive diagnostic tests like mycobacterial culture can spare the health system valuable resources, especially when the burden of TB and HIV is large.

The health systems of S.E. Asia may not be as constrained as those on other continents, but mycobacterial culture and GeneXpert are expensive tools nonetheless and their availability is limited by their cost. The specificity of the CFSW screening tool is too low to make it an effective diagnostic test, but to the extent that it excludes some patients from further evaluation, it will conserve each country's diagnostic resources for use on those more likely to have TB. This could prevent unnecessary expense of time

and resources by individuals and the health system on further evaluation. Depending on the size of the TB/HIV epidemic and the number of people who need TB evaluation in each country, even a modest specificity could generate substantial savings for the health system over time. Resources not spent on unnecessary evaluations could be channeled into expanding TB treatment or other control activities.

4.2 Discussion

We have great confidence in our sensitivity and specificity estimates partly because the ID-TB/HIV study on which our analysis is based used mycobacterial culture of multiple biological specimens from each participant to determine MTB status. Mycobacterial culture is the reference standard among currently available diagnostics, so there is little chance of misclassification of TB affecting our results. The ID-TB/HIV study also employed standardized measurement of signs and symptoms and various quality assurance measures to ensure the correct and consistent classification of disease.

Our analysis studied the effect of immune status on the performance of a TB screening tool in more detail than previous studies by using continuous CD4 count as the main predictor of sensitivity and specificity. Most studies investigating immune status as a predictor CD4 count as above or below 200 cells per microliter. This approach, while statistically less complicated than our own, may over-simplify the relationship between immune status and presence of symptoms. One other study of which we are aware uses a high resolution of CD4 strata (i.e., narrow strata of 50 cell) to characterize changes in clinical and radiological presentation of TB patients in Uganda, but results from that study conflict with our own [16]. Chamie *et* al. (2011) find an increasing probability of having signs and symptoms consistent with TB with increasing immune status, and low overall sensitivity among more immunosuppressed participants. Several possible

explanations for the discrepancy between results exist. One is that representing CD4 count continuously as opposed to narrow strata resulted in a different relationship between immune status and the probability of symptoms.

It is unlikely that representing immune status in slightly more detail would reverse the direction of the relationship since the representation of immune status is a statistical judgment and independent of the biological mechanism linking to the presence of symptoms (also, the relationship we described was consistent between continuous and categorized representations of immune status – see Table 5). Other possible explanations include differences in characteristics between the two study populations or the TB epidemiology therein. We discussed previously the differing epidemiology of TB in populations in S.E. Asia and sSA. The different etiology and clinical presentation of TB in the two populations could explain the different results from the two studies. Patients were recruited from the National TB and Leprosy Program (NTLP) in the Uganda study, which may have resulted in that study population having more severe TB disease on average than the S.E. Asia population, which recruited participants from HIV clinics and treatment facilities. The different referral mechanisms in each study could have resulted in study populations with different severity of TB disease or HIV infection on average, but it is difficult to tell without more detailed information on bacillary burden or CD4 count in the Ugandan population.

The prevalence of smoking in the two populations could also explain the different results. Smoking tends to be rarer in African populations than Asian ones, so more smokers among the S.E. Asia study group could explain a higher prevalence of cough and greater sensitivity of the screening tool [70]. The Uganda study included prolonged

cough and did not include night sweats as a TB symptom, which could explain fewer patients showing signs of TB among that group. Regardless of the reason for the discrepancy, further investigation of TB/HIV in African and Asian populations is needed to fully understand the different driving mechanisms in each.

Many studies of TB and TB diagnostics are restricted to a specific setting or group. Our analysis included a broad cross-section of participants from a variety of sites (including clinical and community settings) in three countries, lending added external validity (i.e., generalizability) to our findings. Two groups not extensively covered in our analysis are children and those with high CD4 counts. The ID-TB/HIV study did not enroll children under 7 years, and only 4 (0.2%) participants were aged <17. The number of participants with high CD4 counts was also limited – not many fell near the higher extreme of the immune status distribution, which created wide variation in our estimates of sensitivity and specificity in that group. While the slope's deviation from zero was not statistically significant in our analysis, more participants with higher CD4 counts could reveal a statistically significant difference among patients with CD4 counts >400.

We remain confident in our conclusions despite this possibility because the slope estimated by our analysis was only slightly higher than zero. Even if this difference proves statistically significant on further investigation, such a weak relationship is unlikely to be clinically useful. Nevertheless, future studies investigating the relationship of symptom screen performance and immune status among children and those with higher CD4 counts are warranted because they would expand our understanding of the performance of the screening tool to additional sub-populations.

Our analysis suffered from slightly limited statistical power because only 276 participants had culture confirmed TB. While statistical power was sufficient for multivariate logistic regression, some potential confounders and effect modifiers (e.g., Karnofsky Score) were prohibitively difficult to assess as such among MTB+ patients because the regression models became unstable with their inclusion as covariates. Bivariate analysis showed such factors did little individually to affect the exposure-outcome relationship, so we consider the final multivariate model valid despite their exclusion.

We did not include MDR-TB or extra-pulmonary TB as potential covariates, which are often important prognostic indicators in TB patients. There is little biological precedent for considering drug resistance as a confounder of the immune status-TB symptom relationship because drug resistance is not linked with the presence of symptoms and those on current TB treatment were excluded from the analysis anyway, but the site of disease may be a confounder because more immunosuppressed participants are more likely to have extra-pulmonary TB and thus less likely to present with a cough. Not considering site of disease is therefore a limitation of this study that should be subject to investigation in future studies.

Previous experience with these data in answering related research questions suggests they would not meaningfully confound the exposure-outcome relationship, and the low frequency of each among MTB+ participants in this study population may have resulted in model convergence issues in any case. Therefore we remain confident in our results despite not controlling for site of disease but recommend its inclusion in future analyses.

