Published in final edited form as:

J Acquir Immune Defic Syndr. 2016 November 01; 73(3): e46–e50. doi:10.1097/QAI.0000000000001142.

Population-based active TB case finding during large-scale mobile HIV testing campaigns in rural Uganda

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Abstract

Background.—Active TB screening outside of clinics and in communities may reduce undiagnosed TB disease.

Methods.—To determine yield of TB screening during community-based HIV testing campaigns (CHC) in seven rural Ugandan communities within an ongoing cluster randomized trial of universal HIV testing and treatment (SEARCH, NCT:01864603), we offered sputum microscopy to participants with prolonged cough (>2 weeks). We determined the number of persons needed to screen to identify one TB case, and the number of cases identified that linked to clinic and completed TB treatment.

Results.—Of 36,785 adults enumerated in seven communities, 27,214 (74%) attended CHCs, and HIV testing uptake was >99%, with 941 (3.5%) HIV-infected adults identified. 5,786 (21%) adults reported cough, and 2,876 (11%) reported cough >2 weeks. Staff obtained sputum in 1,099/2,876 (38%) participants with prolonged cough, and identified 10 adults with AFB-positive sputum; 9 new diagnoses, and one known case already on treatment. The number needed to screen to identify one new TB case was 3,024 adults overall: 320 adults with prolonged cough, and 80 HIV-infected adults with prolonged cough. All nine newly diagnosed AFB+ participants linked to TB care within 2 weeks and initiated TB treatment.

Conclusions.—In a rural Ugandan setting, TB screening as an adjunct to large-scale, mobile HIV testing campaigns provides an opportunity to increase TB case detection.

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Conflicts of Interest: None of the authors have any conflicts of interest.

Introduction

Tuberculosis (TB) and HIV are the leading causes of death due to an infectious disease globally.¹ In East Africa, TB remains a major cause of death despite effective antibiotics, due in part to diagnostic delay and under-diagnosis.^{1–4} Late or non-presentation to health facilities is one major cause of under-diagnosis that contributes to ongoing transmission and persistently high mortality rates.^{5,6} Shifting TB screening out of health facilities and into communities, or “active” case finding, may reduce delays in TB diagnosis and undiagnosed disease.^{7,8} However, how best to perform active TB case finding, and whether patients found through active case finding will complete TB treatment at rates similar to facility-diagnosed TB patients, are unresolved questions.⁹

Similarly, earlier diagnosis of HIV-infected persons is needed to maximize the benefits of effective treatment for both individual health and prevention of transmission. Out-of-facility testing strategies are recognized as an effective method for identifying undiagnosed, HIV-infected persons.¹⁰ With global efforts both to increase HIV testing coverage (with an ambitious goal of 90% of HIV-infected persons knowing their HIV status)¹¹ and to screen HIV-infected persons for TB disease, incorporating TB screening into large-scale, out-of-facility HIV testing approaches may provide an efficient means of increasing TB and HIV diagnosis. In addition, population-based surveys from sub-Saharan Africa have found a large range (29–5000) in the number needed to screen to identify one new case of TB¹², and data from rural settings are lacking. We therefore sought to determine the yield of TB screening during population-based, multi-disease community health campaigns that incorporated universal HIV testing in rural Uganda, and to evaluate the TB treatment outcomes of TB cases identified in the campaigns.

Methods

From 2013–14, seven rural communities in eastern Uganda that are enrolled in an ongoing 32 community cluster-randomized trial of universal HIV testing and treatment in Uganda and Kenya (SEARCH, NCT:01864603), incorporated TB screening services into population-wide HIV testing activities. In each community, study staff worked with local leaders to perform a baseline census enumeration of all residents that included digital fingerprint biometric measurements and to mobilize the community for a subsequent large-scale multi-disease community health campaign (CHC).¹³ The seven communities were chosen from the 32 SEARCH Trial communities based on community input into “add-on” services desired at the health campaigns. Local leaders reached out to their communities to provide information about the multi-disease services available at the CHC, including TB screening.

