UCSF
UC San Francisco Previously Published Works

Title

Yield and Efficiency of Novel Intensified Tuberculosis Case-Finding Algorithms for People Living with HIV

Permalink

https://escholarship.org/uc/item/9rx7684c

Journal

American Journal of Respiratory and Critical Care Medicine, 199(5)

ISSN

1073-449X

Authors

Yoon, Christina
Semitala, Fred C
Asege, Lucy
et al.

Publication Date

2019-03-01

DOI

10.1164/rccm.201803-0490oc

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

ORIGINAL ARTICLE

Yield and Efficiency of Novel Intensified Tuberculosis Case-Finding Algorithms for People Living with HIV

Christina Yoon[1], Fred C. Semitala[2,3], Lucy Asege[4], Jane Katende[3], Sandra Mwebe[4], Alfred O. Andama[2,4], Elly Atuhumuza[4], Martha Nakaye[4], Derek T. Armstrong[5], David W. Dowdy[6], Charles E. McCulloch[7], Moses Kamya[2,3,4], and Adithya Cattamanchi[1,8]

[1]Division of Pulmonary & Critical Care Medicine, Department of Medicine, Zuckerberg San Francisco General Hospital, and [7]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California; [2]Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda; [3]Makerere University Joint AIDS Program, Kampala, Uganda; [4]Makerere University-University of California, San Francisco Research Collaboration, Kampala, Uganda; [5]Johns Hopkins University, School of Medicine, Baltimore, Maryland; [6]Division of Infectious Disease Epidemiology, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; and [8]Curry International Tuberculosis Center, University of California, San Francisco, Oakland, California

Abstract

Rationale: The recommended tuberculosis (TB) intensified case finding (ICF) algorithm for people living with HIV (symptom-based screening followed by Xpert MTB/RIF [Xpert] testing) is insufficiently sensitive and results in unnecessary Xpert testing.

Objectives: To evaluate whether novel ICF algorithms combining C-reactive protein (CRP)-based screening with urine Determine TB-LAM (TB-LAM), sputum Xpert, and/or sputum culture could improve ICF yield and efficiency.

Methods: We compared the yield and efficiency of novel ICF algorithms inclusive of point-of-care CRP-based TB screening and confirmatory testing with urine TB-LAM (if CD4 count $\leq$100 cells/μl), sputum Xpert, and/or a single sputum culture among consecutive people living with HIV with CD4 counts less than or equal to 350 cells/μl initiating antiretroviral therapy in Uganda.

Measurements and Main Results: Of 1,245 people living with HIV, 203 (16%) had culture-confirmed TB including 101 (49%) patients with CD4 counts less than or equal to 100 cells/μl. Compared with the current ICF algorithm, point-of-care CRP-based TB screening followed by Xpert testing had similar yield (56% [95% confidence interval, 49–63] vs. 59% [95% confidence interval, 51–65]) but consumed less than half as many Xpert assays per TB case detected (9 vs. 4). Addition of TB-LAM did not significantly increase diagnostic yield relative to the current ICF algorithm but provided same-day diagnosis for 26% of TB patients with advanced HIV. Addition of a single culture to TB-LAM and Xpert substantially improved ICF yield, identifying 78% of all TB cases.

Conclusions: Point-of-care CRP-based screening can improve ICF efficiency among people living with HIV. Addition of TB-LAM and a single culture to Xpert confirmatory testing could enable HIV programs to increase the speed of TB diagnosis and ICF yield.

Keywords: tuberculosis; intensified case finding; screening; C-reactive protein; urine lipoarabinomannan

(Received in original form March 15, 2018; accepted in final form September 6, 2018)

Supported by the NIH/National Institute of Allergy and Infectious Diseases (K23 AI114363, C.Y.); NIH and University of California, San Francisco Gladstone Institute of Virology and Immunology Center for AIDS Research (P30 AI027763, C.Y.); the University of California, San Francisco Nina Ireland Program for Lung Health (C.Y.); and NIH/National Institute of Allergy and Infectious Diseases Presidential Emergency Plan for AIDS Relief Center for AIDS Research Administrative Supplement (P30 A120163, A.C.). The funding organizations had no role in the design, collection, analysis, and interpretation of data, or in the writing of the manuscript.

Authors Contributions: C.Y. and A.C. designed the study. F.C.S., E.A., D.T.A., A.O.A., and M.K. oversaw the local collection of data. J.K., S.M., and L.A. collected the data. C.Y. analyzed the data and wrote the first draft of the manuscript. A.C., C.E.M., and D.W.D. critically revised the manuscript. C.Y., F.C.S., L.A., J.K., S.M., A.O.A., E.A., M.N., D.T.A., D.W.D., C.E.M., M.K., and A.C. read and approved the final manuscript.

Correspondence and requests for reprints should be addressed to Christina Yoon, M.D., M.A.S., M.P.H., Zuckerberg San Francisco General Hospital, 1001 Potrero Avenue, Building 5, Room 5K1, San Francisco, CA 94110. E-mail: christina.yoon@ucsf.edu.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 199, Iss 5, pp 643–650, Mar 1, 2019
Copyright © 2019 by the American Thoracic Society
Originally Published in Press as DOI: 10.1164/rccm.201803-0490OC on September 7, 2018
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Novel point-of-care screening and diagnostic tools for tuberculosis (TB) have the potential to improve the efficiency and yield of intensified case finding among people living with HIV. C-reactive protein (CRP), an acute-phase reactant whose levels rise in response to systemic inflammatory conditions including active TB, has been identified as the first test to meet the diagnostic accuracy targets (sensitivity, ⩾90%; specificity, ⩾70%) and operational characteristics (⩽$2 per test, measured at the point of care) established by the World Health Organization for an effective TB screening test. The lateral flow urine lipoarabinomannan assay Determine TB-LAM test has recently been endorsed by the World Health Organization to assist in establishing rapid TB diagnosis among patients with advanced HIV.

