# Serial Clinical Screening for Active Tuberculosis among HIV-infected Kenyan Adults

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*Authors' contributions*

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## ABSTRACT

**Setting:** Urban, non-governmental HIV outpatient clinic in Mombasa, Kenya.
**Objective:** To report outcomes and assess feasibility of serial clinical screening for active TB among adults enrolled in outpatient HIV care in a resource-limited setting.
**Design:** Longitudinal analysis of screening conducted during routine clinic visits of HIV-infected Kenyan adults. The provider-initiated screen included TB symptom assessment and targeted physical exam. Participants with >1 symptom/sign were to submit sputum for microscopy and undergo chest radiography.
**Results:** Over 33 months, 4,854 HIV-infected outpatients were serially screened for active

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TB at a median interval of 3 months. Treatment for active TB was started in 127 (2.6%). Of those 127, 77 (60.6%) were diagnosed based on first screen, and 50 (39.4%) were diagnosed thereafter. Among those 50 diagnosed upon subsequent screens, 28 (56%) were identified in association with positive screens, suggesting that 22% (28 of 127) of TB diagnoses could be attributed to the serial screening protocol.

**Conclusion:** Provider-initiated serial clinical screening during routine visits of HIV-infected outpatients continued to prompt treatment of active TB beyond initial screening. Serial screening strategies may lead to earlier TB treatment in patients receiving ongoing HIV care in resource-limited settings.

## 1. INTRODUCTION

Globally, 1.1 million new cases of tuberculosis (TB) were diagnosed in HIV-infected individuals in 2012; 75% of these occurred in sub-Saharan Africa [1]. In Kenya, 2012, 39% of TB cases occurred among HIV-infected individuals [2]. HIV infection and active TB disease doubles mortality risk compared to infection with HIV alone [3].

The World Health Organization (WHO) recommends implementing intensified TB case finding (ICF), isoniazid preventive therapy (IPT), and TB infection control to reduce the burden of TB among HIV-infected persons living in high burden countries [4]. ICF refers to efforts by the health care system "to identify and bring into treatment people with TB who have not sought diagnostic services" [5]. One method of ICF is provider-initiated symptom screening for active TB infection among HIV-infected individuals undergoing routine care. Kenyan national public health guidelines have stipulated ICF for TB in all patients with HIV [6].

Multiple studies have documented the efficacy of ICF and have sought to determine optimal methods for conducting ICF in resource-limited settings [7-22]. These studies provide insight into which combinations of signs or symptoms included in TB screening forms are most predictive of active TB infection, and the extent of added value of obtaining acid fast bacilli (AFB) smear tests and chest radiographs [8,11-17,21]. Despite WHO recommendations to perform symptom screens on HIV patients at each clinic visit [23], no study, to our knowledge, has examined the added value of serial symptom screening in ICF protocols in routine outpatient settings.We describe the results of integrating ICF into care in a busy urban HIV outpatient clinic in Kenya and the utility of serial screening as measured by the incidence of active TB diagnoses made by health care workers.

## 2. METHODS

### 2.1 Setting and Study Population

This longitudinal study was conducted between January 2007 and September 2009 at Bomu Medical Center, an urban, non-governmental outpatient clinic that provides general medical, antenatal and TB services to the residents of Mombasa, Kenya. In 2004, the HIV care and treatment center at Bomu became a US President's Emergency Plan for AIDS Relief (PEPfAR)–funded site with New York University as the technical advisor. The HIV care and

treatment center had 10,532 adult patients in care by the end of 2009 (including 3,000 on antiretroviral therapy [ART]).

Physician or clinical officers routinely evaluated patients at clinic visits that occurred every three to six months. Microscopy laboratory and radiology facilities were located on-site. Mycobacterial culture was not available. Radiographs were read by treating clinicians; difficult cases were referred to a radiologist at a local private hospital. The laboratory participated in the Kenyan national external quality assessment program for AFB sputum smear analysis.

