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Yield and efficiency of intensified tuberculosis case-finding algorithms in two high-risk HIV subgroups in Uganda

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Abstract

Background: Tuberculosis (TB) risk varies among different HIV subgroups, potentially impacting intensified case finding (ICF) performance. We evaluated the performance of the current ICF algorithm (symptom screening, followed by Xpert MTB/RIF [Xpert] testing) in two HIV subgroups and evaluated whether ICF performance could be improved if TB screening was based on C-reactive protein (CRP) concentrations.

Methods: We enrolled consecutive adults with CD4 counts ≤350 cells/uL initiating antiretroviral therapy (ART) and performed symptom screening, CRP testing using a low-cost point-of-care (POC) assay, and collected sputum for Xpert testing. We compared the yield and efficiency of the current ICF algorithm to POC CRP-based ICF among patients new to HIV care and patients engaged in care.

Results: Of 1794 patients, 126/1315 (10%) new patients and 21/479 (4%) engaged patients, had Xpert-positive TB. The current ICF algorithm detected ≥98% of all TB cases in both subgroups but required ≥85% of all patients to undergo Xpert testing. POC CRP-based ICF halved the proportion of patients in both subgroups requiring Xpert testing relative to the current ICF algorithm, and had lower yield among patients engaged in care (81% vs. 100%, difference −19% [95% CI: −41 to +3]). Among patients new to care, POC CRP-based ICF had similar yield as the current ICF algorithm (93% vs. 98%, difference −6% [95% CI: −11 to 0]).

Conclusion: Among patients new to care, POC CRP-based screening can improve ICF efficiency without compromising ICF yield while symptom-based screening may be necessary to maximize ICF yield among patients engaged in care.

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Keywords

Point of Care C-reactive protein; Tuberculosis; screening Algorithm; HIV subgroups

Introduction

Tuberculosis (TB) remains the leading cause of HIV death, accounting for one-third of all HIV deaths worldwide.[1] To reduce TB burden, the World Health Organization (WHO) recommends intensified case finding (ICF) - symptom screening, followed by Xpert MTB/RIF (Xpert) confirmatory testing - for all people living with HIV (PLHIV) at every clinic visit.[2] However, PLHIV constitute a heterogeneous population with respect to TB risk. Patients new to HIV care represent an HIV subgroup with higher TB prevalence and increased mortality risk, frequently due to undiagnosed TB.[3–6] These results suggest that in resource-limited settings, patients new to care should be prioritized for ICF and ICF should be rigorously implemented to maximize TB case detection. However, rigorous implementation of ICF may be associated with high rates of unnecessary Xpert testing due to the poor specificity of symptom-based TB screening, [4, 7–9] which may make routine implementation less likely.

Emerging literature suggests that replacing symptom screening with C-reactive protein (CRP) testing may improve the efficiency and reduce the costs of ICF.[10–14] Our prior work identified CRP [12–14] which can be measured from capillary blood using a rapid and low-cost point-of-care (POC) assay – as the first and only test thus far to meet the WHO target product profile for an effective TB screening test.[15] However, the yield and performance of POC CRP-based ICF among different HIV subgroups is unknown.

To provide routine HIV programs with the evidence needed to efficiently implement ICF, we compared the yield and efficiency of POC CRP-based ICF to the current ICF algorithm among patients new to HIV care and patients already engaged in HIV care. In addition, we also compared the yield and efficiency of symptom- and POC CRP-based ICF between the two HIV subgroups.

METHODS

Study population

Patient recruitment, study procedures, and the diagnostic accuracy of symptom-based and POC CRP-based TB screening in 1177 patients enrolled from July 2013 to December 2015 have been previously reported.[14, 16] Here, we present results on the full cohort of 1794 consecutive patients prospectively enrolled through December 2016 and compare the yield and efficiency of symptom- and POC CRP-based ICF in two sub-populations of PLHIV initiating ART from two urban HIV clinics in Kampala, Uganda: patients new to HIV care and patients engaged in care (pre-ART patients with ≥1 prior HIV clinic visit at the time of study entry). During the study period, the Uganda Ministry of Health revised their ART guidelines to adopt ‘universal test-and-treat’ which eliminated the requirement for repeated

pre-ART counseling visits (ART initiation decisions were based on CD4 count ≤500 cells/uL or other indications [*e.g.,* pregnancy, HIV serodiscordance]).

