Tuberculosis case finding and performance of symptom screening and rapid diagnostic tests in HIV-infected pregnant women in western Kenya

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Abstract

Tuberculosis case finding in HIV-infected pregnant women in Kenya reveals poor performance of symptom screening and rapid diagnostic tests

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Background: Tuberculosis (TB)/HIV during pregnancy is associated with poor maternal and infant outcomes. There are limited data on TB prevalence, optimal TB screening, and performance of rapid diagnostics in pregnant HIV-infected women.

Methods: We conducted a cross-sectional study of HIV-infected pregnant women in western Kenya using a standardized questionnaire, and collected sputum for smear, mycobacterial liquid culture, GeneXpert MTB/RIF, and urine for lipoarabinomannan. We determined prevalence and correlates of culture-confirmed pulmonary TB, and compared diagnostic performance of World Health Organization symptom screening and rapid diagnostic tests to sputum culture.

Results: Between July 2013 and July 2014, we enrolled 306 women. Among 288 women with a valid sputum culture result, 54% were on antiretroviral treatment, and median CD4 cell count was 437 cell/mm^3 (IQR 342-565). Prevalence of culture-confirmed pulmonary TB was 2.4% (CI 1.0-4.9%). Cough >2 weeks (p=0.04) and positive TST ($\geq$5mm, p=0.03) were associated with pulmonary TB. Women with TB were 23-fold (95% CI 4.4-116.6) more likely to report a household member with TB symptoms (p=0.002). WHO symptom screen (43%), AFB smear (0%), Xpert (43%) and LAM (0%) had low sensitivity but high specificity (81%, 99%, 99% and 95%, respectively) for pulmonary TB.

Conclusion: HIV-infected pregnant women had appreciable prevalence of pulmonary TB despite modest immunosuppression. Current TB screening and diagnostic tools perform poorly in pregnant HIV-infected women. Adapted TB screening tools including household member TB symptoms may be useful in this population.

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1.0 INTRODUCTION

Tuberculosis (TB) is a leading cause of morbidity and mortality among women of childbearing age, particularly in areas of high HIV prevalence.[1] Late or missed diagnosis of TB among pregnant HIV-infected women is associated with poor maternal and infant outcomes.[2] Identification and treatment of TB during antenatal care is an opportunity to link pregnant mothers to TB/HIV treatment and prevent morbidity and mortality in both mother and infant.

1.1 TB screening and diagnostic tests

The World Health Organization (WHO) recommends TB screening of HIV-infected individuals using a four-part symptom screen including cough, fever, weight loss, and night sweats.[3] However, the WHO TB symptom screen has performed poorly among HIV-infected pregnant women, perhaps because pregnancy may mask TB symptoms.[4,5] The most commonly used diagnostic tests (acid-fast bacillus [AFB] smear microscopy and chest radiographs), perform poorly in the setting of HIV-infection,[6] and clinicians may be reluctant to order radiographs in pregnancy[7]. Newer rapid tests, including GeneXpert MTB/RIF® (Xpert, Cepheid, Sunnyvale, CA, USA) a DNA PCR-based rapid test, and urine lipoarabinomannan (LAM) (Determine™ TB LAM; Alere, Waltham, MA, USA), an inexpensive lateral flow urine dipstick assay, may improve TB detection among HIV-infected pregnant women; however, performance characteristics in this population are undefined. The gold standard of pulmonary TB diagnosis is culture, however this requires specially trained personnel, and specialized lab safety equipment. The ideal TB screening and diagnostic tool in resource limited settings would be highly accurate, inexpensive, and rapid enough to be performed as a point of care test (Figure 1).

1.2 TB prevalence estimates in pregnancy

The prevalence of TB among HIV-infected pregnant women ranges from 0.8-11% among published estimates in Kenya[8], South Africa[4,9-11], Zambia[12], Rwanda[13], Tanzania[14], and India.[2] (Figure 2). Importantly, the majority of these previous studies used widely varying case definitions including clinical suspicion based on symptoms. Only two previous studies estimated the prevalence of culture-confirmed TB among HIV-infected pregnant women, irrespective of presenting symptoms.[4,12]

1.3 Study aims

We aimed to determine the prevalence of culture-confirmed pulmonary TB, identify cofactors associated with TB, and assess the performance of the WHO TB symptom screen, Xpert, and LAM among HIV-infected pregnant women in western Kenya.

2.0 METHODS

2.1 Study Setting

We performed a cross-sectional study among HIV-infected pregnant women at two antenatal care clinics in the Nyanza region of western Kenya.

2.2 Participants

HIV-infected women 16 years or older accessing prevention of mother-to-child transmission (PMTCT) services as part of antenatal care were eligible for study enrollment. All participants were aware of their HIV diagnosis before enrollment, though may have been diagnosed on the same day. In Kenya, 92% of women are seen in antenatal clinics at least once during pregnancy.[15] The Nyanza region has the highest prevalence of HIV in Kenya at 15% with HIV prevalence estimates in antenatal mothers ranging from 19-26%.[16] Women were ineligible for enrollment if they were unable to provide consent in a

study language (English or Dholuo), were currently on treatment for TB disease or latent TB infection (LTBI), or were treated for TB or LTBI within the prior year.

2.3 Procedures

2.3.1 Enrollment

We recruited consecutive HIV-infected pregnant women from two antenatal clinics and screened for study eligibility. Eligible participants who provided written informed consent were interviewed by study staff using a structured interview tool that included questions on sociodemographic information, pregnancy history, HIV history (date of diagnosis, medications), TB and LTBI history, and the presence of TB symptoms in participants or their household members (as reported by participant). Screening questions for TB symptoms included the WHO 4-part symptom screen (fever, any cough, weight loss, night sweats), prolonged cough (>2 weeks), hemoptysis, and lymphadenopathy. Data extracted from clinic charts included medication history and CD4 cell count. The HIV status of participants was determined by antenatal clinic staff as part of routine antenatal care using two positive rapid ELISA tests in parallel.

2.3.2 TST Testing

TSTs were performed using 5 tuberculin units (0.1ml) of purified protein derivative (RT 23 solution) and read by study nurses using the "ball-point" technique and a ruler within 48 - 96 hours.[17,18] A positive TST was defined as $\geq$5 mm of induration.