## 2.2 ICF Procedures

Using a clinical screening tool for active TB (Fig. 1) physicians and clinical officers screened all patients at each visit (new or follow-up), regardless of presenting symptoms, CD4+ cell count, WHO clinical stage, or whether they were on ART. Clinical screening for active TB was not intended for patients receiving anti-TB therapy or those already with a diagnosis of active TB. With a one-page form, clinicians asked patients about cough lasting for >2 weeks, fevers for >2 weeks, subjective weight loss in the last 4 weeks, and night sweats for >2 weeks. Clinicians were required to document presence of fever (≥38°C measured orally), abnormal lung findings, presence of lymphadenopathy, and weight loss since last visit. A positive clinical TB screen was defined as the presence of at least one of these symptoms or physical exam signs. Providers were instructed to refer patients with a positive screen to the laboratory for three AFB sputum smears and a chest radiograph. All diagnostic services were provided without cost to the patient, however transportation costs of return visits for additional sputum collections were not provided. Funding was allocated for the cost of anticipated increases in the number of laboratory tests and chest radiographs. Clinicians initiated TB treatment based on their clinical judgment.

**Bomu Medical Center TB Screening Form**

Perform chest x-ray and sputum AFB smear if patients have 1 or more of the following findings on history and physical exam:

| Date: | | | | | |
|---|---|---|---|---|---|
| **History**<br>Cough for >2 weeks? | √ **If YES** | | | | |
| Fevers for >2 weeks? | | | | | |
| Weight loss in the last 4 weeks? | | | | | |
| Night sweats for >2 weeks? | | | | | |
| **Physical Exam** | | | | | |
| Fever on exam? | | | | | |
| Abnormal lung exam? | | | | | |
| Lymphadenopathy? | | | | | |
| Weight loss since last exam? | | | | | |
| If yes, amount of weight lost? | ____kg | ____kg | ____kg | ____kg | |

**Fig. 1. Clinical screening form used for intensified case finding of active tuberculosis, Kenya**

## 2.3 Definitions, Analysis and Outcomes

Limited resources did not allow the use of sputum culture for confirmation of a case of active TB in this study and many patients did not receive the recommended diagnostic studies that were available. Thus, we measured the number of patients diagnosed with TB based on the initiation of a full course of TB treatment by health care workers. This approximates the WHO definition of a TB case [24], though was subject to misclassification. Thus, we restricted our outcome terminology to "TB diagnosis made by health care worker" rather than "TB case." We classified TB diagnoses into those that were more clearly made through the ICF protocol and those that were not based on whether TB treatment was started within six weeks following a positive clinical screen. The six-week cutoff was selected to represent a reasonable period in which diagnostic evaluation could be achieved after a positive clinical screen, and thus, a way to reasonably assume a relationship between the screen and the start of TB treatment. The face validity of this timeframe was substantiated through examination of the actual distribution of the intervals between screens and visit dates associated with starting TB treatment: there were no patients with an interval between screen and TB treatment start date from 37 to 75 days, and only nine patients with intervals from 76 to 348 days.

To calculate the incidence of active TB diagnoses made by health care workers potentially resulting from serial screening, we excluded all patients who were started on TB treatment the day of the first (baseline) clinical screen or within the subsequent six weeks. Persons who were not given TB treatment based on the first clinical screen were considered at risk for becoming an incident diagnosis. Their total time at risk from first screen to diagnosis of TB, or to the last visit in those not diagnosed with TB, was the denominator of the calculation of the incidence rate of TB diagnosed by health care workers.

Statistical analysis was performed with the "R" statistical environment version 2.10.1[25]. Chi-square and Fisher exact tests were used to assess the significance of differences in proportions between groups. Risk ratios and their 95% confidence intervals were calculated using R's Epitools package [26]. The Institutional Review Board at NYU School of Medicine and the Ethical Review Board at Kenyatta National Hospitals, Kenya, approved the study.

