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Intensive Tuberculosis Screening for HIV-Infected Patients Starting ART in Durban, South Africa

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Abstract

Background—The World Health Organization (WHO) recommends cough as the trigger for tuberculosis (TB) screening in HIV-infected patients, with acid fast bacillus (AFB) smear as the initial diagnostic test. Our objective was to assess the yield and cost of a more intensive TB screening in HIV-infected patients starting antiretroviral therapy (ART) in Durban, South Africa.

Methods—We prospectively enrolled adults, regardless of TB signs/symptoms, undergoing pre-ART training from May '07–May '08. Following symptom screen, patients expectorated sputum for AFB smear, TB polymerase chain reaction (PCR), and mycobacterial culture. Sensitivity and specificity of different symptoms and tests, alone and in combination, were compared to a gold standard of 6-week TB culture results. Program costs included personnel, materials and cultures.

Results—Of 1,035 subjects, 487 (59%) were female; median CD4 count was 100/μl. Two-hundred and ten (20%) were receiving TB treatment and were excluded. Of the remaining 825 subjects, 158 (19%) had positive sputum cultures, of whom 14 (9%) had a positive AFB smear and 82 (52%) reported cough. The combination of cough, other symptoms, AFB smear, and chest x-ray had 93% (CI 88–97%) sensitivity and 15% (CI 13–18%) specificity. The incremental cost of intensive screening including culture was $360/**additional** TB case identified.

Conclusions—Nearly 20% of patients starting ART in Durban, South Africa had undiagnosed, culture-positive pulmonary TB. Despite WHO recommendations, neither cough nor AFB smear

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were adequately sensitive for screening. TB sputum cultures should be performed before ART initiation, regardless of symptoms, in areas of high HIV/TB prevalence.

Keywords

Tuberculosis; South Africa; WHO guidelines

Introduction

The African continent, which contains only 15% of the world's population, accounts for nearly a third of the global burden of tuberculosis (TB) and TB-related deaths. The rate of new TB cases has tripled since 1990; an estimated 2.8 million new TB cases and 639,000 TB-related deaths occur in Africa annually [1–3]. South Africa has the third highest TB incidence in the world, with 948 cases per 100,000 people per year [3]; the overall adult HIV prevalence is approximately 20% [4]. Further, the risk of developing TB is 20 times higher in HIV-infected Africans than in those without HIV, and is the leading cause of death among HIV-infected patients [3].

Despite the overwhelming and often deadly interaction between these two diseases, the South African Department of Health estimates that only ~25% of HIV-infected people in care were screened for TB in 2006 [5]. Current World Health Organization (WHO) guidelines recommend cough of 2–3 weeks duration as a trigger for screening ambulatory HIV-infected patients, with acid fast bacillus (AFB) sputum smear as the sole recommended screening test at the initial visit [6]. The problem of accurate and timely pulmonary TB diagnosis is hampered, however, by the unreliability of cough-based screening alone, the atypical clinical presentation in many HIV-infected patients, and the high rates of smear negative disease [7, 8].

HIV-infected patients may require a more aggressive screening approach that does not rely solely on cough as a trigger for further TB testing. Our objective was to evaluate the yield and diagnostic accuracy of an intensive pulmonary TB screening strategy compared to current WHO screening guidelines.

Methods

We evaluated the yield of an intensive TB screening strategy using cough, other TB symptoms, AFB smear, and sputum polymerase chain reaction (PCR), compared to mycobacterial culture, in all HIV-infected patients starting antiretroviral therapy (ART) at an HIV clinic in Durban, South Africa. We compared this intensive TB screening strategy with the current WHO recommendation of cough as a trigger for TB screening in ambulatory HIV-infected patients. We assessed the sensitivity, specificity, predictive value and likelihood ratio of individual as well as combinations of tests. We also estimated the incremental cost of the intensive TB screening program compared to cough-based screening.