What This Study Adds to the Field: This is the first study to evaluate novel intensified case finding algorithms inclusive of both point-of-care CRP for TB screening and Determine TB-LAM for confirmatory TB testing. Our results suggest that for HIV-infected adults with CD4 counts less than or equal to 350 cells/μl, replacing symptom-based screening (current recommendation) with point-of-care CRP-based TB screening could improve the efficiency and reduce the cost of intensified case finding, without compromising diagnostic yield. Our study also supports the addition of Determine TB-LAM to Xpert confirmatory testing to improve the speed of TB diagnosis. Costs saved by using point-of-care CRP to select patients for confirmatory testing could enable the routine use of mycobacterial culture to greatly improve the proportion of TB cases detected.

In 2016 alone, an estimated 1 million new cases of tuberculosis (TB) occurred among people living with HIV (PLHIV) and 374,000 patients with TB/HIV died, representing one-third of all HIV deaths worldwide (1). The extremely high frequency of undiagnosed TB reported in multiple postmortem studies of PLHIV suggests that both the number of patients with TB/HIV and the number of TB/HIV deaths are likely substantially higher than estimated (2). To reduce the burden of TB, the World Health Organization (WHO) recommends intensified case finding (ICF) for all PLHIV (3, 4). The recommended ICF algorithm involves symptom-based screening, followed by confirmatory testing with Xpert MTB/RIF (Xpert or Xpert Ultra; Cepheid) for all those who screen positive. However, this algorithm results in high costs (because of the poor specificity of symptom-based screening) (5–11) and suboptimal yield (because of the inadequate sensitivity of Xpert) (10–12) in the context of ICF.

Novel screening and diagnostic tools have the potential to improve the efficiency and yield of ICF. We have previously reported that C-reactive protein (CRP), which can be measured from capillary blood using a rapid (results in 3 min) and low-cost ($2 per test) point-of-care (POC) assay, is the first test to meet the WHO target product profile for an effective TB screening test (sensitivity, ⩾90%; specificity, ⩾70%; ⩽$2 per test) (13) among PLHIV (10). Using a cutpoint of 8 mg/L, POC CRP had 90% sensitivity and 70% specificity in reference to two liquid cultures (10). Compared with symptom screening, POC CRP-based TB screening reduced the proportion of patients requiring Xpert testing from 87% to 37%. These results suggest that POC CRP-based TB screening could improve the efficiency and reduce the cost of ICF. However, its performance in combination with novel confirmatory testing strategies is unknown.

Confirmatory testing strategies that have the potential to improve the yield of ICF include addition of Determine TB-LAM (TB-LAM; Alere) and liquid culture. TB-LAM is a low-cost ($4 per test), POC assay that detects lipoarabinomannan, a lipopolysaccharide present in mycobacterial cell walls from unprocessed urine in 25 minutes. Although multiple studies have evaluated urine TB-LAM in combination with sputum Xpert among inpatient and/or outpatient PLHIV self-presenting with symptoms suggestive for TB (i.e., passive case finding) (14–17) or as an initial TB screening strategy for PLHIV (18, 19), only one study has evaluated TB-LAM and Xpert as a combination confirmatory TB testing strategy among outpatient PLHIV undergoing ICF (20). Although addition of TB-LAM did not significantly increase yield beyond Xpert alone, TB-LAM (when used as the initial confirmatory test) rapidly identified 30% of all culture-confirmed TB cases among patients with CD4 counts less than or equal to 100 cells/μl and enabled same-day TB diagnosis and treatment initiation for those patients at greatest risk of dying from TB. Sputum liquid culture is the gold standard for TB diagnosis. Although addition of culture would undoubtedly increase the yield of ICF, culture is not routinely available in most resource-limited settings because of its high costs, high infrastructure requirements, and need for highly trained laboratory personnel. More efficient TB screening strategies and/or more sensitive POC confirmatory testing strategies may enable the routine use of culture if limited to a smaller subset of patients with higher likelihood of having active TB.

We report on the first prospective study to compare the yield and efficiency of the current ICF algorithm for PLHIV with novel rapid ICF algorithms that include POC CRP-based TB screening and TB-LAM confirmatory testing. In addition, we assess the extent to which a single sputum culture further increases the yield of ICF. These results have been previously reported in the form of an abstract (21).

Methods

Study Population

We previously described patient recruitment, study procedures, and the diagnostic accuracy of screening tests (WHO symptom screen and POC CRP) in reference to a gold standard of two sputum liquid mycobacterial cultures for 1,177 patients initiating antiretroviral therapy (ART) from two HIV clinics in Kampala, Uganda and enrolled between July 2013 and December 2015 (10). Here, we present results on the performance of confirmatory tests (urine TB-LAM, sputum Xpert, and the first sputum culture) and ICF algorithms combining screening and confirmatory tests among consecutive HIV-infected adults (age ⩾18 yr) enrolled from April 2014 to December 2016. Eligible patients were ART-naive and had

a pre-ART CD4 count less than or equal to 350 cells/μl. Patients with a known diagnosis of active TB and/or taking medication with antimycobacterial activity (e.g., fluoroquinolones) within 3 days of enrollment were excluded. All patients provided written informed consent and the study was approved by institutional review boards at the University of California, San Francisco and Makerere University, and by the Uganda National Council for Science and Technology. This study conforms to the Standards for the Reporting of Diagnostic Accuracy Studies initiative guidelines (22).