## 3. RESULTS

### 3.1 Screening Characteristics

During the study period, 4,854 patients received a total of 12,928 clinical screens for active TB. Of 4,854 patients, 1,638 (33.7%) were screened once, 1,049 (21.6%) twice and 2,167 (44.6%) three or more times during routine clinic visits (Fig. 2). The median interval between clinical screens was 85 days (Interquartile range [IQR]: 42-182 days). Among those screened, 1,374 individuals (28.3%) had at least one positive screen.

### 3.2 Prevalence of Active TB Diagnosed through ICF by Health Care Workers

Of the 4,854 patients screened through the ICF protocol, 127(2.6%) initiated TB treatment during the study period as a result of a health care worker's diagnosis. Among those, 77 individuals were considered to be prevalent diagnoses made through ICF because they were started on treatment based on their first clinical screen result (prevalence rate 1.6%).
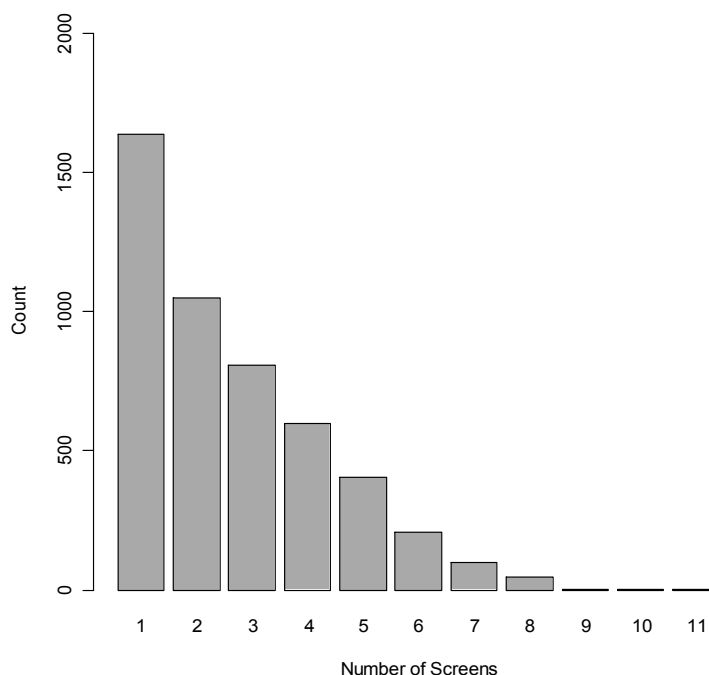
**Fig. 2. Number of clinical screens for active tuberculosis conducted among 4,854 HIV-infected Kenyan adults**

### 3.2 Incidence Rate of Active TB Diagnosed through ICF by Health Care Workers

Among the 4,777 individuals who were not started on treatment based on their first clinical screen and were followed for 981,998 person-days, 50 (1.0%) initiated TB treatment, an incidence rate of 1.86 TB diagnoses per 100 person-years (95% CI 1.38-2.45). Of those 50 patients who were identified as incident active TB diagnoses, 28 had associated positive clinical screens, suggesting that 22% of TB diagnoses (28 of total 127) could be attributed to the serial ICF protocol. The other 22 were treated for TB with no discernible relationship to a positive clinical screen. Thirteen of these 22 patients had a negative screen before TB treatment was started and 9 had a positive screen more than six weeks before treatment (range 76 to 348 days).