We enrolled ART-naïve adults (age ≥18 years) with a pre-ART CD4 count ≤350 cells/uL within three months of study enrollment. We excluded patients taking medication with anti-mycobacterial activity (anti-TB therapy, TB preventive therapy, fluoroquinolones) within three days of enrollment. All patients provided written informed consent and the study was approved by the Institutional Review Boards of the University of California, San Francisco, Makerere University, and the Uganda National Council for Science and Technology. This study conforms to the standards for the reporting of Diagnostic Accuracy Studies (STARD) initiative guidelines.[17]

Study procedures

Data collection and TB screening.—At enrollment, we collected standardized demographic and clinical data, including history of HIV clinic attendance; confirmed pre-ART status; administered the WHO symptom screen; and measured CRP concentrations from capillary blood using a standard sensitivity POC assay (BodiTech, South Korea). In accordance with WHO guidelines, we considered patients to be symptom screen positive if they reported ≥1 TB symptom (current cough, fever, night sweats, weight loss).[2] We defined a POC CRP concentration of ≥8 mg/L (rounding to the nearest whole-number) as screen positive for TB based on receiver-operating characteristics analysis performed in the parent study [14]

Sputum collection and testing.—We collected a spot sputum specimen from all participants at study entry for Xpert MTB/RIF (Cepheid, USA) testing. All staff performing Xpert testing were blinded to clinical and demographic data, including symptom screen status and POC CRP concentrations. We considered patients to have active TB if Xpert results were positive for *Mycobacterium tuberculosis.* Patients with indeterminate Xpert results underwent repeat Xpert testing with remaining sputum. We considered patients not to have active TB if Xpert results were negative.

Statistical analysis

We compared categorical and continuous variables using the Wilcoxon rank-sum test, Fisher's exact test, or chi-square test, as appropriate. To determine the diagnostic yield of symptom-based and POC CRP-based ICF for each HIV subgroup, we combined Xpert confirmatory testing to either symptom- or POC CRP-based screening. The diagnostic yield of each ICF algorithm is equal to the number of screen-positive patients who were diagnosed with Xpert-positive TB divided by the total number of Xpert-positive TB patients, irrespective of screening status. We compared differences in diagnostic yield using the unpaired test of two proportions. To determine the efficiency of each ICF algorithm, we determined the number needed to test (NNT) using Xpert to detect one TB case for each screening strategy and for each HIV subgroup. We performed all analyses using STATA13 (STATA, USA).

RESULTS

Study population

We prospectively enrolled 1,839 consecutive adults initiating ART and excluded 45 patients for the following reasons: 21 did not meet inclusion criteria, 21 had missing CD4 count results, and 3 had missing POC CRP results. Of the remaining 1,794 patients, 1315 (73%) were new to HIV care and 479 (27%) were already engaged in HIV care (Table 1). Compared to patients engaged in care, patients new to care had lower median CD4 cell counts, lower median BMI, and higher prevalence of Xpert-positive TB (10% vs. 4%, p<0.001). More patients new to care than engaged in care screened positive for TB by both symptoms (90% vs. 85%, p=0.01) and POC CRP (41% vs. 30%, p<0.001).

Performance of ICF algorithms among patients new to care.

The current ICF algorithm (symptom screening, followed by Xpert testing for all those who screen-positive) required 1178/1315 (90%) patients new to care to undergo Xpert testing and identified 124/126 (98%) of all Xpert-positive TB cases (Table 2A). Compared to the current ICF algorithm, POC CRP-based ICF reduced by more than half, the proportion of patients requiring Xpert testing (90% vs. 41%; difference −48%, [95% CI: −51 to −45]) and missed 7 more TB cases. Thus, POC CRP-based ICF required half as many Xpert assays to detect one TB case (NNT 5 vs. 10) while maintaining similar diagnostic yield (93% [117/126] vs. 98% [124/126], difference −6% [95% CI: −11 to 0]) as the current ICF algorithm.

Performance of ICF algorithms among patients engaged in care.

A similar pattern was observed among patients engaged in care. Compared to the current ICF algorithm, POC CRP-based ICF required half as many Xpert assays to detect one TB case (NNT 8 vs. 19) but had lower diagnostic yield (100% [21/21] vs. 81% [17/21], difference −19% [95% CI: −41 to +3]; Table 2B), though the difference in yield did not reach statistical significance. Compared to patients new to care, both symptom- and POC CRP-based ICF were less efficient, requiring almost twice as many Xpert assays to detect one TB case.