Study Procedures

Data collection and TB screening. Trained study personnel collected demographic and clinical data and administered the WHO symptom screen at the time of enrollment. In accordance with WHO guidelines, we considered patients to be symptom screen positive if they reported any of four symptoms: *1*) current cough, *2*) fever, *3*) night sweats, and *4*) weight loss (4). CRP concentrations were measured at study entry from capillary blood using a Food and Drug Administration–approved standard sensitivity POC assay (iCHROMA CRP; BodiTech) that provides results in 3 minutes. We defined a POC CRP concentration of greater than or equal to 8 mg/L (rounding to the nearest whole number) as screen positive for TB based on our previous work, which identified that an 8 mg/L cutpoint achieved the WHO thresholds for diagnostic accuracy (sensitivity, ⩾90%; specificity, ⩾70%) for an effective TB screening test (10).

Urine collection and urine LAM testing. Spontaneously voided urine specimens were collected at study entry from all study participants. TB-LAM testing was performed using one drop of fresh unprocessed urine applied to the TB-LAM test strip. After 25 minutes of incubation at ambient temperature, two independent readers, blinded to clinical and demographic data including symptom screen status and POC CRP concentrations, graded the presence and intensity of bands using the manufacturer's reference card; disagreements were resolved by a third independent reader. We defined a band intensity of grade 2 or higher as positive for active TB (23).

Sputum collection, Xpert MTB/RIF testing, and mycobacterial culture. We collected two spot sputum samples from each study participant. Xpert testing was performed using a minimum of 1 ml of sputum from the first specimen and mycobacterial culture was performed on decontaminated sediments from both sputum specimens, as described previously (10). Sediments were cultured on liquid media using the BACTEC 960 Mycobacterial Growth Indicator Tube system. Laboratory technicians confirmed the identity of any growth by acid-fast bacilli smear microscopy and molecular speciation testing (Capilia TB, TAUNS; or MPT64, Standard Diagnostics). All staff performing Xpert testing and culture were blinded to clinical and demographic data including symptom screen status, POC CRP concentrations, and TB-LAM results.

Reference Standard

We considered patients to have active TB if Mycobacterium tuberculosis was isolated from greater than or equal to one sputum culture. We considered patients not to have active TB if all sputum cultures were negative for *M. tuberculosis*, with a required minimum of two cultures, regardless of TB-LAM or Xpert result. Patients with insufficient culture data (e.g., because of contamination) were excluded from analysis.

Statistical Analysis

We compared categorical and continuous variables with the Wilcoxon rank sum test, Fisher exact test, or chi-square test, as appropriate; all tests of statistical significance were two-tailed. We calculated the point estimates and 95% confidence intervals (CIs) for the sensitivity, specificity, predictive values, and area under the receiver operating curve (DeLong method) of individual TB screening and confirmatory tests and confirmatory test combinations, in reference to culture results; we compared differences in paired proportions using McNemar chi-square test. To determine the diagnostic yield of different ICF algorithms (screening, followed by confirmatory testing of all those who screen positive), we combined either symptom-based screening or POC CRP-based screening to the following confirmatory testing strategies: *1*) Xpert; *2*) TB-LAM (if CD4 count ⩽100 cells/μl) and Xpert; and *3*) TB-LAM (if CD4 count ⩽100 cells/μl), Xpert, and first sputum culture (*see* Figure E1 in the online supplement). The diagnostic yield of each ICF algorithm is equal to the proportion of patients with culture-positive TB detected (irrespective of screening status) who tested positive by the selected ICF algorithm.

To determine the incremental yield of each novel ICF algorithm, we determined the number of additional TB cases detected relative to the current ICF algorithm (symptom-based TB screening, followed by Xpert testing if screen positive). The incremental yield of each novel POC CRP-based ICF algorithm is equal to the proportion of patients with culture-positive TB detected by the selected ICF algorithm who were missed by the current ICF algorithm. We compared differences in the proportion of TB cases detected by each novel ICF algorithm relative to the current ICF algorithm using McNemar chi-square test of paired proportions.

To determine the efficiency of each ICF algorithm, we determined the number of confirmatory tests used and the number needed to test (NNT) to detect one case of culture-confirmed TB for each confirmatory test. We performed all analyses using STATA 13 (STATA) (24).