Two-week mobile, multi-disease CHCs were conducted in partnership with the Uganda Ministry of Health (MoH), at well-known, convenient community locations one month after the study census. HIV screening services included rapid, finger prick-blood based HIV antibody testing and counseling (HTC) for all persons 18 months of age using MoH testing algorithms, followed by point-of-care CD4⁺ T cell count measurement (PIMA, Inverness Medical) and referral to HIV care if HIV-infected. Non-HIV services provided included screening for TB, hypertension and diabetes, malaria rapid diagnostic testing for participants

with fever, male condom distribution, and Vitamin A and de-worming treatment (albendazole) for young children. Fingerprint biometrics were used to verify resident status and record CHC attendance; if fingerprint matching failed, name-based matching was used.¹³

For TB screening, all adult (≥ 15 years old) residents that participated in the CHC were asked about current cough, and if present, whether the cough had lasted for more than 2 weeks, consistent with WHO guidelines.¹⁴ HIV-infected persons identified at the CHC underwent additional clinical symptom screening upon linkage to HIV care in the SEARCH Trial; the data presented here are restricted to our findings from the CHC. CHC participants with prolonged cough (>2 weeks) were then asked to provide two spot sputum samples at the CHC in sterile specimen cups, along with a mobile phone contact number. Participants were asked to produce sputum by spontaneous expectoration; induction was not offered. CHCs were outdoor events, and participants provided sputum in a private, designated collection area away from study staff and other campaign participants. All samples were transported to a study laboratory set up at the local government health center for fluorescence microscopy within 1–2 hours of collection, for same-day evaluation. Acid-fast bacilli (AFB) smear results were recorded according to smear grade by IUATLD/WHO standards.¹⁵

Study staff contacted any participants with positive sputum microscopy results within 24 hours of specimen collection by mobile phone. If a participant could not be reached or did not own a phone, study staff attempted to contact them daily by mobile phone or home visits during the 12 days of CHC activities. Once a participant was contacted, he/she was asked to come to the local health center for evaluation and TB treatment initiation. AFB smear-positive participants that could not be reached by phone (or lacked a phone) were visited at home and asked to come to the local health center for further evaluation and treatment. All participants with prolonged cough were counseled to follow-up at the health center in one week if their symptoms of prolonged cough did not resolve, or worsened, even if a TB diagnosis was not made. No clinical diagnoses (i.e. sputum smear negative TB diagnoses) were made at the CHC.

The number of adult campaign participants needed to screen with symptom and sputum evaluation to detect one new AFB smear-positive TB case was determined overall, and by HIV status. We also determined the proportion of TB cases identified that linked to the local government-run health center, and that initiated and completed TB treatment. The number of cases identified at CHCs was compared to the number of adult AFB smear-positive TB cases diagnosed in all local TB clinics in the year prior to the CHC, as recorded in each community in a standardized, Uganda MoH TB registry. Lastly, we compared basic demographic characteristics of AFB+ cases identified by CHCs vs. local TB clinics in the year before the CHC.

Statistical Analyses

Proportions were compared with a χ^2 test or Fischer's exact test, as appropriate. Multivariate logistic regression was used to identify characteristics associated with obtaining sputum among adults reporting prolonged cough at the campaign. Independent variables included age, sex, and HIV.

Ethics Statement

The Makerere University School of Medicine Research and Ethics Committee and the Ugandan National Council on Science and Technology (Uganda), and the Kenya Medical Research Institute Ethical Review Committee (Kenya), and the University of California San Francisco Committee on Human Research approved the consent procedures and the study. All participants provided informed consent in their preferred language.

Results

A total of 36,785 adult residents (≥ 15 years old) were enumerated during the baseline census in the seven communities. Of enumerated adults, 27,214 (74% [range 70–79% across communities]) attended the CHCs. The median age of adult CHC participants was 30 years (interquartile range [IQR]: 20–45), and 15,489 (57%) of participants were women. CHC-based HIV testing uptake was 26,813/27,214 (99%), with 941 (3.5%) HIV infected adults identified. Median CD4 cell count was 474 cells/μL (IQR: 320–665).

At the time of CHC participation, 5,786 (21%) adults reported a cough, and 2,876 (11%) adults reported a prolonged cough (>2 weeks). The proportion of adults reporting prolonged cough increased with age (15–24 years old: 8%; 25–34: 9%; 35–44: 11%; 45–54: 12%; 55–64: 15%; and ≥ 65: 22%), and was greater in women than men (11.4% vs. 9.5% respectively, $p < 0.001$), and in HIV-infected (17%) than uninfected (10%, $p < 0.001$) adults. Staff obtained sputum in 1,099/2,876 (38%) CHC participants with prolonged cough; 62% of participants with prolonged cough were unable to expectorate sputum. Among adults with prolonged cough, success in obtaining a sputum sample was greater in older adults (average age if sputum obtained: 45 years, vs. 34 years if sputum not obtained; t -test: $p < 0.001$), and in HIV-infected adults (sputum obtained in 53% of HIV-infected vs. 37% of HIV-uninfected adults with prolonged cough; χ^2 test: $p < 0.001$). Among adults with prolonged cough, characteristics significantly associated with obtaining sputum in multivariate logistic regression analysis included older age (aOR=1.2, 95% CI: 1.1–1.2, $p < 0.001$, for each ten year age category above 15–24 years of age) and HIV infection (aOR=1.9, 95% CI: 1.4–2.7, $p < 0.001$), but not sex (aOR=0.94, 95% CI: 0.8–1.1, $p = 0.4$).