2.3.3 Sputum Collection and TB Laboratory Testing

Participants were instructed on sputum collection and two expectorated sputa specimens were collected: one as a "spot" sample at the time of enrollment and a second as an early morning specimen collected by the subject upon awakening on the day of TST read. Sputum and urine samples were refrigerated and transported on ice at 4-8°C on a daily basis to the ISO

15189-accredited KEMRI/CDC Laboratory in Kisumu, Kenya. Specimens were decontaminated using *N*-acetyl-L-cysteine and sodium hydroxide and examined by AFB-smear microscopy using Ziehl-Neelsen technique. If one or more AFB per equivalent of 100 immersion fields was observed, the slide was considered positive and graded. After re-suspension with phosphate buffer, equal sample volumes were used to perform mycobacterial culture and Xpert. Mycobacterial culture was performed using a commercial broth method, MGIT Manual Mycobacterial Growth System (Becton-Dickinson, Franklin Lakes, NJ). Isolates were identified as *M. tuberculosis* using the Capilia TB Test Kit (TAUNS, Numazu, Japan). In general, one Xpert was performed on fresh sputum using the "spot" specimen. Xpert was performed on the frozen second sputum sample if the patient was unable to provide a spot sample or if the second sputum specimen was culture positive for *M. tuberculosis.* Urine was collected during the initial visit and LAM testing was performed within 8 hours of collection. Test results were interpreted using the reference scale card per the manufacturer's instructions.[19]

2.3.4 Kenyan National TB Guidelines

Per Kenyan national TB guidelines, it is recommended that all HIV-infected individuals including women in antenatal care undergo intensified case finding using the WHO 4-part TB symptom screen. Women with one or more symptoms receive further evaluation for TB that may include chest radiograph and sputum collection for smear microscopy. However, sputum AFB culture, tuberculin skin tests (TST), Xpert and LAM were not routinely performed at the antenatal sites at which the study was performed during the study period. Isoniazid preventive therapy was not routinely provided at these sites at the time of the study.

2.4 Study Endpoints and Statistical Analysis

Pulmonary TB was defined as at least one sputum culture positive for *M. tuberculosis* and participants who met this definition were referred for TB care through the Kenya National Treatment Program. Urine LAM tests with the presence of a band of any intensity (grade 1 or greater) were considered positive. Univariate logistic regression and Fisher's exact test were used as appropriate to assess the association between potential correlates and the outcome of pulmonary TB. The performance of the WHO TB 4-part symptom screen, AFB-smear, Xpert, and urine LAM was compared to culture using sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and area under the receiver operating characteristic curve (AUC). All estimates were reported using 95% confidence intervals (CI), and all statistical tests were two-sided with $\alpha = 0.05$. Analyses were performed using Stata 13 (StataCorp, College Station, TX).

2.5 Ethics Approval

This study was approved by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee and the University of Washington Institutional Review Board.

3.0 RESULTS

Between July 2013 and July 2014, 429 HIV-infected pregnant women attended routine antenatal care services at the two sites, and 388 were screened for study eligibility (Figure 3). Of women screened, 76 declined study participation and 6 were excluded from enrollment because they had been diagnosed with TB in the preceding year. Of the 306 enrolled women, 18 were excluded from further analysis (14 women were unable to produce sputum and 4 women had contaminated cultures). The remaining 288 women had one or more sputum samples with valid culture results for TB evaluation; of these 244 (85%) had two cultures performed.

3.1 Baseline characteristics

Median maternal age was 25 years (IQR 22-30), and median gestational age was 26 weeks (IQR 20-32) (Table 1). Most women (78%) had completed primary education, and 57% were employed. Twenty-seven percent of women were unaware of their HIV-status prior to the current pregnancy. Over one-half (54%) of participants were taking combination antiretroviral therapy (cART) prior to study enrollment. In general, participants were relatively immunocompetent with a median CD4 cell count of 437 cells/mm^3 (IQR 342-565 cells/mm^3); only 13.8% of subjects had a CD4 cell count $\leq$250 cells/mm^3.

3.2 TST results and TB exposure

Of 246 women who had a TST placed, only 85 (35%) women returned for TST reading between 48 and 96 hours (Table 1). Eighteen (21%) had a positive TST $\geq$5 mm. Twenty-five (9%) women had a history of TB at a mean of 6.5 years prior to enrollment. Women reporting a history of TB were more likely to have a positive TST (OR 18 95% CI 1.87-173.63).

3.3 Prevalence of culture-confirmed TB

The prevalence of TB, defined by a positive sputum culture for *M. tuberculosis*, was 2.4% (CI 1.0-4.9%) (Figure 3, Table 1). Compared to women without TB, women with TB were more likely to report a cough lasting longer than 2 weeks (29% vs 4%, p=0.04) and have a positive TST $\geq$5 mm (75% vs 18%, p=0.03) (Table 1). Women with TB had 22.7-fold (95% CI 4.4-116.6) higher odds of reporting a household member with one of the 4 WHO TB symptoms compared to women without TB (43% vs 3%, p<0.001).

3.4 Performance of WHO symptom screen and rapid diagnostics

3.4.1 WHO TB symptom screen

The WHO TB symptom screen identified 56 (19%) women with TB symptoms, 3 of whom had a positive culture for *M. tuberculosis* (Table 2). Most women (4 of 7, 57%) with positive sputum cultures for *M. tuberculosis* had a negative symptom screen (Figure 4). Overall, WHO screening had sensitivity of 42.9% (95% CI 9.9-81.6%), specificity 81.1% (95% CI 76.1-85.5%), positive predictive value 5.4% (95% CI 1.1-14.9%) and negative predictive value 98.3% (95% CI 95.6-99.5%). (Table 3) Twelve (4.2%) participants reported that a household member had one or more WHO TB symptoms; TB was diagnosed in 3 of these women (Table 1). Inclusion of participant report of either self or household member with a positive WHO TB symptom screen increased sensitivity to 71.4% (95% CI 29.0-96.3%), while maintaining high specificity 80.1% (95% CI 74.9-84.6%) (Table 3).

3.4.2 Xpert

Xpert was positive in 4 women and identified 3 of 7 women with sputum cultures positive for *M. tuberculosis* (Table 2). Xpert had sensitivity 42.9% (95% CI 9.9-81.6%), specificity 99.6% (95% CI 98.0-100%), positive predictive value 75.0% (95% CI 19.4-99.4%) and negative predictive value 98.6% (95% CI 96.4-99.6%) (Table 3).