Results

Study Population

From April 2014 to December 2016, we consecutively enrolled 1,511 eligible patients. We excluded 267 patients for the reasons listed in Figure 1, including 230 patients with insufficient culture data: 57 (4%) patients with two contaminated cultures and 173 (11%) patients with one contaminated culture and one culture negative for *M. tuberculosis*. Table 1 shows the demographics and clinical characteristics of the remaining 1,245 patients. Overall, 439 (35%) patients were eligible for TB-LAM testing based on a baseline CD4 count less than or equal to 100 cells/μl, 1,100 (88%) patients screened positive by symptoms, and 498 (40%) patients screened positive by POC CRP. Table E1 shows the diagnostic accuracy symptom screening and POC CRP in

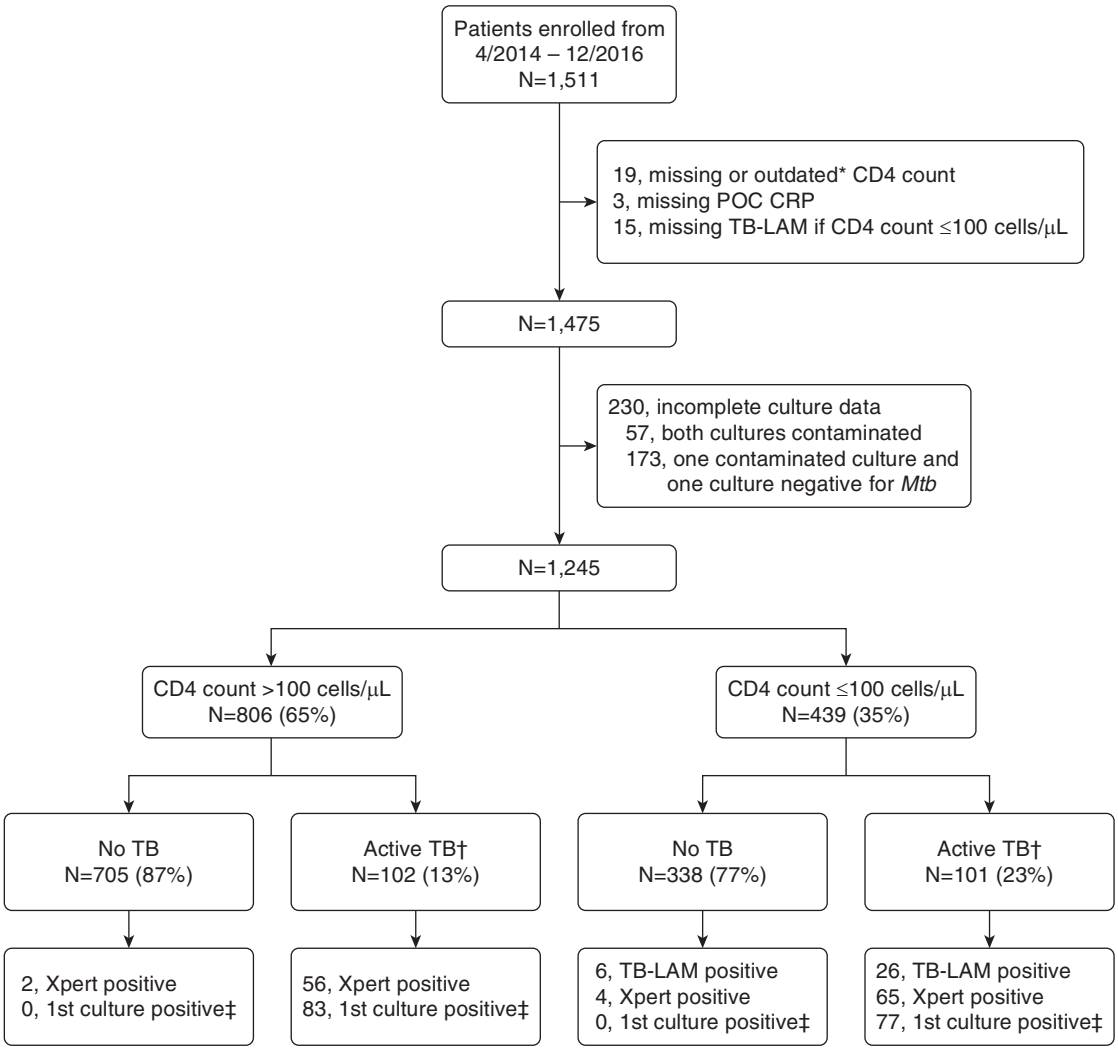

Figure 1. Patient flow diagram. The diagram conforms to the Standards for the Reporting of Diagnostic Accuracy Studies 2015 guidelines for patient flow diagrams. *Outdated CD4 count was defined as CD4 count measured ⩾3 months before study enrollment and antiretroviral therapy initiation. †Active TB was defined as at least one sputum culture positive for *Mtb* in reference to two liquid cultures. ‡Liquid culture result from the first sputum specimen collected. CRP = C-reactive protein; *Mtb* = *Mycobacterium tuberculosis*; POC = point-of-care; TB = tuberculosis.

reference to culture. A total of 203 patients had one or more sputum culture positive for *M. tuberculosis* (16% TB prevalence). Thirty-two patients (7%) tested positive for TB by TB-LAM, 127 (10%) by Xpert, and 160 (13%) by the first sputum culture. Table E2 shows the diagnostic accuracy of each individual confirmatory test and combined confirmatory testing strategy in reference to culture.

Yield of ICF Strategies

The current ICF algorithm (symptom-based screening, followed by Xpert testing for all those who screened positive) required 1,100/1,245 (88%) patients to undergo Xpert testing and identified 119/203 (diagnostic yield, 59%; 95% CI, 51–65%) culture-confirmed TB cases and seven false-positive TB cases. Table 2 shows the diagnostic and incremental yield of all novel symptom-based and POC CRP-based ICF algorithms relative to the current ICF algorithm. Next, we focus on comparing the current ICF algorithm with novel POC CRP-based ICF algorithms.