### 3.3 Clinical Features of Patients Started on TB Treatment in Association with Positive Clinical Screens

Among 1,374 patients who had a positive screen, 105 (7.6%) were treated within six weeks of the screen and therefore their diagnosis was attributable to the use of the TB screening tool (Fig. 3). Among these, 94 (89.5%) reported a history of cough, 76 (72.4%) reported weight loss, 73 (69.5%) reported fever and 59 (56.2%) reported night sweats. On examination, 42 (40%) had abnormal lung examination, 42 (40%) had fever, 36 (34.3%) had lymphadenopathy and 29 (27.6%) had objective weight loss. All clinical features were significantly predictive of starting TB treatment (Table 1). Diagnoses of active TB made through ICF had a median of 3 symptoms or signs at the time of the positive clinical screen.
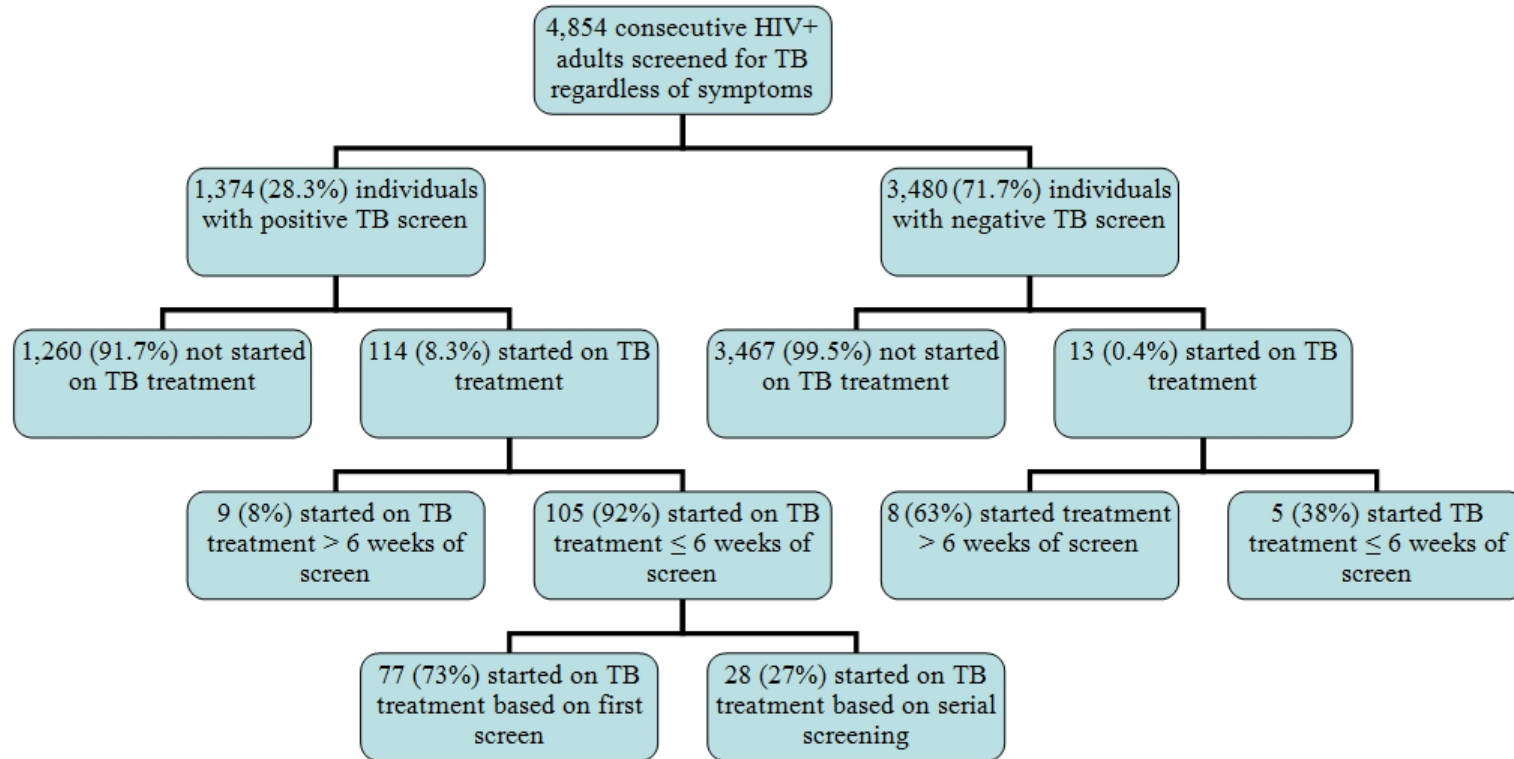
**Fig. 3. Flowchart of HIV-infected adults screened and treated for tuberculosis (TB) during 33 months of implementation of an intensified case finding (ICF) program, Kenya**