Current recommendations by the WHO are to treat those with negative screening results as MTB- and initiate IPT and to schedule those with positive screening results for further TB evaluation [5]. More operational research is needed to suggest what form that further evaluation should take and to determine which inexpensive evaluations are most effective at confirming active TB in PLHIV with varying immune status. Initial analyses from the ID-TB/HIV study (Cain, *et* al. 2010) suggested sputum smear microscopy and radiological examination may have some place in post-screening evaluation, but they did not examine the role of immune status closely and only accounted for diagnostic capacity in the S.E. Asia context [15]. The GeneXpert diagnostic platform was also not available at the time of the ID-TB/HIV study was conducted, so it could not be considered as an option. The advent of GeneXpert could give national TB programs more options than they previously enjoyed, but further research is needed to determine which method is most clinically and fiscally appropriate in each setting, given the effect of immune status on TB etiology and the different ways in which the HIV pandemic manifests itself between countries.

4.4 Conclusions and Recommendations

Our results supported the hypothesis that among patients living with HIV, the log-odds of presenting with TB symptoms increased with more advanced immune suppression <400 CD4 cells when controlling for MTB status and other clinical and behavioral factors. The tool's increasing sensitivity with greater immunosuppression among those with CD4 counts <400 may add utility to the tool in those most severely immunosuppressed and in need of TB and HIV treatment. By contrast, the screening tool's performance in those with CD4 count >400 appeared to suffer to the point of no

longer being very useful for the purpose of confidently recommending patients for further TB evaluation.

Mechanisms for this relationship are as yet poorly understood, but these findings suggest CFSW screening tool can help clinicians accurately rule out TB and initiate IPT in areas with large populations of HIV patients with varying levels of immune competency and that it is less likely to falsely rule out TB in those with the greatest immune suppression. The tool should be strongly promoted in such areas because it can prevent significant morbidity and mortality while sparing health system resources by helping clinicians initiate appropriate treatment sooner and avoid adverse treatment events.

Our analysis suffered a number of limitations, but none of them is serious enough to alter our conclusions that the CFSW screening tool performs better in more immuno-compromised patients in S.E. Asia, and that further investigation of the screening tool and other applications thereof can help national TB programs improve case detection and uptake of IPT as they strive to control the TB epidemic.

References

1. Dye, C., et al., *Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project.* JAMA, 1999. **282**(7): p. 677-86.
2. UNAIDS, *UNAIDS Report on the Global AIDS Epidemic*, 2012, UNAIDS: Geneva, Switzerland.
3. Organization, W.H., *Global Tuberculosis Report 2012*, 2012, World Health Organization: Geneva, Switzerland.
4. Kwan, C.K. and J.D. Ernst, *HIV and tuberculosis: a deadly human syndemic.* Clin Microbiol Rev, 2011. **24**(2): p. 351-76.
5. Organization, W.H., *WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders*, S.T. Department, Editor 2012, World Health Organization: Geneva, Switzerland.
6. Kaplan, J.E., et al., *Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America*, 2009, Centers for Disease Control and Prevention: Washington, D.C. p. 1-198.
7. Frieden, T.R., et al., *Tuberculosis.* Lancet, 2003. **362**(9387): p. 887-99.
8. Balcells, M.E., et al., *Isoniazid preventive therapy and risk for resistant tuberculosis.* Emerg Infect Dis, 2006. **12**(5): p. 744-51.
9. Armstrong, W.S., *The Immune Reconstitution Inflammatory Syndrome: A Clinical Update.* Curr Infect Dis Rep, 2012.
10. Maher, D., A. Harries, and H. Getahun, *Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies.* Trop Med Int Health, 2005. **10**(8): p. 734-42.
11. Cattamanchi, A., et al., *Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis.* J Acquir Immune Defic Syndr, 2011. **56**(3): p. 230-8.
12. Matee, M., et al., *Sputum microscopy for the diagnosis of HIV-associated pulmonary tuberculosis in Tanzania.* BMC Public Health, 2008. **8**: p. 68.
13. Monkongdee, P., et al., *Yield of acid-fast smear and mycobacterial culture for tuberculosis diagnosis in people with human immunodeficiency virus.* Am J Respir Crit Care Med, 2009. **180**(9): p. 903-8.
14. Reid, M.J. and N.S. Shah, *Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings.* Lancet Infect Dis, 2009. **9**(3): p. 173-84.
15. Cain, K.P., et al., *An algorithm for tuberculosis screening and diagnosis in people with HIV.* N Engl J Med, 2010. **362**(8): p. 707-16.
16. Chamie, G., et al., *Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata.* Int J Tuberc Lung Dis, 2010. **14**(10): p. 1295-302.
17. Collins, K.R. and M.E. Quinones-Mateu, *Impact of tuberculosis on HIV-1 replication, diversity, and disease progression.* AIDS Rev, 2002. **4**(3): p. 165-176.