3.4.3 Smear microscopy

Sputum smear microscopy was positive by Ziehl-Neelsen staining in 2 women but did not identify any women with a sputum culture positive for *M. tuberculosis* (Figure 4). Sputum smear microscopy had sensitivity 0% (95% CI 0-41%), specificity 99.3% (95% CI 97.5-99.9%), positive predictive value 0% (95% CI 0-84.2%) and negative predictive value 97.6% (95% CI 95.0-99.0%) (Table 3).

3.4.4 Urine LAM

Urine LAM testing was performed on 266 women, and was grade 1 or 2 in 13 women (4.9%), and grade 2 in 2 women (0.8%) (Table 1). Using grade 1 or higher as a threshold for a positive result, urinary LAM testing had sensitivity 0% (95% CI 0-70.8%), specificity 95.1% (95% CI 91.7-97.3%), positive predictive value 0% (95% CI 0-24.7%) and negative predictive value 98.8% (95% CI 96.6-99.8%) (Table 3).

3.4.5 Overlap of WHO TB symptoms screen, rapid diagnostics, and culture confirmed TB cases

Of the 7 women with culture-confirmed TB, 3 had a positive symptom screen and 3 were Xpert positive (Figure 4). Two women with culture confirmed TB were both positive by WHO TB symptom screen and Xpert. One woman with a positive AFB smear had TB symptoms (cough, night sweats); two women with a positive LAM had TB symptoms (one reported fever and night sweats, and one reported cough and night sweats). None of the smear or LAM positive women had positive TB cultures. Women with positive smear microcopy or M. tuberculosis culture were prescribed anti-tuberculosis therapy by the TB program.

3.4.6 Overall performance of screening and diagnostic tools and combined screening performance

The area under the curve (AUC) of the receiver operator curve (ROC) allows us to assess both sensitivity and specificity in tandem (Figure 5). In terms of overall performance of a single TB screen or diagnostic test as measured by AUC, report of household symptoms (AUC 0.70, 95% CI 0.50-0.90), Xpert (AUC 0.71, 95% CI 0.51-0.91), and TST (AUC 0.78, 95% CI 0.53-1.0) performed similarly (Table 3, Figure 5). Combining WHO symptom screen with the household symptom screen increased the discriminatory value of symptom screening (0.62 to

0.76) (Figures 5 and 6). Using a combination of TST or Xpert yielded the highest combination of sensitivity and specificity (AUC 0.90, 95% CI 0.86-0.95). Xpert or WHO symptom screening including of both the participants and household family member resulted in an AUC of 0.83 (95% CI 0.69-0.77).

4.0 DISCUSSION

4.1 High prevalence of culture confirmed TB

We found a high burden of undiagnosed pulmonary TB disease among Kenyan HIV-infected pregnant women enrolled in antenatal care. Our estimate of TB prevalence, 2.4% (CI 1.0-4.9%), is consistent with estimated TB prevalence in HIV-infected adults from a community-based study in western Kenya (2.1%)[20] and in HIV-infected pregnant women in sub-Saharan Africa (0.3 to 6%).[4,9,11,21-24] Notably, we observed a substantial burden of TB disease in HIV-infected women during pregnancy in the absence of low CD4 cell counts and despite the use of cART. Compared to previous studies assessing the prevalence of culture-confirmed TB among pregnant HIV-infected women regardless of symptoms[4], our cohort had somewhat higher CD4 counts and a higher proportion of women on combination ART. Combination ART decreases the risk of TB by 67%, with increasing CD4 cell counts and duration of therapy associated with greater declines in risk.[25] However, the risk of TB remains higher among HIV-infected individuals at all levels of immunosuppression compared to those without HIV.[26,27]

4.2 WHO TB symptom screening

A novel finding of our study is that screening for the presence of WHO TB symptoms in household members was strongly associated with TB. Inclusion of a positive WHO TB symptom screen in the participant or a household member increased the sensitivity of TB case finding to

71% without compromising specificity. Expansion of TB screening to include symptoms of household members may provide a mechanism to improve active TB case finding in HIV-infected pregnant women, and should be validated in larger cohorts. Importantly, presence of WHO TB symptoms in household members was more predictive than ascertaining a known TB contact in the household. Antenatal screening of women may provide a unique opportunity to diagnose not only pregnant women but others in the household through surrogate screening using the simple WHO symptom screen.

Intensified TB case finding using the WHO 4-part symptom screen of fever, cough, night sweats, or weight loss among pregnant women failed to identify more than half [4 of 7 (57%)] of the cases of culture-confirmed pulmonary TB. Low sensitivity of the WHO symptom screen (28-50%) for excluding TB has been observed in other studies of pregnant HIV-infected women that performed sputum culture independent of clinical symptoms.[4,5,23] An individual participant data meta-analysis that included cohorts of HIV-infected cART-naïve individuals from sub-Saharan Africa and Southeast Asia found that the sensitivity of the WHO TB symptom screen was 79% overall and higher among individuals not previously screened for TB (88%).[6] The sensitivity of the WHO symptom screen may be decreased in the context of cART, and was approximately 50% less sensitive among participants taking cART compared to cART-naïve individuals in a South African study.[28] TB symptoms may be less frequent among women compared to men[29], and pregnancy may further mask symptoms due to an overlap with pregnancy-related physiologic changes[30] or relative suppression of Th1 pro-inflammatory cytokines.[1,31] Despite low sensitivity, prolonged cough was associated with TB in our cohort, which has been also been observed in pregnant women with TB disease in Tanzania.[32]

4.3 Xpert

Although it has been suggested that Xpert may improve TB screening within antenatal care settings,[33] we are unaware of published estimates regarding its performance in pregnant HIV-infected women. In our study, Xpert was less sensitive than the results of a meta-analysis that reported on test performance in HIV-infected individuals.[34] In this same meta-analysis, Xpert performance was decreased among those who were smear negative to 67%. Our sensitivity estimate of 43% is within the range of sensitivities (40-81%) reported by studies evaluating smear-negative HIV-infected individuals [35-37] and is most similar to a South African study evaluating the accuracy of Xpert compared to culture among HIV-infected outpatients regardless of symptoms prior to cART initiation.[37] The use of cryopreserved samples in patients unable to provide "spot" samples may have contributed to the low sensitivity; however in a meta-analysis of Xpert performance, the use of cryopreserved samples led to only marginally decreased sensitivity and similar specificity.[34]

4.4 Urine TB-LAM

In contrast to sputum Xpert, urine LAM did not contribute to case detection of pulmonary TB within our study. Contrary to studies of Xpert and LAM among both hospitalized TB suspects and newly diagnosed HIV outpatients, there was no incremental benefit to the use of urine LAM to Xpert in our study cohort.[38] In previous studies, LAM has performed best in highly immunocompromised individuals with very low CD4 counts,[39] and the mild to modest immunosuppression observed in our sample may have resulted in lower test sensitivity. We did not actively investigate for extra-pulmonary TB and may have missed extra-pulmonary TB cases associated with positive urine LAM testing. From our cross-sectional evaluation, we do not know if these tests were false positives or may have reflected cases of culture-negative TB

disease. Positive urine LAM has been associated with increased mortality among highly immunocompromised adults who were culture negative for tuberculosis;[40] however, this requires further study in less immunocompromised HIV-infected cohorts with longitudinal follow-up.