Study setting

McCord Hospital is a state-aided, semi-private hospital in an urban setting. The Sinikithemba HIV clinic at McCord has been treating patients with ART since 1999; in 2004, the clinic became a US President's Emergency Plan for AIDS Relief (PEPFAR)-funded site which enabled it to rapidly expand its clinical care services. The HIV clinic serves a predominantly African, Zulu-speaking population and has initiated over 7,000 patients on ART [9]. HIV-infected patients with CD4 count ≤200/μl or who meet clinical criteria (WHO Stage 3 or 4) are given a date to commence ART literacy training. The clinic trains approximately 80–120 new patients per month [10], including educational sessions,

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clinical evaluation and baseline laboratory work. Patients are evaluated by a physician following the second training session. HIV-infected patients with TB at McCord are treated on-site according to South African treatment guidelines [11]. The TB notification rate in the province is ~1000 cases/100,000 [12].

Study sample

Patients eligible for this prospective cohort study included adults (≥18 years) commencing ART literacy training from May 2007-May 2008. Consecutive HIV-infected ambulatory patients were offered enrollment prior to physician evaluation, regardless of signs or symptoms of active TB, during the ART training period. A small proportion (9%) of subjects, equally distributed with respect to TB diagnosis, transferred care to Sinikithemba and were already on ART at enrollment; they were included in the analysis.

The study was approved by the McCord Hospital Research Ethics Committee [Durban, South Africa] and the Partners Human Research Committee [Protocol 2007-P-000228, Boston, MA, USA].

Data collection

A trained research nurse enrolled patients undergoing ART literacy training and baseline laboratory investigations. The nurse administered a 12-item questionnaire, including demographic data, TB symptom history, as well as current and prior HIV and TB treatment. Patients were asked specifically about recent cough of any duration, as well as other TB symptoms including self-reported fever, night sweats, weight loss, chest pain or dyspnea. All patients expectorated a single sputum specimen spontaneously or with ultrasonic nebulization (single-use tubing). Subjects who could not expectorate were given a sputum specimen cup and returned with an early morning specimen. All sputum samples were stained to assess for AFB, and were processed for *Mycobacterium tuberculosis* culture and PCR.

A trained nurse, pre-medical student or investigator performed a chart review for each participant to ascertain additional baseline data from the initial clinical evaluation, including a more extensive history related to TB, other opportunistic infections, as well as chest x-ray (CXR) and laboratory results. CXRs are part of the routine baseline evaluation and were interpreted by treating clinicians in the HIV clinic and documented in the patient chart.

Laboratory methods

Specimens were transported on a daily basis to the collaborative TB laboratory of the University of KwaZulu-Natal and the South African Medical Research Council in Durban. Sputa were decontaminated using the N-acetyl-L-cysteine sodium hydroxide method and then inoculated onto Middlebrook 7H11 solid agar medium and mycobacterial growth indicator (MGIT; Becton Dickinson, Franklin Lakes, NJ, USA) tubes. Microscopy was performed using both Ziehl-Neelsen and Auramine stains complete with positive and negative controls to assess for the presence of acid-fast bacilli. Agar plates were read at 3 and 6 weeks while on a 6-week incubation cycle. MGIT broths were incubated in the automated Bactec MGIT 960 (Becton Dickinson) instrument. Final identification of positive cultures as *Mycobacterium tuberculosis* was performed using niacin and nitrate testing.

Decontaminated specimens were tested by PCR for the presence of the IS6110 region of *Mycobacterium tuberculosis* using the QIAmp DNA mini kit (Qiagen, Germantown, MD, USA). The presence of *Mycobacterium tuberculosis* was established by a 123 bp band present at the target site.

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Statistical methods

The outcomes of interest included the prevalence of previously undiagnosed TB and the sensitivity and specificity of an intensive TB screening strategy including cough, any of the other TB symptoms, AFB smear, CXR, and TB PCR. Six-week TB culture results (liquid and/or solid) served as the gold standard. We also examined the optimal TB screening strategy using different combinations of these symptoms and tests to maximize sensitivity and specificity, and compared these combinations to the WHO cough-based screening strategy. Ninety-five percent confidence intervals around sensitivity and specificity estimates were calculated using the binomial distribution. We calculated the positive predictive value (PPV), negative predictive value (NPV), likelihood ratio positive (LR+) and likelihood ratio negative (LR−) for each combination.