POC CRP-based ICF algorithms. An ICF algorithm beginning with POC CRP-based TB screening required only 498/1,245 (40%) patients to undergo confirmatory testing. Compared with the current ICF algorithm, a POC CRP-based ICF algorithm including Xpert only would have detected five fewer TB cases (incremental yield, −2%; 95% CI, −5 to +1%; $P = 0.06$) and would have missed 89 (44%; 95% CI, 37–51%) culture-confirmed TB cases (Table 2). A POC CRP-based ICF algorithm including TB-LAM followed by Xpert would have detected two additional TB cases (incremental yield, +1%; 95% CI, −3 to +5%; $P = 0.59$) relative to the current ICF algorithm and would have missed 82 (40%; 95% CI, 34–47%) culture-confirmed TB cases. A POC CRP-based ICF algorithm including all three confirmatory tests would have detected significantly more TB cases (39 additional TB cases; incremental yield, +19%; 95% CI, +12 to +26%; $P < 0.0001$) than the

Table 1. Demographics and Clinical Characteristics

Characteristic	Total (*n* = 1,245)	No TB (*n* = 1,042)	TB (*n* = 203)	*P* Value
Age, yr	33 (27–40)	32 (27–40)	35 (29–39)	0.01
Female	648 (52)	576 (55)	72 (35)	<0.001
CD4 count, cells/μl	153 (67–252)	166 (74–263)	101 (44–183)	<0.0001
CD4 ⩽100 cells/μl	439 (35)	338 (32)	101 (50)	<0.001
BMI, kg/m^2	20.9 (18.8–23.8)	21.4 (19.2–24.2)	19.1 (17.5–21.1)	<0.0001
Previous TB	39 (3)	34 (3)	5 (2)	0.55
WHO symptom screen positive	1,100 (88)	904 (87)	196 (97)	<0.001
POC CRP ⩾8 mg/L	498 (40)	320 (31)	178 (88)	<0.001
POC CRP, mg/L	4.03 (2.5–24.4)	2.6 (2.5–11.4)	49.4 (18.2–93.7)	<0.0001

Definition of abbreviations: BMI = body mass index; POC CRP = point-of-care C-reactive protein; TB = tuberculosis; WHO = World Health Organization. Cells represent median (interquartile range) or number (%).

current ICF algorithm and would have missed 49 (24%; 95% CI, 18–31%) culture-confirmed TB cases. The number of false-positive TB cases detected was seven for the current ICF algorithm, four for POC CRP-based screening followed by Xpert testing, and 10 for POC CRP-based screening followed by confirmatory testing strategies inclusive of TB-LAM.

Number Needed to Test

Table 3 shows the number of confirmatory tests used and the NNT to detect one case of active TB for each ICF algorithm. The current ICF algorithm would have used 1,100 Xpert assays to detect 119 culture-confirmed TB cases (NNT = 9 Xpert assays used to detect one case of active TB). A symptom-based ICF algorithm that includes TB-LAM testing before Xpert would have used 16 TB-LAM strips to detect one case of active TB and 11 Xpert assays to detect an additional case of active TB. A symptom-based ICF algorithm that includes TB-LAM, Xpert and, a single culture would have required 21 cultures to be performed to detect an additional case of active TB.

For all POC CRP-based ICF algorithms, the NNT (TB-LAM, Xpert, culture) to detect one case of active TB was less than half that for all corresponding symptom-based ICF algorithms. POC CRP-based screening followed by Xpert confirmatory testing would have used 498 Xpert assays to detect 114 culture-confirmed TB cases (NNT = 4 Xpert assays used to detect one case of active TB). A POC CRP-based ICF algorithm that includes TB-LAM testing before Xpert would have used 8 TB-LAM strips to detect one case of active TB and 5 Xpert assays to detect an additional case of active TB. A POC CRP-based ICF algorithm that includes TB-LAM, Xpert, and a single culture would have required 10 cultures to be performed to detect an additional case of active TB.

Test Costs per TB Case Detected

To demonstrate the extent to which novel ICF algorithms could reduce ICF cost and improve efficiency, we performed a simple costing analysis to compare test costs for each ICF algorithm and the cost per TB case detected. If current test costs were applied to this cohort of 1,245 PLHIV undergoing ICF, the current

Table 2. Incremental Yield, Diagnostic Yield, and Number of False-Positive TB Cases of All ICF Algorithms Relative to the Current ICF Algorithm*

ICF Strategy	Diagnostic Yield [*n (%; 95% CI)*], All TB Cases Detected (*n* = 203)	Incremental Yield			Total False Positives (*n*)
		Additional TB Cases Detected (*n*)	Additional TB Cases Detected [*% (95% CI)*]	*P* Value for the Difference	
Current ICF algorithm*	119 (59; 52 to 65)	REF	REF	—	7
Novel ICF algorithms					
WHO symptom screen					
TB-LAM + Xpert	126 (62; 55 to 69)	+7	+4 (0 to +7)	0.008	13
TB-LAM + Xpert + culture	172 (85; 79 to 89)	+53	+27 (+20 to +34)	<0.0001	13
POC CRP ⩾8 mg/L					
Xpert†	114 (56; 49 to 63)	−5	−2 (−5 to +1)	0.06	4
TB-LAM + Xpert†	121 (60; 53 to 66)	+2	+1 (−3 to +5)	0.59	10
TB-LAM + Xpert + culture‡	158 (78; 71 to 83)	+39	+19 (+12 to +26)	<0.0001	10

Definition of abbreviations: CI = confidence interval; ICF = intensified case finding; POC CRP = point-of-care C-reactive protein; REF = reference; TB = tuberculosis; WHO = World Health Organization.