**Table 1. Risk ratios for TB treatment among HIV-infected adults for each symptom and sign included in the TB screening tool, Kenya, 2007-2009**

| Screen component | TB (n=105)[a] N (%) | No TB (n=12,823)[b] N (%) | Risk ratio | 95% CI |
|---|---|---|---|---|
| Cough for>2 weeks | 94 (90) | 801 (6) | 14.4 | 13.1-15.1 |
| Weight loss in the last 4 weeks | 76 (72) | 512 (4) | 18.2 | 15.7-26.7 |
| Fever for>2 weeks | 73 (70) | 393 (3) | 22.7 | 19.4-26.7 |
| Night sweats for>2 weeks | 59 (56) | 372 (3) | 19.4 | 16.0-23.6 |
| Fever on exam | 42 (40) | 160 (1) | 32.1 | 24.3-42.5 |
| Abnormal lung exam | 42 (40) | 134 (1) | 38.4 | 28.8-51.2 |
| Lymphadenopathy | 34 (32) | 171 (1) | 24.3 | 17.8-33.3 |
| Measured weight loss | 29 (28) | 659 (5) | 5.4 | 3.9-7.4 |

*Abbreviations: TB, tuberculosis, CI, confidence interval; [a] Patients started on TB treatment within 6 weeks of a positive screen; [b] All TB screens performed among 4,854 clinic patients*

## 3.4 Feasibility of Implementing Serial ICF

Of the 1,695 positive clinical screens from 1,374 patients, only 126 (7.4%) screens were followed by AFB smears and 263 (15.5%) by chest radiographs as stipulated by ICF protocol. A history of cough was the specific component of the screen most strongly related to having a follow-up chest radiograph and at least one AFB smear performed (RR=6.8, 95% CI=4.9-9.5). Rates of diagnostic tests performed were higher among patients who started TB treatment than in the overall population with positive clinical screens: of the 105 patients who started TB treatment in association with a positive clinical screen, AFB smears were performed in 44 (42.0%), and 65 (62.0%) had chest radiographs.

During focused feedback discussions with providers, laboratory personnel, and study staff, reasons identified for incomplete follow-up testing included: 1) inability of patients to produce sputum, 2) patients' unwillingness to go or wait in line for testing because they did not feel ill, 3) patients' fears that they would have to pay for the studies, 4) a failure to transfer results from source documents in the laboratory or radiology suite to the patient's medical record, 5) HIV positive patients are reluctant to stand in long queues for diagnostic tests as they prefer not be seen in the clinic due to prevailing stigma in the community, and 6) patients in our clinic come from poor socioeconomic background and are mostly casual workers, hence the longer they stay in the clinic, the greater the loss of income for the day and thus the reluctance to spend additional time at the clinic.

## 4. DISCUSSION

In this longitudinal study of integrating serial clinical screening for active TB in a Kenyan outpatient HIV clinic, we found that 22% of all patients who began treatment for active TB were treated in association with positive serially-conducted clinical screens, while the majority (60%) of patients were treated based on the first clinical screen. The remaining minority of patients treated for active TB were diagnosed independent of the clinical screen. This suggests that, in addition to baseline screening, serial clinical screening for outpatients undergoing routine HIV care can help to increase TB case detection in ICF programs in resource-limited settings. Though the incident TB diagnoses made using serial clinical screening may include patients who might have otherwise self-presented with symptoms at a later date, having a protocol to screen on every visit likely encouraged clinicians to "think TB"

rather than ignore non-specific symptoms. Thus, serial clinical screening may have resulted in earlier initiation of TB treatment than would otherwise have occurred, which has important implications for TB control programs.