An additional outcome was the incremental cost of the intensive screening strategy compared to the WHO cough-based strategy for HIV-infected patients. We assessed program costs (2007 US$) for the intensive TB screening program, including clinic nurse salary, specimen collection materials (tubing and cups), and mycobacterial smear and cultures. PCR screening was excluded from the cost estimates because it is not routinely available as an alternative to AFB testing. The subset of patients who described cough at study entry was then analyzed separately to estimate the cost of the WHO recommended cough-based screening.

The incremental cost per case of TB identified in the intensive program was calculated as follows:

$$[(cost\ of\ intensive\ TB\ screening\ program\ -\ cost\ of\ cough-based\ screening)/(number\ of\ TB\ cases\ identified\ in\ intensive\ TB\ screening\ program\ -\ number\ of\ TB\ cases\ identified\ in\ cough\ based\ screening\ program)]$$

Results

Cohort characteristics

During the one-year study, 1,035 patients were enrolled and had complete TB culture results. This study sample represents approximately 90% of adult patients who underwent ART literacy training at Sinikithemba during the study period. Median CD4 count was 100/μl (range 48–159/μl). One-hundred sixty-seven (16%) required nebulized sputum induction. Approximately one-quarter of the patients reported a prior history of TB. Two-hundred ten (20%) patients were already on TB treatment at the time of study enrollment and were excluded from further analyses. Of the remaining 825 patients, 96% were Black African; the median age was 36 years and 59% were female (Table 1). One-hundred fifty-eight (19%) had culture evidence of previously undiagnosed active pulmonary TB (Figure 1).

Performance characteristics of individual screening tests

Cough and other symptoms—The sensitivity of cough alone for the diagnosis of TB was 52% (95% CI 44–60); the specificity of cough was 63% (95% CI 59–66, Table 2). The proportion of subjects with cough who had TB (i.e. positive predictive value of cough) was 25%; the negative predictive value of cough was 85%. Other TB symptoms (aside from cough) had a sensitivity of 72% (95% CI 64–79) and a specificity of 44% (95% CI 40–48), with PPV (23%) and NPV (87%) similar to cough. Sensitivity for individual symptoms was lower than for the combination of other TB symptoms (see Appendix Table A1). The LR+ for cough was 1.39; the LR− was 0.77. The LR+ for other TB symptoms was 1.28; the LR− was 0.64.

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AFB smear—Of the 158 patients with a positive TB sputum culture, only 14 had a positive AFB smear. The sensitivity of AFB smear was 9% (95% CI 4–13) and the specificity was 99.7% (95% CI 98.9–100). The PPV was 88%; AFB smear was the only test to have a LR+ larger than 1.7 (29.5) (Table 2).

Chest X-ray (CXR)—Eighty-three percent of patients with positive TB sputum cultures had **any** abnormality recorded by the evaluating physician on CXR compared to 65% of patients with negative sputum cultures. CXR alone had a sensitivity of 83% (95% CI 75–89) and a specificity of 35% (95% CI 31–39) for the diagnosis of active pulmonary TB. The PPV was only 22% in this study, however, the NPV of CXR was 90% (i.e. 90% of subjects with negative CXR did not have pulmonary TB). The LR+ was 1.27; the LR− was 0.49.

Polymerase Chain Reaction (PCR)—The sensitivity of PCR for the diagnosis of TB was 50% (95% CI 42–58) and the specificity was 70% (95% CI 67–74). The PPV was 29% and the NPV was 86%. The LR+ was 1.68; the LR-was 0.71.