4.5 Poor performance of WHO TB symptom screen and rapid diagnostic tests

In HIV-infected pregnant women, the sensitivities of screening tests, including WHO 4-part symptom screen, Xpert, and AFB sputum smear microscopy, were poor compared to liquid sputum culture in identifying women with pulmonary TB. This is of particular concern given the adverse effects of untreated TB on mother and infant. Additionally, the high proportion of false negative tests for pulmonary TB has implications for effective screening prior to the initiation of isoniazid preventive therapy (IPT). In our study, more than half of the women found to have culture confirmed TB would have been offered IPT based on their negative WHO symptom screen. Although combining TST or Xpert maximized diagnostic accuracy to detect pulmonary TB [AUC 0.90 (95%CI 0.86-0.95)], there are multiple barriers to the widespread use of TST including the need for a return visit (35% compliance rate in our study) and refrigeration that may make it infeasible in low resource settings. With the inclusion of Xpert in the most recent Kenya national guidelines for TB screening in HIV-infected individuals,[41] and the ease of an extended symptom screen that includes household member TB symptoms, this combination screening approach [AUC 0.83 (95% CI 0.69-0.97)] may be a more viable option for determining who is safe for IPT and who requires further TB evaluation using sputum culture.

4.6 Promising future directions

Recent efforts have yielded promising results in developing TB diagnostics in high burden settings,[42,43] including those that may perform well specifically in HIV-infected women,[44] and point-of-care tests[45] that may contribute to TB screening in HIV-infected individuals. Our results

highlight the urgent need for improved TB diagnostic tests for use in HIV-infected pregnant women that have been rigorously evaluated in this vulnerable population.[46]

4.7 Strengths and limitations

Our study had several limitations. We may have underestimated the burden of TB by performing culture on a single sputum in 28% of patients. Subjects unable to spontaneously expectorate sputum did not undergo sputum induction, which may have resulted in further under-diagnosis of TB. We did not perform chest radiographs in subjects and may have missed radiographically-apparent cases of TB. Xpert testing was performed on only one of 2 sputum samples; for one positive culture from the 2nd sputum culture, Xpert was performed on a cryopreserved sputum sample to ensure adequate estimation of sensitivity. Our study had limited power for estimates of diagnostic performance. A strength of our study is the performance of diagnostic tests, including culture, in all participants regardless of symptoms.

4.8 Conclusions

In conclusion, we found a significant burden of undiagnosed tuberculosis among HIV-infected pregnant women. Symptom screening and available diagnostic tests including sputum smear microscopy, Xpert and urinary LAM testing had poor performance in this population. Household TB symptom screening improved sensitivity to detect pulmonary TB. Untreated tuberculosis during pregnancy is associated with poor maternal and infant outcomes, and future studies to investigate optimal screening algorithms and novel tests in this vulnerable population are warranted.

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APPENDIX: Tables and figures

Characteristic	Culture	Symptom screen	Smear	Xpert DNA PCR	Urine LAM Antigen
Cost	$$$	$	$	$$	$
Resource requirement	++++	-	+	++	-
Sensitivity	Gold standard	variable	Low in HIV	High	Low
Results	3 weeks	5 mins	<24 hrs	2 hours	15 mins
Resistance testing	Yes	No	No	Yes	No

Figure 1: Characteristics of TB screening and diagnostic tests.

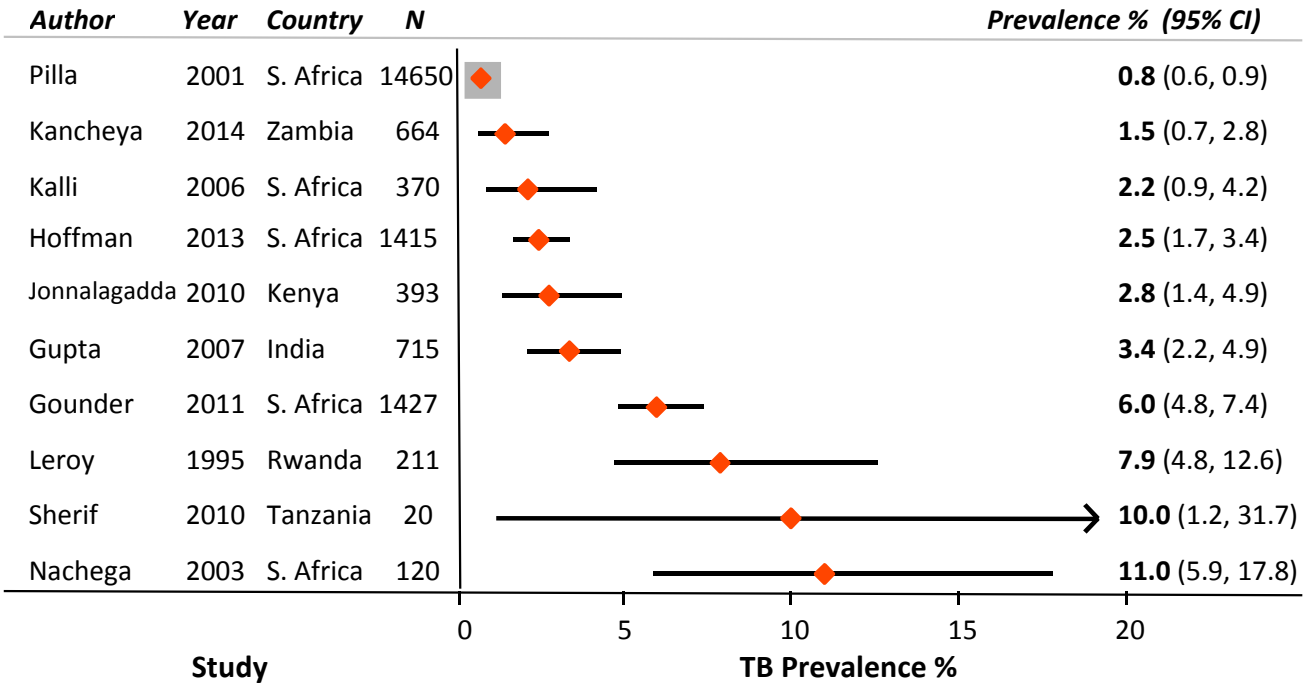

Figure 2: Prevalence of TB in HIV-infected pregnant women.