18. Knechel, N.A., *Tuberculosis: pathophysiology, clinical features, and diagnosis.* Crit Care Nurse, 2009. **29**(2): p. 34-43; quiz 44.
19. DeRiemer, K., et al., *Quantitative impact of human immunodeficiency virus infection on tuberculosis dynamics.* Am J Respir Crit Care Med, 2007. **176**(9): p. 936-44.
20. Organization, W.H., *Tuberculosis World Report 2010*, S.T. Department, Editor 2011, World Health Organization: Geneva, Switzerland.
21. Suthar, A.B., et al., *Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis.* PLoS Med, 2012. **9**(7): p. e1001270.
22. (CDC), C.f.D.C.a.P., *Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Disease Society of America*, 2003.
23. (CDC), C.f.D.C.a.P., *Targeted tuberculin testing and treatment of latent tuberculosis infection*, 2000. p. 1-42.
24. Eng, B., et al., *Impact of a public antiretroviral program on TB/HIV mortality: Banteay Meanchey, Cambodia.* Southeast Asian J Trop Med Public Health, 2009. **40**(1): p. 89-92.
25. Franke, M.F., et al., *Effectiveness of early antiretroviral therapy initiation to improve survival among HIV-infected adults with tuberculosis: a retrospective cohort study.* PLoS Med, 2011. **8**(5): p. e1001029.
26. Lawn, S.D., et al., *Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa.* AIDS, 2009. **23**(13): p. 1717-25.
27. Manabe, Y.C., et al., *Unmasked tuberculosis and tuberculosis immune reconstitution inflammatory disease: a disease spectrum after initiation of antiretroviral therapy.* J Infect Dis, 2009. **199**(3): p. 437-44.
28. French, M.A., *HIV/AIDS: immune reconstitution inflammatory syndrome: a reappraisal.* Clin Infect Dis, 2009. **48**(1): p. 101-7.
29. Lawn, S.D. and G. Meintjes, *Pathogenesis and prevention of immune reconstitution disease during antiretroviral therapy.* Expert Rev Anti Infect Ther, 2011. **9**(4): p. 415-30.
30. Haddow, L.J., et al., *Incidence, clinical spectrum, risk factors and impact of HIV-associated immune reconstitution inflammatory syndrome in South Africa.* PLoS One, 2012. **7**(11): p. e40623.
31. Abdool Karim, S.S., et al., *Timing of initiation of antiretroviral drugs during tuberculosis therapy.* N Engl J Med, 2010. **362**(8): p. 697-706.
32. Blanc, F.-X., et al. *Early (2 weeks) vs. late (8 weeks) initiation of highly active antiretroviral treatment (HAART) significantly enhance survival of severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis: results of the CAMELIA clinical trial*. in *Institut Pasteur International Network Annual Scientific Meeting*. 2011. Hong Kong: BMC.
33. Ayles, H., et al., *Prevalence of Tuberculosis, HIV and Respiratory Symptoms in Two Zambian Communities: Implications for Tuberculosis Control in the Era of HIV.* PLoS One, 2009. **4**(5): p. e5602.

34. Huerga, H., et al., *Performance of the 2007 WHO Algorithm to Diagnose Smear-Negative Pulmonary Tuberculosis in a HIV Prevalent Setting.* PLoS One, 2012. **7**(12): p. e51336.
35. Sculier, D., H. Getahun, and C. Lienhardt, *Improving the prevention, diagnosis and treatment of TB among people living with HIV: the role of operational research.* J Int AIDS Soc, 2011. **14 Suppl 1**: p. S5.
36. Organization, W.H., *Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings.*, 2007, World Health Organization: Geneva, Switzerland.
37. Boehme, C.C., et al., *Rapid molecular detection of tuberculosis and rifampin resistance.* N Engl J Med, 2010. **363**(11): p. 1005-15.
38. Small, P.M. and M. Pai, *Tuberculosis diagnosis--time for a game change.* N Engl J Med, 2010. **363**(11): p. 1070-1.
39. Partnership, S.T., *UPDATE - Implementation and roll-out of Xpert MTB/RIF, February 2012*, 2012, World Health Organization: Geneva, Switzerland.
40. Getahun, H., et al., *HIV infection-associated tuberculosis: the epidemiology and the response.* Clin Infect Dis, 2010. **50 Suppl 3**: p. S201-7.
41. Mtei, L., et al., *High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania.* Clin Infect Dis, 2005. **40**(10): p. 1500-7.
42. Mugusi, F., et al., *HIV co-infection, CD4 cell counts and clinical correlates of bacillary density in pulmonary tuberculosis.* Int J Tuberc Lung Dis, 2006. **10**(6): p. 663-9.
43. Tamhane, A., et al., *Predictors of smear-negative pulmonary tuberculosis in HIV-infected patients, Battambang, Cambodia.* Int J Tuberc Lung Dis, 2009. **13**(3): p. 347-54.
44. Steingart, K.R., et al., *Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review.* Lancet Infect Dis, 2006. **6**(10): p. 664-74.
45. Wallis, R.S., et al., *Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice.* Lancet, 2010. **375**(9729): p. 1920-37.
46. Agizew, T., et al., *Association of chest radiographic abnormalities with tuberculosis disease in asymptomatic HIV-infected adults.* Int J Tuberc Lung Dis, 2010. **14**(3): p. 324-31.
47. Greenberg, S.D., et al., *Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance).* Radiology, 1994. **193**(1): p. 115-9.
48. Harries, A.D., et al., *Clinical diagnosis of smear-negative pulmonary tuberculosis: an audit of diagnostic practice in hospitals in Malawi.* Int J Tuberc Lung Dis, 2001. **5**(12): p. 1143-7.
49. Day, J.H., et al., *Screening for tuberculosis prior to isoniazid preventive therapy among HIV-infected gold miners in South Africa.* Int J Tuberc Lung Dis, 2006. **10**(5): p. 523-9.