Patients with incident TB diagnosed through serial screening likely fall into one of five categories: first, patients with subclinical tuberculosis at the time of initial screening who later progressed to symptomatic TB disease; second, patients with recent acquisition of TB; third, patients with TB unmasked by immune-reconstitution syndrome (IRIS) after ART initiation; four, patients with overlooked symptoms or signs of TB at the first screen; and five, misdiagnoses. We were unable to further delineate our incident diagnoses into these categories because we did not conduct routine sputum cultures, did not have access to TB exposure history, and did not have data on timing of ART initiation.

Few studies of ICF have examined outcomes of integrating serial clinical screening for active TB in HIV-infected individuals in resource-limited settings [10], and none in an outpatient clinic setting. In a study of a clinical TB screening tool at an ART home-based program in Uganda, TB incidence during 1.4 median years after the first three months of ART was 2.4 per 100 person-years, however, frequency of screening was not reported [10].

The prevalence of TB in our study, defined as new TB diagnoses made upon first time clinical screening during ICF, was lower (1.6%) than prior ICF studies in HIV-infected, resource-constrained clinic populations [8,11]. In a meta-analysis of 78 studies of ICF in resource-limited settings, median prevalence of new TB diagnoses as a result of ICF was 8.6% in HIV clinics in sub-Saharan Africa (range 3.6-24.7%) [8]. The lower rate of prevalent TB disease found in our study may reflect a true lower-risk population or, more likely, reflects a lower effectiveness of the ICF strategy at our site. Many ICF studies have been conducted in the context of cohort studies or controlled trials of screening interventions [9,12-16] and therefore, the efficacy of ICF may be higher compared to the real-life setting represented in our study. Similar to a recent evaluation of ICF in Swaziland that observed nearly half of screened patients were lost to follow up before diagnostic tests could be completed, [27] we found it significantly challenging to obtain sputum AFB and chest radiograph in the vast majority of patients with a positive TB screen. Thus, a substantial proportion of active TB may have been missed by our health care workers due to the incomplete implementation of the ICF protocol.

Other challenges may have limited the effectiveness of the ICF strategy. The introduction of ICF into the clinic led to higher workload in the laboratory and radiology departments. Funding increases for additional personnel did not occur. This led to poor communication between the clinician and these services. Results were frequently recorded in the primary source documents in the laboratory and radiology suite, but were not documented in the patient chart, preventing the treating clinician from making decisions based on those results.

Further limitations of this study may have led to miscalculation of true prevalence and incidence of tuberculosis within our population. We lacked resources to establish bacteriologically confirmed cases of TB as a gold standard*,* and were limited to measuring TB diagnosis rates based on the decision of health care workers to initiate TB treatment. This was the standard of care in Kenya and in line with the WHO definition, but is subject to misclassification. In addition, the clinical screening tool used in this study included the symptom of chronic cough rather than current cough. Recently, current cough was found to be a more sensitive indicator of TB disease in HIV patients than chronic cough; [11,23] thus our tool may have missed some TB diagnoses.

## 5. CONCLUSION

Provider-initiated serial clinical screening conducted during routine visits of HIV-infected outpatients approximately every three months prompted treatment of active TB in the majority of incident diagnoses made beyond baseline screening. Thus, serial screening for signs and symptoms of active TB may be useful if integrated into routine HIV care where patients are followed over time and remain at risk for active TB. Such screening may reduce the time to treatment in patients with HIV and active TB disease in resource-limited settings. Operational challenges in obtaining follow-up diagnostic studies after positive screens may reduce effectiveness of serial ICF. In addition, future studies can include screening for multiple symptoms which may have a greater specificity.

## 6. SOURCES OF FUNDING

## CONSENT

This study utilized data that are routinely collected by the study site for service delivery and were de-identified for analysis.

## ETHICAL APPROVAL

This study was approved by the Institutional Review Board of New York University School of Medicine, New York and the Ethical Review Committee of Kenyatta National Hospital, Nairobi, Kenya.

## ACKNOWLEDGMENTS

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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