*Current ICF strategy (symptom-based TB screening, followed by Xpert confirmatory testing of all those who screen positive). Incremental yield (n, %) of all evaluated ICF strategies are shown above relative to the current ICF strategy.

†Diagnostic yield of POC CRP–based ICF algorithm similar to corresponding symptom-based ICF algorithm ($P \geq 0.06$).

‡Diagnostic yield of POC CRP–based ICF algorithm less than corresponding symptom-based ICF algorithm ($P = 0.0003$).

Table 3. Number of Confirmatory Tests Used and NNT to Detect One Case of Active TB for All ICF Algorithms

ICF Algorithms	Number of Confirmatory Tests Used			NNT to Detect One Case of Active TB		
	LAM	Xpert	Culture	LAM	Xpert	Culture
WHO symptom screen						
Xpert	—	1,100	—	—	9	—
TB-LAM + Xpert	411	1,062	—	16	11	—
TB-LAM + Xpert + culture	411	1,062	956	16	11	21
POC CRP (⩾8 mg/L)						
Xpert	—	498	—	—	4	—
TB-LAM + Xpert	210	460	—	8	5	—
TB-LAM + Xpert + culture	210	460	357	8	5	10

Definition of abbreviations: ICF = intensified case finding; NNT = number needed to test; POC CRP = point-of-care C-reactive protein TB = tuberculosis; WHO = World Health Organization.

ICF algorithm would cost $102 per TB case detected, whereas the corresponding POC CRP-based ICF algorithm (POC CRP-based screening followed by Xpert testing) would cost $70 per TB case detected (Table 4). Addition of TB-LAM would not change the cost per TB case detected for either ICF algorithm. Addition of a single liquid culture would greatly increase both the proportion of TB cases detected and cost per TB case detected. However, an ICF algorithm that begins with POC CRP-based screening and includes all three confirmatory tests (TB-LAM, Xpert, a single liquid culture) would substantially increase the proportion of TB cases (78% vs. 59%; $P < 0.0001$), but cost less per TB case detected ($92 vs. $102 per TB case detected) than the current ICF algorithm.

Discussion

In the first study to evaluate novel ICF algorithms inclusive of POC CRP-based TB screening among HIV-positive adults initiating ART, we compared the current ICF algorithm (symptom-based screening followed by Xpert testing) with novel ICF algorithms combining POC CRP-based TB screening with confirmatory testing strategies inclusive of TB-LAM, Xpert, and/or a single sputum culture. We found that the current ICF algorithm required 88% of all patients screened to undergo Xpert testing but only identified 59% of all culture-confirmed TB cases. In contrast, POC CRP-based ICF required only 40% of all patients screened to undergo Xpert confirmatory testing while identifying a similar proportion of culture-confirmed TB cases. Moreover, the inclusion of TB-LAM and a single culture resulted in substantially higher (78%) diagnostic yield compared with the current ICF algorithm, and the inclusion of TB-LAM enabled rapid TB diagnosis for 26% of all TB patients with CD4 counts less than or equal to 100 cells/μl. These data provide evidence to support the immediate use and scale-up of POC CRP-based screening, followed by TB-LAM and Xpert testing to improve the efficiency and speed of TB diagnosis among PLHIV initiating ART. Costs saved from having to perform fewer rapid diagnostics (e.g., TB-LAM and Xpert) could be invested in liquid culture, which would further increase ICF yield.

Our study confirms that the current ICF algorithm has low diagnostic yield (59%), primarily because of the low sensitivity (60%) of Xpert. Other outpatient studies evaluating Xpert in the context of ICF among PLHIV have reported similarly low sensitivity (range, 52–58%) (10–12). In our study, we found that the first sputum culture had almost 20% higher sensitivity than Xpert and that POC CRP-based ICF algorithms that included a single culture after TB-LAM and Xpert testing substantially improved diagnostic yield, detecting 78% of all confirmed TB cases. Although Xpert Ultra (the next-generation Xpert MTB/RIF cartridge) has been shown to be more sensitive than the standard cartridge and just

Table 4. Individual Test Costs, ICF Test Costs, and Costs per TB Case Detected for All ICF Algorithms

ICF Algorithms	Individual Test Costs (*U.S. $*)				ICF Test Costs (*U.S. $*)	Cost per TB Case Detected (*U.S. $*)
	POC CRP	LAM	Xpert	Culture		
WHO symptom screen						
Xpert	—	—	12,000	—	12,000	102
TB-LAM + Xpert	—	1,644	11,682	—	13,326	106
TB-LAM + Xpert + culture	—	1,644	11,682	16,252	29,578	172
POC CRP (⩾8 mg/L)						
Xpert	2,490	——	5,478	—	7,968	70
TB-LAM + Xpert	2,490	840	5,060	—	8,390	69
TB-LAM + Xpert + culture	2,490	840	5,060	6,069	14,459	92

Definition of abbreviations: ICF = intensified case finding; POC CRP = point-of-care C-reactive protein; TB = tuberculosis; WHO = World Health Organization.
Assume $2 per POC CRP assay, $11 per Xpert assay, $4 per TB-LAM assay, and $17 per sputum liquid culture (26).

as sensitive as a single liquid culture among PLHIV self-presenting with TB symptoms (i.e., passive case finding) (25), its performance among PLHIV undergoing ICF, where pauci-bacillary disease is more frequent, is unknown. Future studies comparing the diagnostic yield of ICF algorithms inclusive of Xpert Ultra with and without culture, are needed, as are more efficient TB screening strategies to enable routine and efficient implementation of ICF.