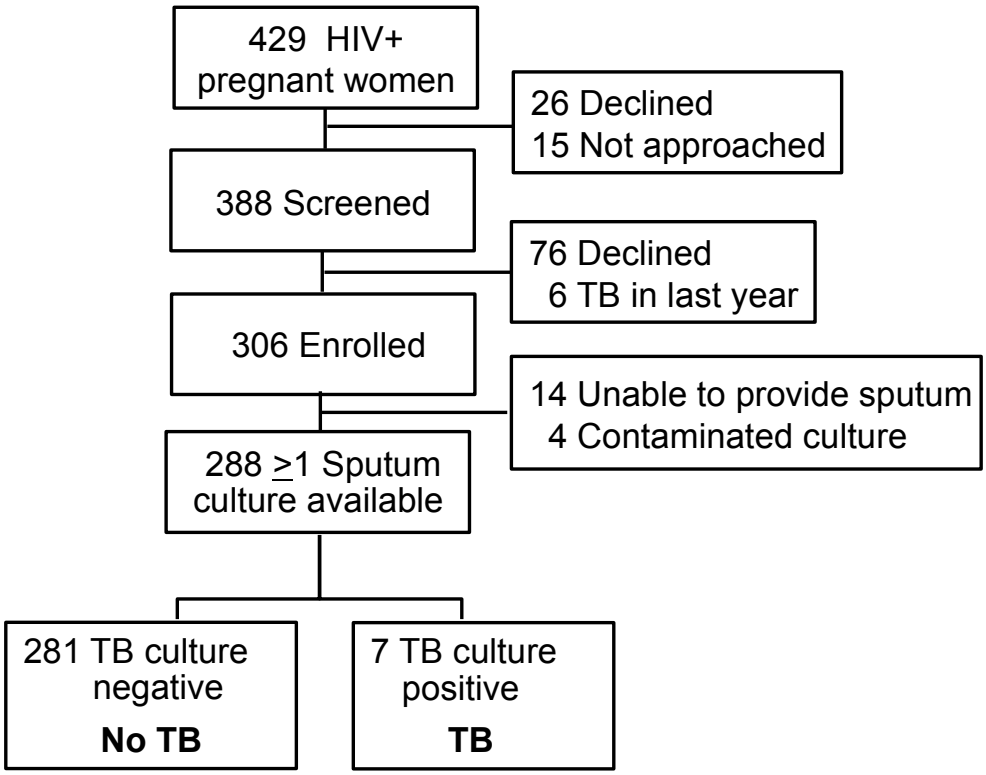

Figure 3: Study flow of HIV-infected pregnant women screened for pulmonary TB in western Kenya.

Table 1. Correlates of culture confirmed pulmonary TB among HIV-infected pregnant women.

Correlate	**All patients** N=288 n(%), or median (IQR)		**TB** N=7 n(%), or median (IQR)		**No TB** N=281 n(%), or median (IQR)		OR	95% CI	p^a
Sociodemographic characteristics									
Age (years)	25	(22-30)	21	(20-23)	25	(22-30)	0.84	(.69-1.02)	0.07
Gestational age (weeks)	26	(20-32)	24	(18-28)	26	(20-32)	0.96	(.87-1.06)	0.39
BMI (kg/m^2)	23.6	(21.9-25.8)	21.3	(20.3-22.3)	23.6	(21.9-25.8)	0.78	(.59-1.03)	0.08
Education (years)	8	(8-10)	8	(7-10)	8	(8-10)	0.98	(.72-1.34)	0.92
Completed primary school									
Yes	225	(78.1)	5	(71.4)	220	(78.3)	0.69	(.13-3.67)	0.65
No	63	(21.9)	2	(28.6)	61	(21.7)	ref		
Employed									
Yes	163	(56.6)	3	(42.9)	160	(56.9)	0.57	(.12-2.58)	0.47
No	125	(43.4)	4	(57.1)	121	(43.1)	ref		
Currently married									
Yes	240	(83.3)	7	(100.0)	233	(82.9)	-		0.61
No	48	(16.7)	0	(0.0)	48	(17.1)			
Residential Conditions									
Persons in household	4	(3-5)	3	(2-3)	4	(3-5)	0.48	(.23-1.00)	**0.05**
Single room household									
Yes	100	(34.7)	4	(57.1)	184	(65.5)	1.42	(.31-6.49)	0.68
No	188	(65.3)	3	(42.9)	97	(34.5)	ref		
HIV									
CD4 cell count (cells/ $cell/mm^3$)(N=239)	437	(342-565)	621	(439-888)	430	(340-558)	1.00	(.99-1.00)	0.11
≤250	33	(13.8)	0	(0.0)	33	(14.2)	-		1.00
>250	206	(86.2)	6	(100.0)	200	(85.8)			
HIV status known prior to this pregnancy									
Yes	210	(72.9)	6	(85.7)	204	(72.6)	2.26	(.27-19.11)	0.68
No	78	(27.1)	1	(14.3)	77	(27.4)	ref		