Ten adults with AFB-positive sputum were identified at the CHCs; three were HIV-infected (Table 2). One of the three HIV-infected adults with AFB-positive sputum was newly diagnosed with HIV at the campaign. Nine were new TB diagnoses (9/27,214 [0.03%; 95% CI: 0.02–0.06%]), and one (an HIV-infected adult) was already on TB treatment at the local health center prior to attending the CHC. Six of the nine newly diagnosed AFB-positive cases had a smear grade of 3+ on at least one sputum specimen, and three had scanty AFB smear positive specimens. Eight of the 10 AFB-positive cases had two AFB-positive sputum samples, and two had one AFB-positive and one negative sputum sample.

Overall, the new TB diagnosis yield of sputum screening was 9/2,876 (0.31%; 95% CI: 0.14–0.59%) among adult CHC participants reporting prolonged cough. The number needed to screen with symptoms and microscopy to identify one new TB case was 3,024 (27,214/9; 95% CI: 1,593–6,614). The number needed to screen with microscopy to identify one new TB case was 320 (95% CI: 169–698) among all adults with a prolonged cough, and 80 (95%

CI: 23–659) among HIV-infected adults with a prolonged cough (see Table 1). Among CHC participants with prolonged cough that were able to produce sputum (1,099), the number needed to screen to identify one new TB case was 122 (95% CI: 65–267). All nine newly diagnosed, AFB smear-positive adults linked to TB care and initiated TB treatment. Six of the nine (67%) adults initiated on TB treatment successfully completed therapy. One adult failed treatment and started second line therapy, one was lost to follow up, and one died of trauma prior to completing TB treatment.

In the one year prior to each community's campaign, a total of ten adult, AFB-positive TB cases were identified in all local TB clinics. Basic demographic and clinical characteristics of the CHC-diagnosed vs. the clinic-diagnosed TB cases are shown in Table 2.

Discussion

Our data suggest that coupling population-based HIV and TB screening within a multi-disease health campaign approach provides an innovative method to increase detection of smear-positive TB cases while rapidly increasing HIV testing coverage. The burden of undiagnosed TB disease and the number needed to screen to identify one new TB case are within the ranges of prior estimates from TB prevalence surveys in sub-Saharan Africa.^{9,12} With international efforts to increase HIV testing coverage in sub-Saharan Africa,¹¹ community-based approaches to rapidly scale up HIV testing can also serve as an effective platform to increase TB detection.

The traditional approach to TB detection using facility-based TB case finding, even when properly implemented with directly observed therapy, has failed to sufficiently reduce TB incidence in settings with a high HIV prevalence.^{16,17} Resource-rich settings use active, out-of-facility, case-finding strategies, such as household contact investigation, to reduce morbidity and ongoing TB transmission by identifying and treating patients with TB infection or disease early.^{18,19} Despite the potential of active TB case finding to increase TB case detection and reduce TB incidence, optimal strategies for active case finding in areas such as sub-Saharan Africa with higher TB incidence and fewer resources remain unknown.⁹ Population-wide TB case finding approaches, including community TB education and door-to-door home screening, have met with mixed success.^{7,20,21} Multi-disease community health campaigns have been shown to rapidly increased HIV testing coverage at a community level and provide a novel platform for active TB case finding.

Although the absolute number of HIV-TB cases identified with the CHC-based approach was few, combination screening may allow for improved coordination of HIV and TB linkage to care and treatment, including prompt antiretroviral therapy initiation following TB treatment start. Interestingly, the yield of TB screening was greater in HIV-infected than uninfected adult participants, even though sputum microscopy is relatively less sensitive in HIV-infected vs. uninfected persons. This may be a result of the significantly increased risk of TB in HIV-infected persons, and the relatively high CD4⁺ cell count at HIV diagnosis with community-based HIV testing,¹⁰ as the proportion of HIV/TB cases with AFB-positive sputum is greater at higher CD4⁺ counts.²²

Despite the potential advantages of active TB case finding, there are several unresolved questions regarding its effectiveness. One potential concern is the possibility that TB cases identified outside of clinics may be less likely to complete TB therapy than those who present to health clinics for evaluation, as persons “actively” diagnosed with TB may be less symptomatic.⁹ In the rural communities studied, the TB cases identified at CHCs were as likely to complete TB treatment as cases identified at local TB clinics. Another unresolved question is the impact of active case finding on TB transmission.^{7,20} Although our data do not address TB transmission, more than half (6/9) of the TB patients diagnosed at the CHC had a high smear grade, and as such, may have been highly contagious to others.