Performance characteristics of combinations of screening tests

The combination of cough and AFB smear, the WHO-recommended TB screening tools at first visit for HIV-infected ambulatory patients, had a sensitivity of 56% (95% CI 48–63) and a specificity of 62% (95% CI 59–66). Table 2 show the sensitivity and specificity of selected combinations of screening tests and illustrates the trade-off between these measures of performance (results stratified by CD4 ≤ 100/μl and CD4 >100/μl are available in the Appendix). The most sensitive combination of tests available at a baseline assessment includes cough or any other symptoms or AFB smear or CXR. This combination had a sensitivity of 93% (95% CI 89–98), but a poor specificity of 15% (95% CI 12–18). The addition of PCR to this test combination improved the sensitivity slightly, to 96% (95% CI 93–99%), without improvement in specificity (11%, 95% CI 8–13). All test combinations have a likelihood ratio close to 1.0, indicating minimal impact of the test results on the post-test odds of disease.

Costs

The overall cost of screening all enrolled patients not on TB treatment at study entry, regardless of symptoms, including personnel time, specimen collection materials, and mycobacterial cultures was $47,000 or $57/patient. The cost for screening only those with cough was $20,000. The cost per pulmonary TB case identified with intensive TB screening was $300. The cost per pulmonary TB case identified, screening patients with only cough using smear and mycobacterial cultures, was $240. The incremental cost (cost per added case identified beyond those with cough alone) to identify all cases of active TB, was an additional $360 per case.

Discussion

We assessed the yield and diagnostic accuracy of intensive TB screening, regardless of symptoms, among ART-eligible patients at a high-volume, urban HIV clinic in Durban, South Africa. The severe state of immune suppression of the cohort initiating ART, with a median CD4 count of 100/μl, is similar to that seen in other resource-limited settings [13]; this puts patients at very high risk for TB and its complications. We found an enormous TB burden; 20% of study subjects were already on TB treatment at the time of starting ART literacy training, and this study identified an additional 19% of the remaining patients with culture evidence of previously undiagnosed pulmonary tuberculosis. These findings are consistent with observations from the Gugulethu outpatient ART program in Cape Town,

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where prevalent TB was present in 25% of patients and was associated with a greater than two-fold **excess** mortality risk over 3 years [14].

Though current WHO guidelines for TB evaluation in ambulatory patients in high HIV prevalence settings use cough of 2–3 weeks duration as the trigger for obtaining an AFB smear, in this study neither cough, nor sputum AFB alone, nor the combination, were adequately sensitive to be an effective screening tool [6]. Though cough as a screening trigger and AFB smear as the initial test was the most specific combination (specificity 62%), the goal of a screening strategy must also maximize sensitivity to avoid false negative results [15]. Only 9% of subjects with positive sputum cultures for TB had a positive AFB smear. This is despite the fact that samples were induced with hypertonic saline when necessary, were sent to an experienced research laboratory, and both ZN and Auramine staining techniques were performed to improve the yield of microscopy [16, 17]. Because smear-negative disease is both more common and more fatal among the HIV-infected [18, 19], the development of improved rapid TB diagnostic tests or the use of cultures is of paramount importance.

A paucity of classic symptoms in HIV-infected patients at the time of TB diagnosis has been documented in other studies using active case finding, including in a population-based survey in Cape Town, South Africa [20] and a clinic-based study in Dar es Salaam, Tanzania [7]. The symptom screen in the current study improved the sensitivity of baseline tests available for TB diagnosis, but was inadequate as the sole trigger for further TB screening (sensitivity 72%, negative predictive value 87%). A recent Ugandan study in HIV-infected patients starting ART revealed a high sensitivity and negative predictive value for the presence of several baseline factors (one of cough ≥ 3 weeks, fever ≥ 4 weeks, lymphadenopathy, or reduced body mass index) [21]; this study population had a much lower TB prevalence and included physical examination data that the current study did not. In the current study, the most sensitive strategies included a baseline CXR; the addition of baseline CXR to symptom screening and AFB smear has shown improved sensitivity of TB diagnosis in other African settings with high HIV prevalence [22, 23]. However, the most sensitive combinations of screening tools had very low specificity (15%), such that relying solely on tests available at baseline would lead to many patients being treated for TB who do not have the disease, incurring unnecessary toxicity and costs.