Table 1 continued

Correlate	**All patients** N=288 n(%), or median (IQR)	**TB** N=7 n(%), or median (IQR)	**No TB** N=281 n(%), or median (IQR)	OR	95% CI	p^a
Current ART						
PMTCT	62 (20.3)	3 (42.9)	52 (18.5)	2.19	(.47-10.12)	0.10
cART	165 (53.9)	4 (57.1)	152 (54.1)	ref		
None	79 (25.8)	0 (0)	77 (27.4)	-		
Current co-trimoxazole						
Yes	234 (81.2)	5 (71.4)	229 (81.5)	0.57	(.11-3.01)	0.62
No	54 (18.8)	2 (28.6)	52 (18.5)	ref		
Partner's HIV status						
Positive	133 (46.1)	3 (42.9)	130 (46.3)	0.57	(.09-3.49)	0.77
Negative	51 (17.7)	2 (28.6)	49 (17.4)	ref		
Unknown	104 (36.1)	2 (28.6)	102 (36.3)	0.48	(.07-3.51)	
TB Symptoms and Exposure						
History of TB (n=270)						
Yes	25 (9.3)	1 (14.3)	239 (90.9)	1.66	(0.19-14.37)	0.645
No	245 (90.7)	6 (85.7)	24 (9.1)	ref		
Cough						
Yes	43 (14.9)	2 (28.6)	41 (14.6)	2.34	(.44-12.47)	0.28
No	245 (85.1)	5 (71.4)	240 (85.4)	ref		
Fever						
Yes	14 (4.9)	1 (14.3)	13 (4.6)	3.43	(.38-30.67)	0.30
No	274 (95.1)	6 (85.7)	268 (95.4)			
Weight loss						
Yes	3 (1.0)	0 (0.0)	3 (1.1)	-		1.00
No	285 (99.0)	7 (100.0)	278 (98.9)			
Night sweats						
Yes	20 (6.9)	1 (14.3)	19 (6.8)	2.30	(.26-20.08)	0.40
No	268 (93.1)	6 (85.7)	262 (93.2)	ref		
Any WHO TB symptom positive[b]						
Yes	56 (19.4)	3 (42.9)	53 (18.9)	3.22	(.70-14.85)	0.14
No	232 (80.56)	4 (57.1)	228 (81.1)	ref		

Table 1 continued

Correlate	**All patients** N=288 n(%), or median (IQR)	**TB** N=7 n(%), or median (IQR)	**No TB** N=281 n(%), or median (IQR)	OR	95% CI	p^a
Cough >2 weeks						
Yes	14 (4.9)	2 (28.6)	12 (4.3)	8.97	(1.58-51.01)	**0.04**
No	274 (95.1)	5 (71.4)	269 (95.7)	ref		
Lymphadenopathy						
Yes	6 (2.1)	1 (14.3)	5 (1.8)	9.2	(0.92-91.2)	0.14
No	282 (97.9)	6 (85.7)	276 (98.2)	ref		
Hemoptysis						
Yes	1 (0.4)	0 (0.0)	1 (0.4)	-		1.0
No	287 (99.7)	7 100.0	280 99.6			
TST ≥5mm (N=85)						
Yes	18 (21.2)	3 (75.0)	15 (18.5)	13.2	(1.28-135.88)	**0.03**
No	67 (78.8)	1 (25.0)	66 (81.5)	ref		
TB exposure						
Yes	44 (15.4)	2 (28.6)	42 (15.1)	2.26	(.42-12.02)	0.29
No	242 (84.6)	5 (71.4)	237 (84.9)	ref		
Household TB contact (N=286)						
Yes	17 (5.9)	1 (14.3)	16 (5.7)	2.74	(.31-24.14)	0.35
No	269 (94.1)	6 (85.7)	263 (94.3)	ref		
Household WHO TB symptom positive						
Yes	12 (4.2)	3 (42.9)	9 (3.2)	22.67	(4.40-116.57)	**0.002**
No	276 (95.8)	4 (57.1)	272 (96.8)	ref		

[a]Fisher's exact for all categorical variables
[b]Cough (any duration), fever, weight loss, or night sweats

Abbreviations: BMI, body mass index; ART, antiretroviral therapy; PMTCT, prevention of maternal to child transmission; cART, combination antiretroviral therapy; TST, tuberculin skin test; mm, millimeter.

Table 2: HIV-infected pregnant women with positive *M. tuberculosis* sputum culture.

ID	CD4 (cells/mm^3)	ART regimen, duration	Symptoms	Household symptoms	TST (induration)	Xpert
1	nd	TDF+3TC+EFV 2 years	None	Weight loss	Negative (0 mm)	Negative
2	439	TDF+3TC+NVP 3 years	Cough >2 weeks Lymphadenopathy	Cough	Positive (12 mm)	Positive
3	643	No	Cough >2 weeks	None	nd	Negative
4	695	No	Night sweats Fever	None	Negative (0 mm)	Positive
5	370	No	None	None	Negative (0 mm)	Positive
6	600	TDF+3TC+EFV 5 years	None	None	Positive (5 mm)	Negative
7	888	TDF+AZT+3TC+LPV/r 3 years	None	Cough	Positive (7 mm)	Negative

Abbreviations: nd, not done; TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; NVP, nevirapine; AZT, zidovudine; LPV/r, lopinavir-ritonavir

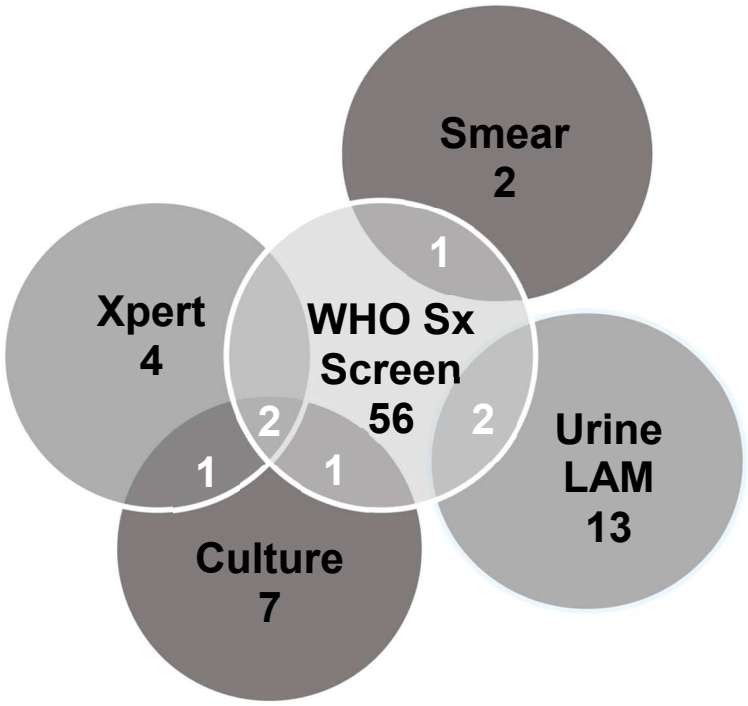

Figure 4: Overlap of TB screening and diagnostic tests.

Table 3. Diagnostic accuracy of WHO TB symptom screen and rapid TB diagnostic tests compared to sputum culture in HIV-infected pregnant women.