Replacing symptom screening with POC CRP-based TB screening improves the efficiency and reduces the cost of ICF among PLHIV, without reducing ICF yield. Our prior work identified POC CRP as the only test to date to meet the accuracy targets (sensitivity, ⩾90%; specificity, ⩾70%) established by the WHO for an effective TB screening test (10). Here, we show POC CRP-based TB screening reduced the proportion of patients requiring Xpert confirmatory testing by more than half (40% vs. 88%; $P < 0.0001$) without reducing the yield of ICF. Furthermore, if TB-LAM and a single culture were combined with Xpert, POC CRP-based ICF can be expected to substantially improve diagnostic yield (78% vs. 59%; $P < 0.0001$) without greatly increasing overall ICF test costs ($14,459 vs. $13,326) and at lower cost per TB case detected ($92 vs. $102), relative to the current ICF algorithm. Formal cost-effectiveness analyses are needed to provide policymakers and HIV programs with the expected estimates of costs, yield, and number of TB cases averted (via provision of TB preventive therapy) when ICF is performed using POC CRP-based versus symptom-based screening.

Our findings strongly support increased use of TB-LAM as part of ICF among PLHIV to facilitate rapid diagnosis and treatment initiation. Consistent with the prior study evaluating TB-LAM in combination with Xpert among symptomatic HIV-infected outpatients (20), our study found that addition of TB-LAM to Xpert offered modest incremental benefit (incremental yield 1–4%, depending on the screening strategy used). We also found that if used as the initial confirmatory test for those who screen positive by either screening strategy, TB-LAM provided same-day diagnosis and allowed for same-day treatment initiation for 26% of all TB cases among patients with CD4 counts less than or equal to 100 cells/μl. Furthermore, a stepwise approach to confirmatory TB testing beginning with TB-LAM led to small reductions in the number of more expensive sputum tests (Xpert and culture) needed. Clinic-based studies evaluating the impact of ICF algorithms inclusive of TB-LAM on patient outcomes are now needed to encourage uptake of TB-LAM testing.

Our study has several strengths. First, we prospectively enrolled a large, consecutive sample of HIV-infected clinic attendees initiating ART to determine precise sensitivity and specificity estimates for each screening and confirmatory TB test in reference to two sputum liquid cultures. Second, to identify more sensitive and/or more efficient approaches to TB case detection, we combined two screening tests with three confirmatory testing strategies to evaluate the yield, efficiency, and false-positive rate of five novel ICF algorithms. Therefore, our study represents the most comprehensive evaluation of ICF algorithms in PLHIV conducted to date. Lastly, our findings are likely generalizable to several other HIV programs in settings with a high TB/HIV burden because our study participants are representative of a prototypical population for whom ICF is recommended.

Our study also has limitations. First, we chose to study patients with advanced HIV initiating ART because TB risk is highest and the need for ICF greatest in this population. Additional studies of POC CRP-based TB screening are needed to confirm our findings among other HIV subgroups, especially as the median CD4 count at ART initiation rises over time. Second, CD4 counts were available for all patients in our study. CD4 counts would need to be available to implement POC CRP-based ICF algorithms inclusive of TB-LAM testing. Third, patients who tested TB-LAM positive did not go on to Xpert testing. Settings with high rates of multidrug-resistant TB should consider the added value of Xpert-based rifampin susceptibility testing in patients who test positive by TB-LAM. Lastly, we did not perform additional tests to confirm or rule-out extrapulmonary TB, which may impact accuracy estimates, or evaluate formally the relative cost of each ICF algorithm.

In summary, our findings have important implications for global TB/HIV public health policy. First, consideration should be given to revising the WHO recommendation for ICF to replace symptom-based screening with POC CRP-based TB screening among PLHIV with CD4 counts less than or equal to 350 cells/μl initiating ART. This change would considerably reduce the costs of ICF without significantly reducing yield. Second, as the largest study to evaluate TB-LAM in the context of clinic-based ICF, we believe that our findings provide the strongest and most definitive evidence to date to support the use of a confirmatory testing strategy inclusive of TB-LAM for HIV-infected clinic attendees with CD4 count less than or equal to 100 cells/μl. Following scale-up of an ICF algorithm inclusive of POC CRP-based TB screening and TB-LAM and Xpert confirmatory testing, HIV programs should consider reallocating costs saved to include more sensitive confirmatory tests, such as culture for patients who screen positive but test negative by TB-LAM and/or Xpert. In summary, these results clearly demonstrate the need for more targeted selection of PLHIV for intensive confirmatory TB testing. POC CRP and TB-LAM are simple, inexpensive, and available POC tools that could limit the proportion of PLHIV requiring confirmatory testing to a smaller subset of high-risk individuals and increase the speed of TB diagnosis, respectively. These tests are important tools for ICF and should be immediately scaled-up to reduce the burden of TB among PLHIV in resource-limited settings. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the patients and staff of the Mulago Hospital Joint AIDS Program Immune Suppression Syndrome Clinic and The AIDS Support Organization.