Adding a rapid, sensitive and specific TB screen to the care provided to all HIV-infected patients at entry into care could have a major impact on both diagnosis and clinical outcomes. PCR testing has previously shown promise as a means of detecting TB rapidly and reliably, even when sputum smear microscopy is negative. In low HIV prevalence settings, the sensitivity of PCR for smear-positive and smear-negative TB is 97–100% and 53–91% [24–26]. A small study of the performance of PCR in an area of TB endemnicity and high HIV prevalence in Kenya yielded a sensitivity of 86% and a specificity of 90% on the first sputum sample [27], however, the sensitivity and specificity of nucleic acid amplification techniques for the diagnosis of TB has been low and highly variable across studies [28, 29]. In the current study, PCR had a sensitivity of only 50%. This may reflect the high rate of smear-negative and asymptomatic disease, and that all subjects evaluated were HIV-infected. The addition of PCR to other baseline screening tools, including cough, other TB-related symptoms, CXR, and AFB smear only minimally improved the sensitivity of these diagnostic tests to detect TB. The GeneXpert, a single-use sample-processing cartridge system with same-day results, has the potential to greatly simplify PCR testing and has shown promising results in a small study [30].

Compared to screening based on cough, intensive screening with AFB smear and culture, regardless of symptoms, doubles the number of TB cases identified with only a modest

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increase in cost per case identified. Given the extremely high burden of disease in this population, the incremental cost per case of identifying all 158 cases beyond those with cough was $360. In the absence of a widely available, rapid and sensitive TB diagnostic test for HIV-infected patients, in a middle income country such as South Africa with high HIV prevalence and increasing TB reporting rates [3], intensive TB screening using cultures is likely feasible in most settings.

This study has several limitations. Data on some of the “warning signs” used by the WHO to classify patients as fitting into the ambulatory TB diagnostic algorithm, such as documented fever and respiratory rate [6], were not available. This may bias the results against the use of symptoms. However, patients were ambulatory and self-presented for care at the outpatient clinic; therefore the majority likely met the WHO definition. This study likely underestimates the overall burden of active TB because the study focused only on screening for pulmonary TB. Two sputum specimens would have increased the sensitivity of culture for the diagnosis of TB and potentially minimized the risk of cross-contamination [20]. Although only a single specimen was available, sensitivity was increased somewhat by using both solid and liquid culture media [31]. The McCord Hospital HIV clinic is a semi-private site where patients pay a monthly fee for HIV care; the results may not be generalizable to Department of Health sites where care is free of charge and where many HIV-infected South Africans are treated. Department of Health clinics may have even higher rates of HIV/TB co-infection, as patients who seek free care may live in more crowded settings.

This study points to the need to dramatically lower the threshold for TB screening and to improve screening diagnostic capacity for HIV-infected people living in TB endemic areas. While a combination of signs and symptoms and diagnostic tests available at initiation of ART is sensitive for the detection of pulmonary TB, the very low specificity limits the utility of this combination. Given the enormous burden of TB disease, the high mortality rates among HIV-infected people with smear negative TB, and the suboptimal accuracy of symptoms as a trigger for further screening, increasing laboratory capacity for performing mycobacterial cultures and rapid TB diagnostics is imperative. Active screening for TB with sputum microscopy and culture upon entry into care, regardless of symptoms, should be considered in populations such as those in South Africa, where TB and HIV are both common and deadly.