50. Hargreaves, N.J., et al., *What causes smear-negative pulmonary tuberculosis in Malawi, an area of high HIV seroprevalence?* Int J Tuberc Lung Dis, 2001. **5**(2): p. 113-22.
51. Getahun, H., et al., *Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies.* PLoS Med, 2011. **8**(1): p. e1000391.
52. Partnership, S.T. *STOP TB Partnership, Tuberculosis Country Profiles*. 2013 [cited 2013 3/15].
53. Cain, K.P., et al., *Causes of death in HIV-infected persons who have tuberculosis, Thailand.* Emerg Infect Dis, 2009. **15**(2): p. 258-64.
54. Cain, K.P., et al., *The epidemiology of HIV-associated tuberculosis in rural Cambodia.* Int J Tuberc Lung Dis, 2007. **11**(9): p. 1008-13.
55. Mukadi, Y.D., D. Maher, and A. Harries, *Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa.* AIDS, 2001. **15**(2): p. 143-52.
56. Quy, H.T., et al., *Treatment outcomes by drug resistance and HIV status among tuberculosis patients in Ho Chi Minh City, Vietnam.* Int J Tuberc Lung Dis, 2006. **10**(1): p. 45-51.
57. Chartier, L., et al., *Factors associated with negative direct sputum examination in Asian and African HIV-infected patients with tuberculosis (ANRS 1260).* PLoS One, 2011. **6**(6): p. e21212.
58. Kingkaew, N., et al., *HIV-associated extrapulmonary tuberculosis in Thailand: epidemiology and risk factors for death.* Int J Infect Dis, 2009. **13**(6): p. 722-9.
59. Manosuthi, W., et al., *Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy.* J Acquir Immune Defic Syndr, 2006. **43**(1): p. 42-6.
60. Khue, P.M., et al., *Drug resistance and HIV co-infection among pulmonary tuberculosis patients in Haiphong City, Vietnam.* Int J Tuberc Lung Dis, 2008. **12**(7): p. 763-8.
61. Klotz, S.A., et al., *Clinical features of HIV/AIDS patients presenting to an inner city clinic in Ho Chi Minh City, Vietnam.* Int J STD AIDS, 2007. **18**(7): p. 482-5.
62. Thuy, T.T., et al., *HIV-associated TB in An Giang Province, Vietnam, 2001-2004: epidemiology and TB treatment outcomes.* PLoS One, 2007. **2**(6): p. e507.
63. Davis, J.L., et al., *Clinical and radiographic factors do not accurately diagnose smear-negative tuberculosis in HIV-infected inpatients in Uganda: a cross-sectional study.* PLoS One, 2010. **5**(3): p. e9859.
64. Akksilp, S., et al., *Antiretroviral therapy during tuberculosis treatment and marked reduction in death rate of HIV-infected patients, Thailand.* Emerg Infect Dis, 2007. **13**(7): p. 1001-7.
65. Pepe, M.S., *The statistical evaluation of medical tests for classification and prediction*. 2004: Oxford University Press, USA.
66. Kim, L., et al., *Symptom Screen for Identification of Highly Infectious Tuberculosis in People Living with HIV in Southeast Asia.* J Acquir Immune Defic Syndr, 2012. **60**(5): p. 519-524.
67. Murray, P.R., *Manual of Clinical Microbiology*. 9th ed. 2007, Washington, D.C.: ASM Press.

68. Yates, J.W., B. Chalmer, and F.P. McKegney, *Evaluation of patients with advanced cancer using the karnofsky performance status.* Cancer, 1980. **45**(8): p. 2220.
69. Durrleman, S. and R. Simon, *FLEXIBLE REGRESSION-MODELS WITH CUBIC-SPLINES.* Statistics in Medicine, 1989. **8**(5): p. 551-561.
70. Organization, W.H. *Percentage of tobacco use among adults, 2005*. Global Health Obervatory Map Gallery 2008 [cited 2013 4/16]; Available from: http://gamapserver.who.int/mapLibrary/app/searchResults.aspx.

Appendices

Appendix 1. Acronyms and Abbreviations

HIV	human immunodeficiency virus
LTBI	latent TB infection
MTB	*Mycobacterium tuberculosis*
TB	Tuberculosis, active TB disease
IPT	isoniazid preventive therapy
PLHIV	people living with HIV
TB treatment	4-drug treatment regimen for active TB disease
ART	anti-retroviral therapy
WHO	World Health Organization
IRIS	Immune reconstitution inflammatory syndrome
CFSW	cough, fever, night sweats, or weight loss clinical screening algorithm
ID-TB/HIV	Improving Diagnosis of TB in HIV-infected persons study
CDC	U.S. Centers for Disease Control and Prevention
CPT	co-trimoxazole preventive therapy
MDR-TB	multi-drug resistant TB
Xpert MTB/RIF	GeneXpert nucleic amplification assay
RIF	Rifampicin
AFB	acid-fast bacilli
CXR	chest radiography
TST	tuberculin skin test
IGRA	interferon gamma release assay
BCG	Bacille Calmette Guerin vaccine for TB
sSA	sub-Saharan Africa
S.E. Asia	South-East Asia
PCP	*Pneumocystis jiroveci* pneumonia
HCW	healthcare worker
INH	isoniazid
IDU	injection drug use
NTLP	Uganda National TB and Leprosy Program

Appendix 2. IRB Approval

EMORY UNIVERSITY | Institutional Review Board

DATE: March 26, 2013

RE: **Determination:** No IRB Review Required
Title: *The Effect of Immune Status on the Performance of Tuberculosis Symptom Screening Algorithm in Southeast Asia*
PI: William Ford

Dear Mr. Ford:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition of "human subjects" as set forth in Emory policies and procedures or federal regulations. During this project you will not have interaction with subjects and all data will be obtained from a deidentified data set. In particular, this project is a secondary data analysis of data collected by the Centers for Disease Control and Prevention during a study of HIV patients seeking treatment in Cambodia, Thailand, and Vietnam between September 2006 and October 2008.

Please note that this determination does not mean that you cannot publish the results. If you have questions about this issue, please contact me.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Kevin Wack, BA
Analyst Assistant
Education and Quality Assurance
Emory University Institutional Review Board
1599 Clifton Rd, Atlanta, GA 30322

Appendix 3. Regression Models

Appendix 3a. All possible regression models for MTB+ patients, Cambodia, Thailand, Viet Nam, 2006-2008 (N=276)