DISCUSSION

Although ICF was introduced in 2011 as the cornerstone of TB control activities for PLHIV, [2] there are few published data describing the yield of the current ICF algorithm in reference to Xpert, the confirmatory test used in the vast majority of settings with high TB burden. Therefore, to provide HIV program managers and country-level policymakers the evidence to support ICF scale-up using routine diagnostics, we compared the performance of two rigorously implemented ICF algorithms in reference to Xpert and compared ICF yield in two pre-ART HIV subgroups. We found that TB prevalence was high among all patients, but 2.5-times higher among patients new to care, highlighting the need for increased vigilance in this subgroup and the importance of avoiding unnecessary delays in ART initiation. We also found that the current ICF algorithm, when performed in strict accordance with TB/HIV guidelines,[2] detected nearly all (≥98%) TB cases but required most (≥85%) patients to undergo confirmatory testing with Xpert. In contrast, we found that POC CRP-based ICF

reduced by half the proportion of patients in both subgroups requiring Xpert confirmatory testing. Among patients engaged in care, the improved efficiency of POC CRP-based ICF came at the expense of lower diagnostic yield while POC CRP-based ICF had similar diagnostic yield as the current ICF algorithm among patients new to care. These results support the use of POC CRP-based ICF for all patients new to HIV care to improve the efficiency and reduce the cost of TB case detection.

A growing body of evidence suggests that using CRP to screen PLHIV for active TB could improve ICF efficiency.[10–14] Consistent with these studies, we found that POC CRP-based ICF could substantially reduce the proportion of PLHIV in both subgroups requiring Xpert confirmatory testing, relative to the current ICF algorithm. Among patients new to care, POC CRP-based ICF detected 93% of all TB cases, exceeding the 90% sensitivity target recommended by the WHO for an effective TB screening test. However, among pre-ART patients engaged in care, POC CRP-based ICF detected only 17/21 (81%) of all Xpert-positive TB cases. Although the number of TB cases in this subgroup was small, the reduced yield of POC CRP-based ICF in this HIV subgroup may have important implications for all PLHIV. First, the lower TB prevalence among pre-ART patients engaged in care suggests that prior to study enrollment, patients with active TB either died, had their TB diagnosed, or transferred or defaulted from care. Multiple studies have shown that patients waiting to initiate ART have higher rates of clinic attrition and mortality (frequently due to undiagnosed TB),[18, 19] stressing the importance of immediate ART and rigorous ICF when PLHIV are first presenting for care. Second, the reduced yield of POC CRP-based ICF is likely due to the selective loss of the sickest TB/HIV patients (those most likely to die or have their TB diagnosed) while awaiting ART initiation,[20] which may have significant implications for serial ICF. Because the accuracy of any test depends on the degree of prior testing in the population, the yield and efficiency of each repeat round of ICF can be expected to be lower than the last. Large well-powered studies are needed to evaluate whether lower POC CRP cut-points could improve the yield of POC CRP-based ICF, when applied to a population that has undergone prior TB screening.

Strengths of this study include 1) a large and well-characterized cohort that is prototypical of patients initiating ART in high TB/HIV burden countries; 2) implementation of ICF in accordance with a strict protocol and in reference to Xpert, thus providing HIV programs estimates of expected ICF yield in settings where culture is not routinely available; and 3) prospective measurement of CRP concentrations using an US FDA-approved, simple and low-cost POC assay that is available for immediate scale-up. Our study also has limitations. First, we restricted enrollment to ART-naïve patients with advanced HIV because TB risk is highest and the need for ICF is greatest in this population. Future studies of ICF yield are needed in HIV subgroups with lower TB risk. Second, the number of TB cases among pre-ART patients engaged in care is small, which may have impacted measured estimates. Third, while scale-up of HIV test-and-treat will eventually eliminate pre-ART patients engaged in care as an HIV subgroup, the lower TB prevalence and reduced ICF yield in this subgroup suggests that serial ICF can be expected to have lower yield among patients who have previously undergone TB screening. Fourth, some patients new to care may have been misclassified (patients may have received HIV care previously, which may have included prior TB screening) thus, the yield of ICF among patients new to care may be even greater

than reported here. Lastly, we evaluated the yield of symptom- and POC CRP-based ICF in reference to Xpert (standard cartridge); future studies of ICF yield should combine symptom- and POC CRP-based screening with more sensitive rapid diagnostics (*e.g.,* Xpert Ultra) to further expand the evidence base needed to support routine ICF scale-up.