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References

1. United Nations, Department of Economic and Social Affairs, Population Division. [Accessed 24 December 2009.] World Population Prospects: The 2006 Revision, Highlights, Working Paper No. ESA/P/WP.202. 2007. Available at: http://www.un.org/esa/population/publications/wpp2006/English.pdf
2. Lawn SD, Bekker LG, Middelkoop K, Myer L, Wood R. Impact of HIV infection on the epidemiology of tuberculosis in a peri-urban community in South Africa: the need for age-specific interventions. Clin Infect Dis. 2006; 42(7):1040–7. [PubMed: 16511773]

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3. World Health Organization. [Accessed 24 December 2009.] Global tuberculosis control: a short update to the 2009 report. Available at http://www.who.int/tb/publications/global_report/2009/update/tbu_9.pdf
4. [Accessed 24 December 2009.] Epidemiological Country Profile on HIV and AIDS: South Africa. 2008. Available at:<http://www.who.int/globalatlas/predefinedReports/EFS2008/short/EFSCountryProfiles2008_ZA.pdf>
5. Republic of South Africa Department of Health. [Accessed 24 December 2009.] Tuberculosis strategic plan for South Africa: 2007–2011. Available at: http://www.doh.gov.za/docs/index.html
6. World Health Organization. [Accessed 24 December 2009.] Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings. Available at: http://www.who.int/tb/publications/2006/tbhiv_recommendations.pdf
7. Mtei L, Matee M, Herfort O, et al. High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. Clin Infect Dis. 2005; 40(10):1500–7. [PubMed: 15844073]
8. Perkins MD, Roscigno G, Zumla A. Progress towards improved tuberculosis diagnostics for developing countries. Lancet. 2006; 367(9514):942–3. [PubMed: 16546544]
9. Ojikutu BO, Zheng H, Walensky RP, et al. Predictors of mortality in patients initiating antiretroviral therapy in Durban, South Africa. S Afr Med J. 2008; 98(3):204–8. [PubMed: 18350223]
10. Bassett IV, Wang B, Chetty S, et al. Loss to care and death before antiretroviral therapy in Durban, South Africa. J Acquir Immune Defic Syndr. 2009; 51(2):135–9. [PubMed: 19504725]
11. Republic of South Africa Department of Health. [Accessed 24 December 2009.] The South African national tuberculosis control programme practical guidelines. 2004. Available at: http://www.kznhealth.gov.za/chrp/documents/Guidelines/Guidelines%20National/Tuberculosis/SA%20TB%20Guidelines%202004.pdf
12. South African Department of Health. [Accessed 18 March 2010.] Notification System. Pretoria. Downloaded from Health Systems Trust. Available at: http://www.hst.org.za/healthstats/16/data
13. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet. 2006; 367(9513):817–24. [PubMed: 16530575]
14. Lawn SD, Myer L, Bekker LG, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. AIDS. 2006; 20(12):1605–12. [PubMed: 16868441]
15. Nielsen C, Lang RS. Principles of screening. Med Clin North Am. 1999; 83(6):1323–37. [PubMed: 10584597]
16. Bell DJ, Dacombe R, Graham SM, et al. Simple measures are as effective as invasive techniques in the diagnosis of pulmonary tuberculosis in Malawi. Int J Tuberc Lung Dis. 2009; 13(1):99–104. [PubMed: 19105886]
17. Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis. 2006; 6(9):570–81. [PubMed: 16931408]
18. Kang'ombe CT, Harries AD, Ito K, et al. Long-term outcome in patients registered with tuberculosis in Zomba, Malawi: mortality at 7 years according to initial HIV status and type of TB. Int J Tuberc Lung Dis. 2004; 8(7):829–36. [PubMed: 15260273]
19. Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. AIDS. 2001; 15(2):143–52. [PubMed: 11216921]
20. Wood R, Middelkoop K, Myer L, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. Am J Respir Crit Care Med. 2007; 175(1):87–93. [PubMed: 16973982]
21. Were W, Moore D, Ekwaru P, et al. A simple screening tool for active tuberculosis in HIV-infected adults receiving antiretroviral treatment in Uganda. Int J Tuberc Lung Dis. 2009; 13(1):47–53. [PubMed: 19105878]

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22. Bakari M, Arbeit RD, Mtei L, et al. Basis for treatment of tuberculosis among HIV-infected patients in Tanzania: the role of chest x-ray and sputum culture. BMC Infect Dis. 2008; 8:32. [PubMed: 18325120]