		MTB + (N=276)					
		CD4 < 400 (N=247)			CD4 > 400 (N=28)		
Model no.	**Terms**	**Beta**	***P***	**OR (95% C.I.)**	**Beta**	***P***	**OR (95% C.I.)**
1	Crude	-0.987	0.0002	0.373 (0.223, 0.622)	0.141	0.46	1.151 (0.793, 1.671)
2	CPT	-1.053	0.0002	0.349 (0.201, 0.604)	0.206	0.32	1.228 (0.820, 1.841)
3	ART	-0.973	0.0002	0.378 (0.226, 0.633)	0.134	0.48	1.143 (0.786, 1.663)
4	IDU	-1.002	0.0001	0.367 (0.219, 0.615)	0.140	0.45	1.150 (0.798, 1.657)
5	Hospitalized	-0.969	0.0002	0.380 (0.227, 0.635)	0.134	0.47	1.144 (0.792 , 1.651)
6	Low Karnofsky Score	-0.967	0.0002	0.380 (0.227, 0.636)	0.143	0.44	1.154 (0.800, 1.663)
7	Country	-0.827	0.0015	0.438 (0.263, 0.729)	0.096	0.64	1.101 (0.739, 1.640)
8	ART CPT	-1.044	0.0002	0.352 (0.202, 0.612)	0.200	0.34	1.221 (0.813, 1.834)
9	ART Hospitalized	-0.956	0.0003	0.384 (0.229, 0.645)	0.128	0.50	1.136 (0.785, 1.644)
10	ART Low Karnofsky Score	-0.956	0.0003	0.384 (0.229, 0.646)	0.137	0.46	1.147 (0.794, 1.658)
11	ART Country	-0.822	0.0017	0.440 (0.263, 0.735)	0.093	0.65	1.098 (0.735, 1.639)
12	IDU CPT	-1.059	0.0002	0.347 (0.200, 0.600)	0.215	0.30	1.239 (0.824, 1.865)
13	IDU Hospitalized	-0.988	0.0002	0.372 (0.222, 0.625)	0.135	0.47	1.144 (0.797, 1.642)
14	IDU Low Karnofsky Score	-1.001	0.0002	0.367 (0.218, 0.620)	0.143	0.43	1.154 (0.806, 1.652)
15	IDU Country	-0.849	0.0013	0.428 (0.255, 0.718)	0.099	0.62	1.105 (0.745, 1.637)
16	Hospitalized CPT	-1.030	0.0002	0.357 (0.206, 0.619)	0.197	0.33	1.218 (0.818, 1.813)
17	Hospitalized Low Karnofsky Score	-0.952	0.0003	0.386 (0.231, 0.644)	0.143	0.44	1.154 (0.801, 1.663)
18	Hospitalized Country	-0.825	0.0015	0.438 (0.263, 0.730)	0.095	0.64	1.100 (0.740, 1.636)
19	Low Karnofsky Score CPT	-1.029	0.0003	0.357 (0.206, 0.620)	0.204	0.31	1.227 (0.826, 1.822)
20	Low Karnofsky Score Country	-0.827	0.0016	0.437 (0.262,	0.098	0.63	1.103 (0.743,

				0.731)			1.636)
21	Country CPT	-0.873	0.0019	0.418 (0.241, 0.724)	0.154	0.48	1.166 (0.760, 1.788)
22	ART IDU	-0.984	0.0002	0.374 (0.223, 0.627)	0.129	0.49	1.138 (0.788, 1.643)
23	ART IDU CPT	-1.044	0.0002	0.352 (0.203, 0.610)	0.204	0.33	1.226 (0.814, 1.849)
24	ART IDU Hospitalized	-0.972	0.0002	0.378(0.225, 0.636)	0.125	0.50	1.133 (0.788, 1.630)
25	ART IDU Low Karnofsky Score	-0.987	0.0002	0.373 (0.221, 0.630)	0.135	0.47	1.144 (0.797, 1.641)
26	ART IDU Country	-0.842	0.0015	0.431 (0.256, 0.724)	0.095	0.64	1.099 (0.741, 1.632)
27	ART Hospitalized CPT	-1.022	0.0003	0.360 (0.207, 0.627)	0.192	0.35	1.211 (0.811, 1.808)
28	ART Hospitalized Low Karnofsky Score	-0.942	0.0004	0.390 (0.233, 0.654)	0.138	0.46	1.148 (0.794, 1.658)
29	ART Hospitalized Country	-0.820	0.0018	0.440 (0.263, 0.736)	0.093	0.65	1.097 (0.736, 1.635)
30	ART Low Karnofsky Score CPT	-1.023	0.0003	0.360 (0.206, 0.627)	0.200	0.32	1.221 (0.820, 1.819)
31	ART Low Karnofsky Score Country	-0.824	0.0018	0.439 (0.261, 0.736)	0.096	0.63	1.101 (0.741, 1.637)
32	ART Country CPT	-0.871	0.0021	0.418 (0.240, 0.728)	0.153	0.49	1.165 (0.757, 1.791)
33	IDU Hospitalized CPT	-1.042	0.0002	0.353 (0.203, 0.611)	0.207	0.31	1.230 (0.822, 1.842)
34	IDU Hospitalized Low Karnofsky Score	-0.990	0.0002	0.372 (0.221, 0.626)	0.143	0.43	1.154 (0.806, 1.652)
35	IDU Hospitalized Country	-0.847	0.0013	0.429 (0.256, 0.719)	0.099	0.62	1.104 (0.746, 1.633)
36	IDU Low Karnofsky Score CPT	-1.057	0.0002	0.347 (0.199, 0.605)	0.215	0.29	1.240 (0.831, 1.849)
37	IDU Low Karnofsky Score Country	-0.866	0.0012	0.421 (0.249, 0.712)	0.103	0.60	1.108 (0.753, 1.632)
38	IDU Country CPT	-0.900	0.0015	0.407 (0.233, 0.709)	0.165	0.45	1.180 (0.769, 1.811)
39	Hospitalized Low Karnofsky Score CPT	-1.013	0.0003	0.363 (0.210, 0.629)	0.203	0.31	1.225 (0.825, 1.817)
40	Hospitalized Low Karnofsky Score Country	-0.825	0.0016	0.438 (0.263, 0.732)	0.099	0.62	1.104 (0.744, 1.637)
41	Hospitalized Country CPT	-0.870	0.0019	0.419 (0.242, 0.726)	0.152	0.48	1.165 (0.761, 1.782)
42	Low Karnofsky Score Country CPT	-0.873	0.002	0.418 (0.240, 0.727)	0.153	0.48	1.166 (0.765, 1.777)
43	ART IDU Hospitalized CPT	-1.029	0.0003	0.358 (0.206,	0.198	0.34	1.219 (0.813,