Screen or test	Positive among total N=288 (%)		Positive among TB cases N=7 (%)		Sensitivity % (95% CI)		Specificity % (95% CI)		PPV % (95% CI)		NPV % (95% CI)		AUC (95% CI)	
Symptom screening														
WHO TB symptoms														
Cough	43	(14.9)	2	(28.6)	28.6	(3.7-71.0)	85.4	(80.7-89.3)	4.7	(0.6-15.8)	98.0	(95.3-99.3)	.57	(.39-.75)
Fever	14	(4.9)	1	(14.3)	14.3	(0.4-57.9)	95.4	(92.2-97.5)	7.1	(0.2-33.9)	97.8	(95.3-99.2)	.55	(.41-.69)
Weight loss	3	(1.0)	0	(0.0)	0.0	(0.0-41.0)	98.9	(96.9-99.8)	0	(0.0-70.8)	97.5	(95.0-99.0)	.49	(.49-.50)
Night sweats	20	(6.9)	1	(14.3)	14.3	(0.4-57.9)	93.2	(89.6-95.9)	5.0	(0.1-24.9)	97.8	(95.2-99.2)	.54	(.40-.68)
Any WHO TB symptom	56	(19.4)	3	(42.9)	42.9	(9.9-81.6)	81.1	(76.0-85.5)	5.4	(1.1-14.9)	98.3	(95.6-99.5)	.62	(.42-.82)
Cough >2 weeks	14	(4.9)	2	(28.6)	28.6	(3.7-71.0)	95.7	(92.7-97.8)	14.3	(1.8-41.8)	98.2	(95.8-99.4)	.62	(.44-.80)
Hemoptysis	1	(0.4)	0	(0.0)	0	(0.0-40.9)	99.6	(98.0-100)	0	(0.0-97.5)	97.6	(95.0-99.0)	.50	(.49-.50)
Lymphadenopathy	6	(2.1)	1	(14.3)	14.3	(0.4-57.9)	98.2	(95.9-99.4)	16.7	(0.4-64.1)	97.9	(95.4-99.2)	.56	(.42-.70)
Household TB symptom screen	12	(4.2)	3	(42.9)	42.9	(9.9-81.6)	96.8	(94.0-98.5)	25.0	(5.5-57.2)	98.6	(96.3-99.6)	.70	(.50-.90)
TB diagnostic test														
Smear microscopy	2	0.7	0	(0.0)	0	(0.0-41.0)	99.3	(97.5-99.9)	0	(0.0-84.2)	97.6	(95.0-99.0)	.50	(.49-.50)
Xpert	4	1.4	3	(42.9)	42.9	(9.9-81.6)	99.6	(98.0-100)	75.0	(19.4-99.6)	98.6	(96.4-99.6)	.71	(.51-.91)
Urine TB LAM (N=266)	13	4.9	0	(0.0)	0	(0.0-70.8)	95.1	(91.7-97.3)	0	(0.0-24.7)	98.8	(96.6-99.8)	.48	(.46-.49)
TST (N=85)	18	21.2	3	(75.0)	75.0	(19.4-99.4)	81.5	(71.3-89.2)	16.7	(3.6-41.4)	98.5	(92.0-100)	.78	(.53-1.0)
Combined screening														
WHO symptoms[a]	61	21.2	5	(71.4)	71.4	(29.0-96.3)	80.1	(74.9-84.6)	8.2	(2.7-18.1)	99.1	(96.9-99.9)	.76	(.58-.94)
WHO symptoms[a] or TST (N=129)	72	55.8	6	(100)	100	(54.1-100)	46.3	(37.3-55.6)	8.3	(3.1-17.3)	100	(93.7-100)	.73	(.69-.78)
WHO symptoms[a] or Xpert	63	21.9	6	(85.7)	85.7	(42.1-99.6)	79.7	(74.5-84.3)	9.5	(3.6-19.6)	99.6	(97.5-100)	.83	(.69-.97)
TST or Xpert (N=87)	21	24.1	5	(100)	100	(47.8-100)	80.5	(70.3-88.4)	23.8	(8.2-47.2)	100	(94.6-100)	.90	(.86-.95)
WHO symptoms[a] or Xpert or TST (N=131)	74	56.5	7	(100)	100	(59.0-100)	46.0	(37.0-55.1)	9.5	(3.9-18.5)	100	(93.7-100)	.73	(.69-.77)

[a]Extended WHO symptom screen including report of TB symptoms in participant or household member

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; Xpert, GeneXpert MTB/RIF; TB LAM,