The study has several limitations. First, the TB screening tools used are relatively insensitive compared with culture or PCR-based assays.^{20,23} Microscopy is also non-specific, and without culture confirmation we cannot exclude the possibility that some of the smear positive samples represented non-tuberculous mycobacteria. In addition, a significant proportion of campaign participants with prolonged cough (62%) were unable to produce sputum. Some studies have suggested that obtaining two same-day spot sputum samples (“front-loading”) may result in decreased sensitivity compared to a standard approach of collecting sputum over two to three days for TB diagnosis,²⁴ although a systematic review found no difference between these two approaches.²⁵ Finally, we based our symptom screening approach (cough >2 weeks) on WHO guidelines for mass screening, rather than the four-symptom screen recommended for HIV-infected adults,²⁶ as the majority of persons screened at the CHC were HIV-uninfected. All of these factors likely decreased our ability to diagnose TB. However, these screening tools were selected to facilitate mass screening over a short time period (particularly as culture is costly and not routinely available in eastern Uganda), along with other disease services, and to identify highly contagious (i.e. AFB smear-positive and coughing) patients. Second, though the assessment of facility-based TB case identification relied on government registry data from all local TB clinics, we cannot exclude the possibility that some community members received TB diagnosis and treatment outside of the local clinics, resulting in underestimation of facility-based diagnosis. Finally, the cost-effectiveness of this approach remains to be determined. However, the incremental costs associated with adding TB symptom and sputum microscopy screening is likely to be relatively small, compared to the cost of large-scale HIV testing.²¹

In conclusion, our multi-disease community health campaign approach provided an opportunity to increase TB case detection and treatment and to reduce the burden of undiagnosed TB disease in rural Uganda, in the context of population-wide, HIV testing scale-up.

Acknowledgements

We thank the residents of the study communities for their generous participation in our study. We also thank the Uganda National TB Reference Laboratory and the Uganda Ministry of Health.

Source of Funding: This work was supported by grants from the National Institute of Allergy and Infectious Diseases (UM1AI069502 and U01AI099959; D.V.H.) at the National Institutes of Health and by the President’s Emergency Plan For AIDS Relief, the Office of the Global AIDS Coordinator, and the Office of AIDS Research.

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Table 1.

Yield of large-scale, multi-disease Community Health Campaign (CHC)-based TB screening, stratified by HIV status of campaign participants.

Adult CHC participants N=26,813*	HIV+ (N=941)	%	HIV- (N=25,802)	%	p-value
Cough	258	27%	5,426	21%	<0.001
Cough >2 weeks	160	17%	2,665	10%	<0.001
	Screened for TB with microscopy (N=160)		Screened for TB with microscopy (N=2665)		
Sputum obtained	85	53%	980	37%	<0.001
AFB Smear+	3	3.5%	7	0.7%	0.01
New TB Diagnosis	2	2.4%	7	0.7%	0.088
Number of adults with cough >2 weeks needed to screen with sputum microscopy to detect one new AFB smear+ case	80		381		
Number of adults needed to screen with cough screening & sputum microscopy to detect one new AFB smear+ case	471		3,686		

* 70 adults had indeterminate HIV test results and are not included in the table. None of the AFB smear+ cases had indeterminate HIV test results.

Table 2.

Comparison of sputum microscopy (acid fast bacilli [AFB]) positive, adult TB cases identified at large-scale community health campaigns, vs. in local clinics in the 12 months prior to the campaign, in the seven study communities in rural eastern Uganda.

	CHC-Identified AFB+ Cases	%	Clinic-Identified AFB+ Cases	%
N	9		10	
HIV+	2	22%	4	40%
Female	6	67%	3	30%
Mean age	45		40	
Completed Treatment	6	67%	4	40%
Treatment Failure	1	11%	-	0%
Incomplete Treatment	2 *	22%	-	0%
Unknown Outcome	-	0%	6	60%

* 1 lost to follow-up, and 1 died of traumatic injury