				0.621)			1.828)
44	ART IDU Hospitalized Low Karnofsky Score	-0.976	0.0003	0.377 (0.223, 0.636)	0.135	0.46	1.144 (0.798, 1.642)
45	ART IDU Hospitalized Country	-0.840	0.0015	0.432 (0.257, 0.726)	0.094	0.64	1.099 (0.742, 1.627)
46	ART IDU Low Karnofsky Score CPT	-1.045	0.0002	0.352 (0.201, 0.614)	0.206	0.31	1.229 (0.823, 1.837)
47	ART IDU Low Karnofsky Score Country	-0.860	0.0014	0.423 (0.250, 0.717)	0.099	0.62	1.104 (0.749, 1.628)
48	ART IDU Country CPT	-0.895	0.0017	0.409 (0.234, 0.714)	0.161	0.46	1.175 (0.764, 1.807)
49	ART Hospitalized Low Karnofsky Score CPT	-1.006	0.0004	0.366 (0.210, 0.636)	0.199	0.33	1.220 (0.820, 1.815)
50	ART Hospitalized Low Karnofsky Score Country	-0.822	0.0018	0.440 (0.262, 0.737)	0.097	0.63	1.102 (0.741, 1.637)
51	ART Hospitalized Country CPT	-0.869	0.0021	0.419 (0.241, 0.730)	0.151	0.49	1.163 (0.758, 1.785)
52	ART Low Karnofsky Score Country CPT	-0.873	0.0022	0.418 (0.239, 0.730)	0.154	0.48	1.166 (0.763, 1.783)
53	IDU Hospitalized Low Karnofsky Score CPT	-1.045	0.0002	0.352 (0.202, 0.613)	0.214	0.29	1.238 (0.831, 1.845)
54	IDU Hospitalized Low Karnofsky Score Country	-0.863	0.0013	0.422 (0.250, 0.713)	0.104	0.60	1.109 (0.754, 1.632)
55	IDU Hospitalized Country CPT	-0.897	0.0015	0.408 (0.234, 0.710)	0.164	0.45	1.178 (0.769, 1.804)
56	IDU Low Karnofsky Score Country CPT	-0.919	0.0014	0.399 (0.227, 0.702)	0.169	0.43	1.184 (0.777, 1.806)
57	Hospitalized Low Karnofsky Score Country CPT	-0.870	0.002	0.419 (0.241, 0.728)	0.154	0.47	1.166 (0.765, 1.777)
58	ART IDU Hospitalized Low Karnofsky Score CPT	-1.033	0.0003	0.356 (0.204, 0.621)	0.205	0.31	1.228 (0.823, 1.833)
59	ART IDU Hospitalized Low Karnofsky Score Country	-0.857	0.0014	0.424 (0.251, 0.718)	0.100	0.61	1.105 (0.750, 1.628)
60	ART IDU Hospitalized Country CPT	-0.892	0.0017	0.410 (0.234, 0.716)	0.160	0.46	1.174 (0.765, 1.801)
61	ART IDU Low Karnofsky Score Country CPT	-0.915	0.0016	0.401 (0.227, 0.706)	0.166	0.44	1.181 (0.773, 1.803)
62	ART Hospitalized Low Karnofsky Score Country CPT	-0.871	0.0022	0.419 (0.240, 0.731)	0.154	0.48	1.166 (0.763, 1.782)
63	IDU Hospitalized Low Karnofsky Score Country CPT	-0.916	0.0014	0.400 (0.228, 0.703)	0.169	0.43	1.184 (0.777, 1.805)
64	ART IDU Hospitalized Low Karnofsky Score Country CPT	-0.912	0.0016	0.402 (0.228, 0.708)	0.166	0.44	1.181 (0.773, 1.802)

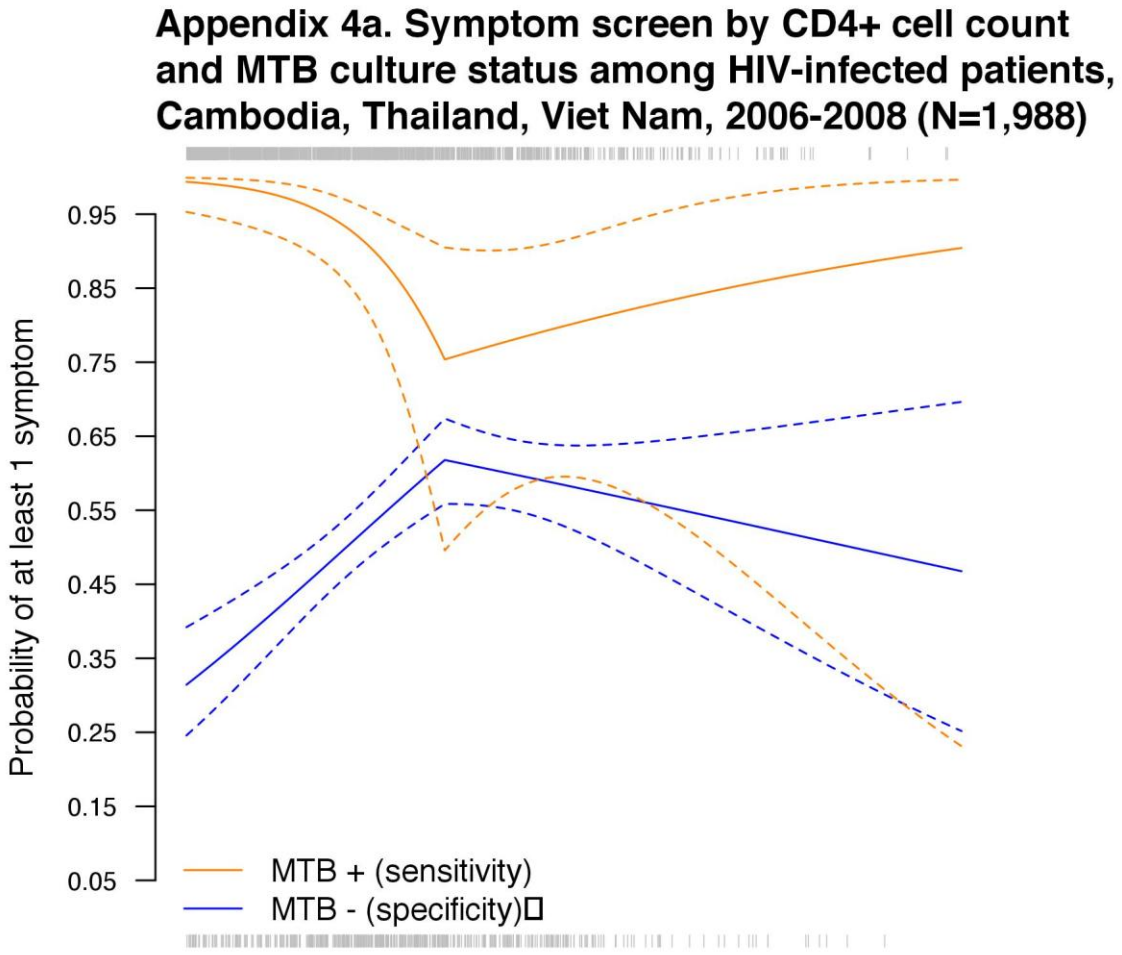
Appendix 3b. All possible regression models for MTB- patients, Cambodia, Thailand, Viet Nam, 2006-2008 (N=1,712)