References

1. World Health Organization. Global Tuberculosis Report. Geneva, Switzerland: WHO; 2017 [accessed 2018 May 27]. Available from: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1.
2. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. *AIDS* 2015;29:1987–2002.
3. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland: WHO; 2011 [accessed 2018 May 27]. Available from: http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.pdf.
4. World Health Organization. Systematic screening for active tuberculosis: principles and recommendations. Geneva, Switzerland: WHO; 2013 [accessed 2018 May 27]. Available from: http://www.who.int/tb/tbscreening/en/.
5. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, *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:e1000391.
6. Kufa T, Mngomezulu V, Charalambous S, Hanifa Y, Fielding K, Grant AD, *et al*. Undiagnosed tuberculosis among HIV clinic attendees: association with antiretroviral therapy and implications for intensified case finding, isoniazid preventive therapy, and infection control. *J Acquir Immune Defic Syndr* 2012;60:e22–e28.
7. Hanifa Y, Fielding KL, Charalambous S, Variava E, Luke B, Churchyard GJ, *et al*. Tuberculosis among adults starting antiretroviral therapy in South Africa: the need for routine case finding. *Int J Tuberc Lung Dis* 2012;16:1252–1259.
8. Ahmad Khan F, Verkuijl S, Parrish A, Chikwava F, Ntumy R, El-Sadr W, *et al*. Performance of symptom-based tuberculosis screening among people living with HIV: not as great as hoped. *AIDS* 2014;28:1463–1472.
9. Swindells S, Komarow L, Tripathy S, Cain KP, MacGregor RR, Achkar JM, *et al*.; AIDS Clinical Trials Group 5253 Study Team. Screening for pulmonary tuberculosis in HIV-infected individuals: AIDS Clinical Trials Group Protocol A5253. *Int J Tuberc Lung Dis* 2013;17:532–539.
10. Yoon C, Semitala FC, Atuhumuza E, Katende J, Mwebe S, Asege L, *et al*. Point-of-care C-reactive protein-based tuberculosis screening for people living with HIV: a diagnostic accuracy study. *Lancet Infect Dis* 2017;17:1285–1292.
11. Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A, Vogt M, *et al*. Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. *PLoS Med* 2011;8:e1001067
12. Al-Darraji HA, Abd Razak H, Ng KP, Altice FL, Kamarulzaman A. The diagnostic performance of a single GeneXpert MTB/RIF assay in an intensified tuberculosis case finding survey among HIV-infected prisoners in Malaysia. *PLoS One* 2013;8:e73717.
13. World Health Organization. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. Geneva, Switzerland: WHO; 2014 [accessed 2018 May 27]. Available from: http://www.who.int/tb/publications/tpp_report/en/.
14. Shah M, Ssengooba W, Armstrong D, Nakiyingi L, Holshouser M, Ellner JJ, *et al*. Comparative performance of urinary lipoarabinomannan assays and Xpert MTB/RIF in HIV-infected individuals. *AIDS* 2014;28:1307–1314.
15. Nakiyingi L, Moodley VM, Manabe YC, Nicol MP, Holshouser M, Armstrong DT, *et al*. Diagnostic accuracy of a rapid urine lipoarabinomannan test for tuberculosis in HIV-infected adults. *J Acquir Immune Defic Syndr* 2014;66:270–279.
16. Huerga H, Ferlazzo G, Bevilacqua P, Kirubi B, Ardizzoni E, Wanjala S, *et al*. Incremental yield of including Determine TB-LAM assay in diagnostic algorithms for hospitalized and ambulatory HIV-positive patients in Kenya. *PLoS One* 2017;12:e0170976.
17. Lawn SD, Kerkhoff AD, Burton R, Schutz C, Boulle A, Vogt M, *et al*. Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort. *BMC Med* 2017;15:67.
18. Lawn SD, Kerkhoff AD, Vogt M, Wood R. Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. *Lancet Infect Dis* 2012;12:201–209.
19. Floridia M, Ciccacci F, Andreotti M, Hassane A, Sidumo Z, Magid NA, *et al*. Tuberculosis case finding with combined rapid point-of-care assays (Xpert MTB/RIF and Determine TB LAM) in HIV-positive individuals starting antiretroviral therapy in Mozambique. *Clin Infect Dis* 2017;65:1878–1883.
20. Peter J, Theron G, Chanda D, Clowes P, Rachow A, Lesosky M, *et al*.; TB-NEAT team. Test characteristics and potential impact of the urine LAM lateral flow assay in HIV-infected outpatients under investigation for TB and able to self-expectorate sputum for diagnostic testing. *BMC Infect Dis* 2015;15:262.
21. Yoon C, Semitala FC, Asege L, Katende J, Mwebe S, Andama AO, *et al*. Yield and efficiency of novel intensified tuberculosis case-finding algorithms for people living with HIV [abstract]. *Am J Respir Crit Care Med* 2018;197:A5380.
22. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, *et al*.; STARD Group. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015;351:h5527.
23. World Health Organization. The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV. Policy guidance. Geneva, Switzerland: WHO; 2015 [accessed 2018 May 27]. Available from: http://apps.who.int/iris/bitstream/10665/193633/1/9789241509633_eng.pdf?ua=1&ua=1.
24. StataCorp. Stata statistical software: release 13. College Station, TX: StataCorp LP; 2013.
25. Dorman SE, Schumacher SG, Alland D, Nabeta P, Armstrong DT, King B, *et al*.; study team. Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis* 2018;18:76–84.
26. Chihota VN, Grant AD, Fielding K, Ndibongo B, van Zyl A, Muirhead D, *et al*. Liquid vs. solid culture for tuberculosis: performance and cost in a resource-constrained setting. *Int J Tuberc Lung Dis* 2010;14:1024–1031.