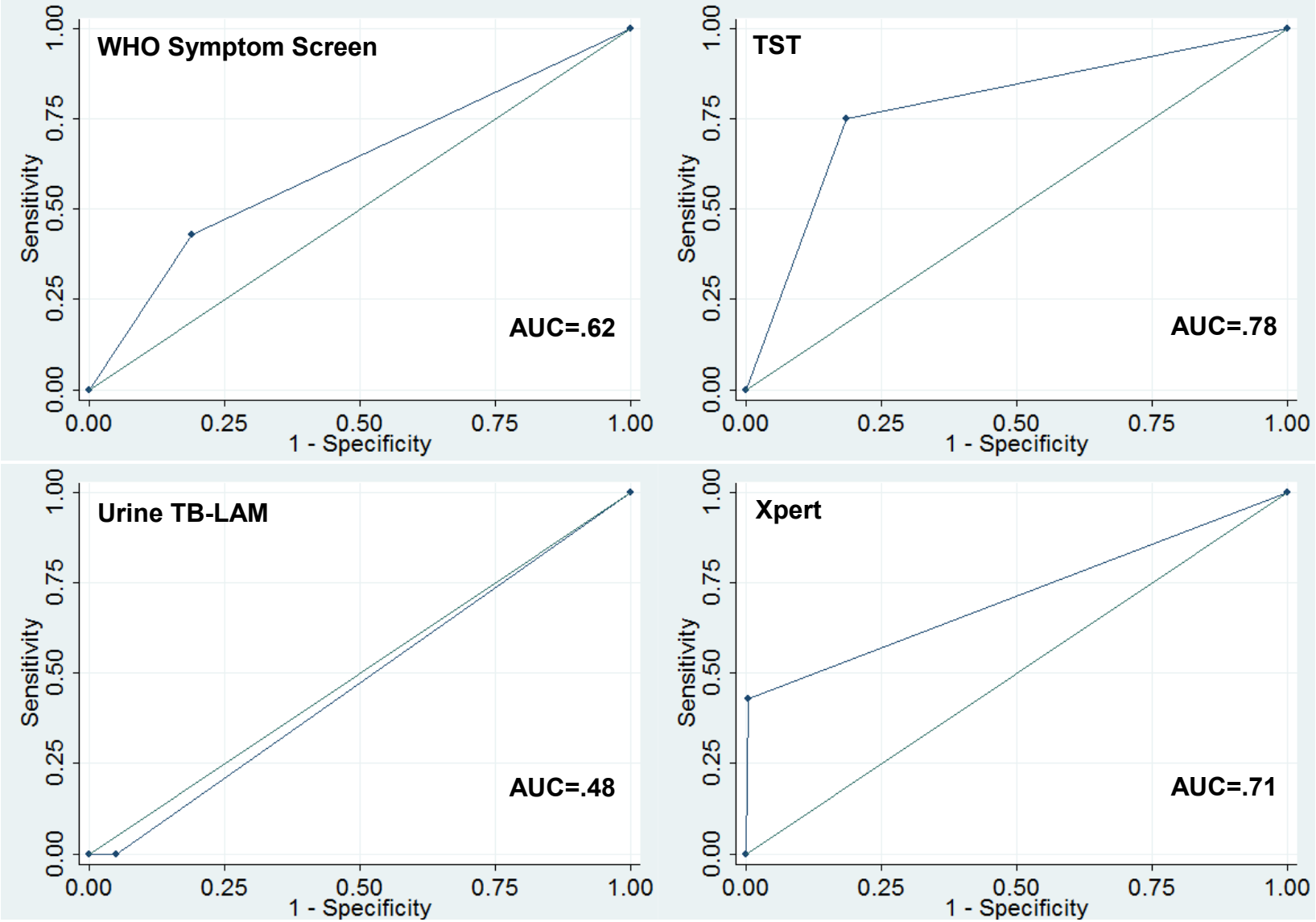

Figure 5: Area under the curve of individual TB screening and diagnostic tests.

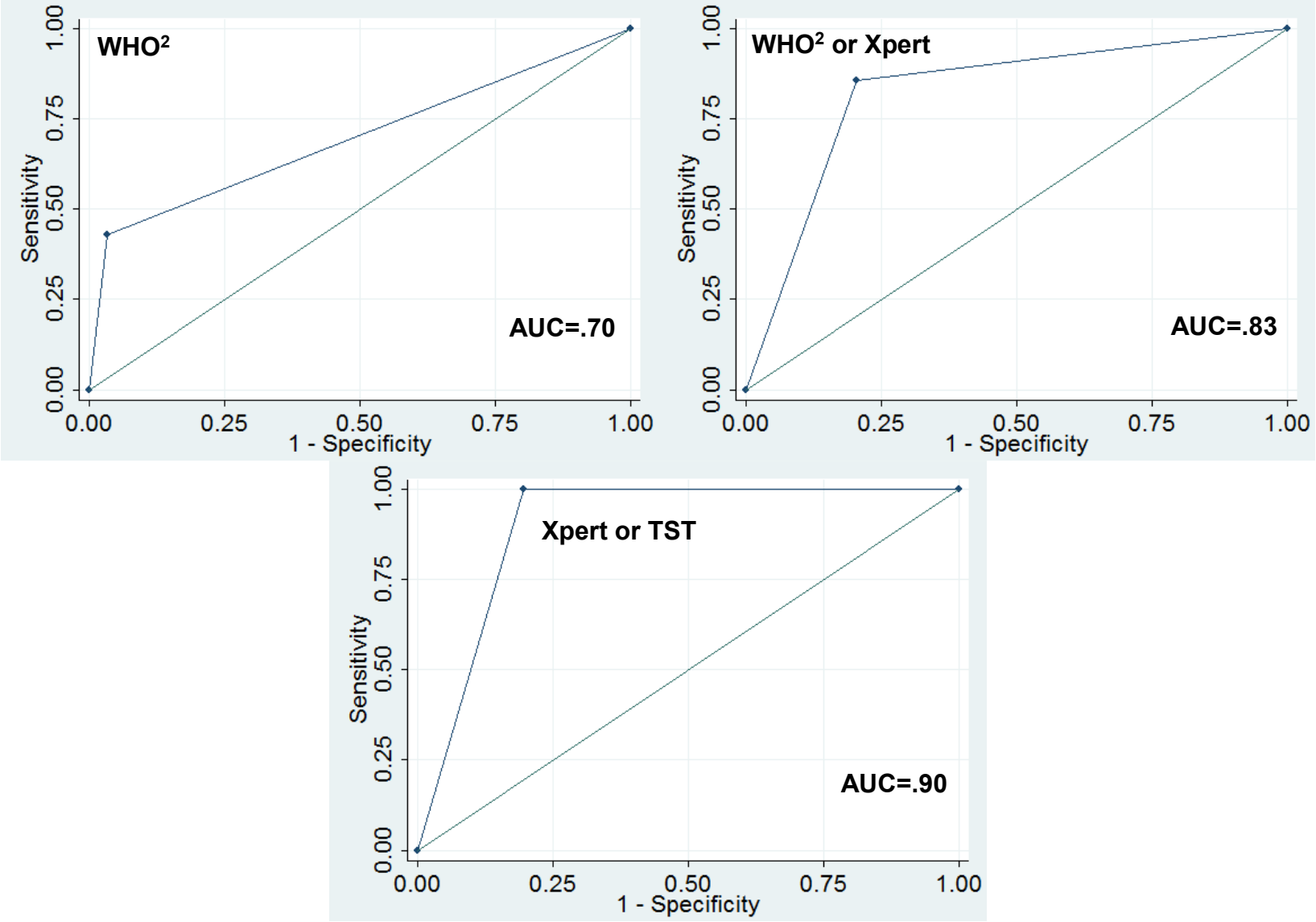

Figure 6: Area under the curve (AUC) of combination TB screening and diagnostic tests.

Abbreviations: WHO^2= WHO symptom screen including report of TB symptoms in participant or household member

VITA

Dr. LaCourse is trained in Internal Medicine and Pediatrics and is currently an Infectious Disease Fellow at the University of Washington, pursuing a Masters in Public Health in Epidemiology-Global Health Track. In collaboration with Drs. David Horne (Pulmonary Critical Care/Global Health) and Grace John-Stewart (Medicine/Pediatrics/Global Health/Epidemiology/Infectious Disease) she has been involved in a cross-sectional study evaluating the prevalence of pulmonary TB and MTB infection, including an evaluation of the performance of the WHO TB symptom screen, Xpert MTB/RIF, and urine TB-LAM tests, among HIV-infected pregnant women in western Kenya.