		MTB - (N=1,712)					
		CD4 < 400 (N=1,229)			CD4 > 400 (N=470)		
Model no.	Terms	Beta	*P*	OR (95% C.I.)	Beta	*P*	OR (95% C.I.)
1	Crude	-0.315	<.0001	0.730 (0.665, 0.800)	0.076	0.14	1.079 (0.974, 1.195)
2	CPT	-0.335	<.0001	0.715 (0.650, 0.787)	0.076	0.15	1.079 (0.974, 1.195)
3	ART	-0.295	<.0001	0.745 (0.678, 0.818)	0.067	0.20	1.069 (0.965, 1.185)
4	IDU	-0.319	<.0001	0.727 (0.662, 0.797)	0.073	0.16	1.076 (0.971, 1.192)
5	Hospitalized	-0.311	<.0001	0.733 (0.668, 0.804)	0.078	0.14	1.081 (0.976, 1.197)
6	Low Karnofsky Score	-0.298	<.0001	0.742 (0.676, 0.815)	0.080	0.13	1.083 (0.977, 1.201)
7	Country	-0.277	<.0001	0.758 (0.689, 0.835)	0.062	0.25	1.064 (0.958, 1.182)
8	ART CPT	-0.306	<.0001	0.736 (0.668, 0.811)	0.072	0.17	1.074 (0.969, 1.191)
9	ART Hospitalized	-0.291	<.0001	0.747 (0.680, 0.821)	0.069	0.19	1.071 (0.966, 1.187)
10	ART Low Karnofsky Score	-0.278	<.0001	0.758 (0.689, 0.833)	0.070	0.19	1.072 (0.966, 1.190)
11	ART Country	-0.262	<.0001	0.769 (0.698, 0.848)	0.057	0.29	1.059 (0.952, 1.178)
12	IDU CPT	-0.343	<.0001	0.710 (0.645, 0.782)	0.073	0.17	1.075 (0.97, 1.191)
13	IDU Hospitalized	-0.315	<.0001	0.729 (0.665, 0.801)	0.075	0.15	1.077 (0.973, 1.194)
14	IDU Low Karnofsky Score	-0.302	<.0001	0.739 (0.673, 0.812)	0.077	0.14	1.08 (0.974, 1.197)
15	IDU Country	-0.271	<.0001	0.762 (0.692, 0.840)	0.062	0.25	1.064 (0.957, 1.182)
16	Hospitalized CPT	-0.332	<.0001	0.718 (0.652, 0.790)	0.078	0.14	1.081 (0.976, 1.198)
17	Hospitalized Low Karnofsky Score	-0.297	<.0001	0.743 (0.677, 0.816)	0.082	0.12	1.085 (0.978, 1.203)
18	Hospitalized Country	-0.275	<.0001	0.759 (0.689, 0.837)	0.064	0.24	1.066 (0.959, 1.184)
19	Low Karnofsky Score CPT	-0.320	<.0001	0.726 (0.659, 0.8)	0.080	0.13	1.083 (0.977, 1.202)
20	Low Karnofsky Score Country	-0.265	<.0001	0.767 (0.696, 0.845)	0.065	0.23	1.067 (0.96, 1.187)
21	Country CPT	-0.296	<.0001	0.744 (0.673, 0.823)	0.061	0.26	1.062 (0.956, 1.181)