In conclusion, high TB prevalence among patients initiating ART in high TB/HIV burden settings confirms the need for rigorous ICF and immediate ART, when patients first present for HIV care. POC CRP-based ICF at this critical time could improve the efficiency of ICF, thus, increasing the likelihood of ICF implementation, while maintaining similarly high diagnostic yield as the current ICF algorithm. POC CRP-based ICF should be prioritized for PLHIV new to HIV care, and where resources for Xpert testing are limited.

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Table 1.

Demographics and clinical characteristics of patients engaged and new to care.

Characteristic, N (%)	Total (N= 1794)	New to care (N=1315)	Engaged in care (N=479)	p-value
Age (years)	33 (27-40)	33 (27-40)	33 (27-40)	0.56
Female	941 (52%)	663 (50%)	278 (58%)	0.004
CD4 count (cells/μL)	157 (66-260)	147 (64-246)	196 (74-294)	<0.0001
BMI (kg/m^2)	21.0 (18.9-23.9)	20.9 (18.9-23.6)	21.4 (19.2-24.4)	0.004
Prior TB	60 (3%)	40 (3%)	20 (4%)	0.24
WHO symptom screen positive	1587 (88%)	1178 (90%)	409 (85%)	0.01
Cough	909 (51%)	685 (52%)	224 (47%)	0.05
Fever	936 (52%)	697 (53%)	239 (50%)	0.24
Night sweats	632 (35%)	467 (36%)	165 (34%)	0.68
Weight loss	1331 (74%)	1025 (78%)	306 (64%)	<0.001
Elevated POC CRP (≥8 mg/L)	687 (38%)	545 (41%)	142 (30%)	<0.001
POC CRP (mg/L)	4.0 (2.5-22.9)	4.3 (2.5-27.7)	3.6 (2.5-9.8)	0.07
Xpert-positive TB	147 (8%)	126 (10%)	21 (4%)	<0.001

Abbreviations: BMI (body mass index); TB (tuberculosis); WHO (World Health Organization); POC CRP (point-of-care C-reactive protein).

Legend: Median values (interquartile range [IQR]) presented for continuous variables.

Table 2A.

Performance of TB screening/Xpert-based ICF strategies among patients new to HIV care (N=1315).

	TB screening strategy		Difference (95% CI)
	WHO symptom screen	POC CRP	
% (#) Screen-positive	90% (1178)	41% (545)	−49%
95% CI	88-92%	39-44%	(−51 to −45%)
% (#) Xpert positive cases detected among screen-positive patients (n=126)	98% (124)	93% (117)	−6%
95% CI	94-100%	87-97%	(−11 to 0)
# of Xpert assays per TB case detected	10	5	--

Abbreviations: TB (tuberculosis); ICF (intensified case finding); WHO (World Health Organization); POC CRP (point-of-care C-reactive protein); CI (confidence interval).

Table 2B.

Performance of TB screening/Xpert-based ICF strategies among patients engaged in HIV care (N=479).

	TB screening strategy		Difference (95% CI)
	WHO symptom screen	POC CRP	
% (#) Screen-positive	85% (409)	30% (142)	−55%
95% CI	82-88%	26-34%	(−51 to −61%)
% (#) Xpert-positive cases detected among screen-positive patients (n=21)	100% (21)	81% (17)	−19%
95% CI	84-100%	58-95%	(−41 to +3)
# of Xpert assays per TB case detected	19	8	--

Abbreviations: TB (tuberculosis); ICF (intensified case finding); WHO (World Health Organization); POC CRP (point-of-care C-reactive protein); CI (confidence interval).

Legend: Compared to patients new to care (Table 2A), the current ICF algorithm had higher diagnostic yield (98% [95% CI: 94-100] vs. 100% [95% CI: 84-100], difference +2% [95% CI: +0.8 to +2]) and POC CRP-based ICF had lower higher diagnostic yield (93% [95% CI: 87-97] vs. 81% [95% CI: 58-95], difference −12% [95% CI: −19 to −5]).