23. Shah S, Demissie M, Lambert L, et al. Intensified tuberculosis case finding among HIV-Infected persons from a voluntary counseling and testing center in Addis Ababa, Ethiopia. J Acquir Immune Defic Syndr. 2009; 50(5):537–45. [PubMed: 19223783]

24. Cohen RA, Muzaffar S, Schwartz D, et al. Diagnosis of pulmonary tuberculosis using PCR assays on sputum collected within 24 hours of hospital admission. Am J Respir Crit Care Med. 1998; 157(1):156–61. [PubMed: 9445294]

25. Rajalahti I, Vuorinen P, Nieminen MM, Miettinen A. Detection of Mycobacterium tuberculosis complex in sputum specimens by the automated Roche Cobas Amplicor Mycobacterium Tuberculosis Test. J Clin Microbiol. 1998; 36(4):975–8. [PubMed: 9542919]

26. Wang SX, Tay L. Evaluation of three nucleic acid amplification methods for direct detection of Mycobacterium tuberculosis complex in respiratory specimens. J Clin Microbiol. 1999; 37(6): 1932–4. [PubMed: 10325349]

27. Kivihya-Ndugga L, van Cleeff M, Juma E, et al. Comparison of PCR with the routine procedure for diagnosis of tuberculosis in a population with high prevalences of tuberculosis and human immunodeficiency virus. J Clin Microbiol. 2004; 42(3):1012–5. [PubMed: 15004046]

28. Kambashi B, Mbulo G, McNerney R, et al. Utility of nucleic acid amplification techniques for the diagnosis of pulmonary tuberculosis in sub-Saharan Africa. Int J Tuberc Lung Dis. 2001; 5(4): 364–9. [PubMed: 11334256]

29. Ling DI, Flores LL, Riley LW, Pai M. Commercial nucleic-acid amplification tests for diagnosis of pulmonary tuberculosis in respiratory specimens: meta-analysis and meta-regression. PLoS ONE. 2008; 3(2):e1536. [PubMed: 18253484]

30. Helb D, Jones M, Story E, et al. Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. J Clin Microbiol J. 48(1):229–37.

31. Lee JJ, Suo J, Lin CB, Wang JD, Lin TY, Tsai YC. Comparative evaluation of the BACTEC MGIT 960 system with solid medium for isolation of mycobacteria. Int J Tuberc Lung Dis. 2003; 7(6):569–74. [PubMed: 12797700]

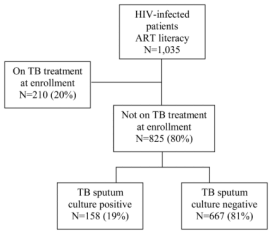

Figure 1. Flow chart of study population, Sinikithemba HIV clinic, McCord Hospital, Durban, South Africa, 2007–2008

A schematic of HIV-infected participants undergoing ART literacy training at the HIV clinic who were screened, enrolled, and diagnosed with pulmonary TB by sputum culture. ART: antiretroviral therapy; TB: Tuberculosis

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Table 1

Baseline characteristics of patients with no TB and TB by sputum culture in Durban, South Africa, 2007–2008*

Characteristic	No TB N=667 (%)	TB N=158 (%)	Overall N=825
Demographic characteristics			
Female	403 (60)	85 (54)	488 (59)
Employed	341 (51)	85 (54)	426 (52)
Married	139 (21)	26(16)	165 (20)
Age, in years, median (IQR)	36 (31–43)	37 (31–43)	36 (31–43)
HIV-related characteristics			
Baseline CD4 count/μl, median (IQR)	105 (49–162)	81 (46–131)	100 (48–159)
WHO Stage 3 or 4	381 (57)	106 (67)	487 (59)
History of OI	334 (50)	75 (47)	409 (50)
On ART at study entry	57 (9)	14 (9)	71 (9)
Other clinical characteristics			
Hospitalized in last 5 years	179 (27)	31 (20)	210 (25)
Prior history of TB	187 (28)	33 (21)	220 (27)
Household member with history of TB	154 (23)	35 (22)	189 (23)
Baseline hemoglobin, median (IQR)	11.6 (10.1–13.1)	10.3 (8.5–12.0)	11.4 (9.8–12.9)
Baseline weight, kg, median (IQR)	63.7 (54.7–75.0)	57.6 (50.7–66.0)	62.5 (54.0–74.4)
Current or past smoker	173 (26)	52 (33)	225 (27)
Cough	250 (37)	82 (52)	332 (40)
Other symptoms†	372 (56)	113 (72)	485 (59)
AFB smear **positive**	2 (0.3)	14 (9)	16 (2)
CXR documented abnormal	392 (65)	110 (83)	502 (68)
TB PCR **positive**	198 (30)	79 (50)	277 (34)