22	ART IDU	-0.299	<.0001	0.741 (0.675, 0.815)	0.063	0.23	1.065 (0.961, 1.181)
23	ART IDU CPT	-0.313	<.0001	0.731 (0.663, 0.806)	0.068	0.20	1.070 (0.965, 1.187)
24	ART IDU Hospitalized	-0.296	<.0001	0.744 (0.677, 0.817)	0.065	0.22	1.067 (0.962, 1.183)
25	ART IDU Low Karnofsky Score	-0.283	<.0001	0.754 (0.685, 0.829)	0.066	0.21	1.068 (0.963, 1.186)
26	ART IDU Country	-0.257	<.0001	0.774 (0.701, 0.853)	0.057	0.29	1.059 (0.952, 1.178)
27	ART Hospitalized CPT	-0.303	<.0001	0.739 (0.670, 0.815)	0.074	0.16	1.076 (0.971, 1.194)
28	ART Hospitalized Low Karnofsky Score	-0.277	<.0001	0.758 (0.690, 0.834)	0.072	0.18	1.074 (0.968, 1.192)
29	ART Hospitalized Country	-0.261	<.0001	0.770 (0.698, 0.849)	0.059	0.28	1.061 (0.953, 1.18)
30	ART Low Karnofsky Score CPT	-0.290	<.0001	0.748 (0.678, 0.826)	0.075	0.16	1.078 (0.971, 1.197)
31	ART Low Karnofsky Score Country	-0.251	<.0001	0.778 (0.705, 0.858)	0.060	0.27	1.062 (0.954, 1.183)
32	ART Country CPT	-0.273	<.0001	0.761 (0.687, 0.843)	0.059	0.28	1.061 (0.953, 1.180)
33	IDU Hospitalized CPT	-0.339	<.0001	0.712 (0.647, 0.785)	0.074	0.16	1.077 (0.972, 1.193)
34	IDU Hospitalized Low Karnofsky Score	-0.301	<.0001	0.740 (0.674, 0.813)	0.078	0.14	1.082 (0.975, 1.199)
35	IDU Hospitalized Country	-0.270	<.0001	0.764 (0.693, 0.841)	0.063	0.24	1.065 (0.959, 1.184)
36	IDU Low Karnofsky Score CPT	-0.328	<.0001	0.721 (0.654, 0.794)	0.077	0.15	1.080 (0.973, 1.198)
37	IDU Low Karnofsky Score Country	-0.260	<.0001	0.771 (0.7, 0.85)	0.065	0.23	1.067 (0.96, 1.187)
38	IDU Country CPT	-0.291	<.0001	0.748 (0.676, 0.828)	0.060	0.27	1.062 (0.955, 1.180)
39	Hospitalized Low Karnofsky Score CPT	-0.319	<.0001	0.727 (0.66 0.801)	0.082	0.12	1.085 (0.978, 1.204)
40	Hospitalized Low Karnofsky Score Country	-0.265	<.0001	0.767 (0.696, 0.846)	0.067	0.22	1.069 (0.961, 1.189)
41	Hospitalized Country CPT	-0.294	<.0001	0.745 (0.673, 0.824)	0.062	0.25	1.064 (0.957, 1.183)
42	Low Karnofsky Score Country CPT	-0.288	<.0001	0.750 (0.677, 0.83)	0.064	0.24	1.066 (0.958, 1.186)
43	ART IDU Hospitalized CPT	-0.310	<.0001	0.733 (0.665, 0.809)	0.070	0.19	1.072 (0.967, 1.189)
44	ART IDU Hospitalized Low Karnofsky Score	-0.282	<.0001	0.754 (0.686, 0.830)	0.068	0.20	1.070 (0.964, 1.188)

45	ART IDU Hospitalized Country	-0.256	<.0001	0.774 (0.702, 0.854)	0.059	0.28	1.061 (0.953, 1.180)
46	ART IDU Low Karnofsky Score CPT	-0.297	<.0001	0.743 (0.673, 0.820)	0.071	0.18	1.074 (0.967, 1.192)
47	ART IDU Low Karnofsky Score Country	-0.246	<.0001	0.782 (0.709, 0.863)	0.060	0.28	1.062 (0.953, 1.182)
48	ART IDU Country CPT	-0.268	<.0001	0.765 (0.691, 0.848)	0.058	0.29	1.060 (0.953, 1.179)
49	ART Hospitalized Low Karnofsky Score CPT	-0.289	<.0001	0.749 (0.679, 0.827)	0.077	0.15	1.08 (0.973, 1.199)
50	ART Hospitalized Low Karnofsky Score Country	-0.251	<.0001	0.778 (0.705, 0.858)	0.062	0.26	1.064 (0.955, 1.184)
51	ART Hospitalized Country CPT	-0.272	<.0001	0.762 (0.688, 0.844)	0.060	0.27	1.062 (0.955, 1.182)
52	ART Low Karnofsky Score Country CPT	-0.264	<.0001	0.768 (0.693, 0.851)	0.062	0.26	1.064 (0.955, 1.185)
53	IDU Hospitalized Low Karnofsky Score CPT	-0.326	<.0001	0.722 (0.654, 0.795)	0.078	0.14	1.081 (0.975, 1.2)
54	IDU Hospitalized Low Karnofsky Score Country	-0.259	<.0001	0.772 (0.7, 0.851)	0.067	0.22	1.069 (0.961, 1.189)
55	IDU Hospitalized Country CPT	-0.289	<.0001	0.749 (0.677, 0.829)	0.061	0.26	1.063 (0.957, 1.182)
56	IDU Low Karnofsky Score Country CPT	-0.283	<.0001	0.754 (0.681, 0.835)	0.064	0.24	1.066 (0.958, 1.185)
57	Hospitalized Low Karnofsky Score Country CPT	-0.288	<.0001	0.75 (0.678, 0.83)	0.066	0.23	1.068 (0.96, 1.188)
58	ART IDU Hospitalized Low Karnofsky Score CPT	-0.296	<.0001	0.744 (0.673, 0.821)	0.073	0.17	1.076 (0.969, 1.195)
59	ART IDU Hospitalized Low Karnofsky Score Country	-0.245	<.0001	0.782 (0.709, 0.864)	0.061	0.26	1.063 (0.955, 1.184)
60	ART IDU Hospitalized Country CPT	-0.266	<.0001	0.766 (0.692, 0.849)	0.060	0.27	1.062 (0.954, 1.181)
61	ART IDU Low Karnofsky Score Country CPT	-0.258	<.0001	0.772 (0.697, 0.856)	0.061	0.26	1.063 (0.955, 1.184)
62	ART Hospitalized Low Karnofsky Score Country CPT	-0.264	<.0001	0.768 (0.693, 0.851)	0.064	0.25	1.066 (0.957, 1.187)
63	IDU Hospitalized Low Karnofsky Score Country CPT	-0.282	<.0001	0.754 (0.681, 0.835)	0.065	0.23	1.067 (0.959, 1.187)
64	ART IDU Hospitalized Low Karnofsky Score Country CPT	-0.258	<.0001	0.773 (0.697, 0.857)	0.063	0.25	1.065 (0.956, 1.186)

Appendix 4. Sensitivity and Specificity plots



Appendix 4b. Symptom screen by CD4+ cell count and MTB culture status among HIV-infected patients, Cambodia, Thailand, Viet Nam, 2006-2008 (N=1,988)