*Excludes 210 patients who were eligible for the study and screened but who were taking treatment for active TB at study entry.

†Other TB symptoms include any one of the following: fever, night sweats, weight loss, chest pain and dyspnea.

TB: Tuberculosis; IQR: Inter-quartile range; OI: Opportunistic infection; WHO: World Health Organization; ART: antiretroviral therapy; AFB: Acid Fast Bacillus smear; CXR: chest x-ray; PCR: polymerase chain reaction

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Table 2

Performance of symptoms, AFB smear, CXR, and TB PCR testing and combinations of these compared with TB culture for the diagnosis of pulmonary tuberculosis among HIV-infected adults undergoing ART literacy training in Durban, South Africa*

Diagnostic Procedure	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Positive Predictive Value (%)	Negative Predictive Value (%)	Likelihood Ratio Positive	Likelihood Ratio Negative
Single screening test						
Cough	52 (44–60)	63 (59–66)	25	85	1.39	0.77
Other TB symptoms*	72 (64–79)	44 (40–48)	23	87	1.28	0.64
AFB Smear	9 (4–13)	99.7 (99.2–100)	88	82	29.5	0.91
CXR	83 (76–89)	35 (31–39)	22	90	1.27	0.49
TB PCR	50 (42–58)	70 (67–74)	29	86	1.68	0.71
WHO recommendation						
Cough + AFB smear	56 (48–63)	62 (59–66)	26	86	1.48	0.71
Other combinations of screening tests with highest sensitivity and specificity, in order of increasing sensitivity						
Other symptom + AFB smear	76 (69–83)	44 (40–48)	24	89	1.36	0.54
Cough + other symptoms	78 (71–84)	37 (33–40)	23	87	1.23	0.60
Cough + other symptoms + AFB smear	81 (75–87)	36 (33–40)	23	89	1.28	0.52
AFB smear + CXR	83 (76–89)	35 (31–39)	22	90	1.27	0.49
Other symptoms + AFB smear + PCR	88 (83–93)	30 (26–33)	23	91	1.25	0.41
Cough + CXR	89 (83–94)	25 (22–29)	21	91	1.19	0.45
Cough + AFB smear + CXR	89 (83–94)	25 (22–29)	21	91	1.19	0.45
Cough + other symptoms + PCR	89 (85–94)	24 (21–28)	22	91	1.18	0.44
CXR + PCR	90 (85–95)	26 (22–29)	21	92	1.21	0.38
AFB smear + CXR + PCR	90 (85–95)	26 (22–29)	21	92	1.21	0.38
Other symptoms + CXR	92 (88–97)	18 (15–21)	20	92	1.13	0.42
Other symptoms + AFB smear + CXR	92 (88–97)	18 (15–21)	20	92	1.13	0.42
Cough + other symptoms + CXR	93 (89–98)	15 (12–18)	20	91	1.10	0.44
Cough + other symptoms + AFB smear + CXR	93 (89–98)	15 (13–18)	20	91	1.10	0.44
Cough + PCR + CXR	93 (89–98)	18 (15–22)	20	93	1.14	0.37
Cough + other symptoms + AFB smear + CXR + PCR	96 (93–99)	11 (8–13)	19	93	1.10	0.35

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AFB: acid fast bacillus smear; CXR: Chest x-ray; PCR: polymerase chain reaction

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