Tuberculosis among adults starting antiretroviral therapy in South Africa: the need for routine case finding

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ABSTRACT

Background: We investigated the prevalence of, and evaluated screening modalities for, undiagnosed tuberculosis in ART-eligible adults in South Africa.

Methods: Individuals were screened for tuberculosis using symptoms, chest radiograph and two sputum specimens for microscopy and culture, then followed for <6 months to determine tuberculosis diagnoses.

Results: Among 361 participants (67% female, median age 38, median CD4 count 120 cells/mm^3), 64/361 (18%) participants were sputum culture positive. 114 (32%) fulfilled any tuberculosis case definition (culture and/or smear positive; or improvement on specific treatment). A symptom screen comprising any of: cough or appetite loss or night sweats >2 weeks had sensitivity and specificity of 74.5% and 50.8% respectively. Sensitivity was increased by chest radiography (to 96.1%) but not by sputum microscopy. The WHO symptom screen had sensitivity and specificity of 96.1% and 5.2% respectively in our study population; addition of chest radiography increased sensitivity to 100%. Median time to TB treatment was 8 days for diagnoses based on chest radiograph (N=72), vs. 37 days for diagnoses based only on sputum culture (N=14).

Conclusions: The very high prevalence of undiagnosed tuberculosis among patients presenting for ART mandates their routine investigation. Chest radiography improved sensitivity substantially, allowed rapid treatment initiation and should be routine, where available, pending better point-of-care diagnostics.

INTRODUCTION

Tuberculosis remains a key cause of death among people with HIV[1] in sub-Saharan Africa despite wider use of antiretroviral therapy (ART).[2-4] Diagnosis is complicated by the high proportion who are smear-negative,[5,6] and atypical chest radiograph findings.[7]

Intensified tuberculosis case finding (ICF) is recommended by the World Health Organization (WHO)[8] but is poorly implemented.[9] Screening prior to ART is particularly important because risk of tuberculosis and death is high for immunosuppressed individuals.[4,10] Individuals diagnosed with tuberculosis after, rather than before, ART initiation are more likely to die while on tuberculosis treatment, emphasising the need for prompt diagnosis and treatment initiation.[3] High tuberculosis incidence within the first few months of ART initiation suggests that cases are either missed at screening or subclinical disease is unmasked by immunological recovery.[10-12]

The aim of our study was to determine the prevalence of previously undiagnosed active tuberculosis amongst ART-eligible adults at enrolment to a public sector HIV clinic in South Africa, and to evaluate the performance of combinations of symptoms and standard investigations in the diagnosis of tuberculosis.

METHODS

Study design and population

Between August 2007 and January 2008, we recruited ART-eligible (WHO stage 4 or CD4<200 cells/mm^3)[13] adults (>17 years) to a prospective cohort study. Patients taking tuberculosis treatment currently or within the previous three months were excluded.

Patients were referred to this clinic for ART initiation. South African guidelines[13] at the time of this study did not specify systematic screening for tuberculosis prior to ART. Clinic policy was for routine chest radiography at enrolment, but systematic tuberculosis screening was not routine; patients were assessed by clinicians for ART eligibility and investigated as deemed appropriate. All patients with CD4<200

cells/mm^3, or CD4<350 cells/mm^3 and WHO stage 2, 3 or 4 received cotrimoxazole; isoniazid preventive therapy was not given. Patients on tuberculosis treatment started ART after two weeks if CD4 count<50 cells/mm^3 or other serious HIV-related illness, or two months if CD4 count between 50 and 200 cells/mm^3 or WHO stage 4.

Study procedures

Trained nurses administered a symptom questionnaire and collected two spot sputum specimens for smear and mycobacterial culture from all participants. Chest radiographs were read by a consultant physician blinded to clinical details, using a standardised form adapted from a validated tool,[14] assigning radiographic diagnoses according to overall impression. We reviewed patients 3-6 months post enrolment, performing repeat symptom questionnaire and record review, and investigated symptomatic patients with chest radiography and two further sputum specimens. Symptomatic patients were those with any of: cough, night sweats, fever, appetite loss, tiredness for >2 weeks; or haemoptysis, chest pain, difficulty breathing, observed weight loss >1.5kg in previous month; or self-reported weight loss over the preceding 6 months. Patient records were used to ascertain CD4 and full blood counts, WHO clinical stage, tuberculosis diagnoses made outside of study visits, and evidence of clinical improvement at two months amongst those on tuberculosis treatment. Tuberculosis diagnosed at recruitment was not used to assign WHO stage.

Laboratory methods

Sputum specimens were examined at the National Health Laboratory Services by fluorochrome staining for acid-fast bacilli (AFB), and cultured using the BACTEC^{TM} MGIT 960^{TM} system (Becton Dickinson Microbiology Systems, Sparks, MD, USA). Scanty positive smears were considered positive. All positive cultures were identified using a nucleic amplification technique (AccuProbe®, Gen-Probe, San Diego, CA, USA).

Case definition for tuberculosis

Patients were classified as having pulmonary tuberculosis (PTB) if they had compatible clinical or radiological features and: sputum culture-positive for *M. tuberculosis* (*definite* PTB); sputum smear-positive, culture-negative (*probable* PTB); or no other cause of disease found and clinical improvement after two months of tuberculosis treatment, or lost to follow-up or died before two months (*possible* PTB).

Patients were classified as having extrapulmonary tuberculosis (EPTB) if they had compatible clinical features and either had: *M. tuberculosis* cultured from a relevant site (*definite* EPTB); other diagnostic evidence of EPTB and improved after two months of tuberculosis treatment (*probable* EPTB); or no other cause of disease was found and the patient improved after two months of tuberculosis treatment or was lost to follow-up or died before two months (*possible* EPTB). Tuberculosis episodes were considered to start on the date tuberculosis treatment was started.

Prevalent tuberculosis was defined as any tuberculosis episode fulfilling case definitions within three months of enrolment. Only study screening tests performed on the day of enrolment were used to calculate sensitivity, specificity, negative and positive predictive values for screening methods. Information from all available sources was used to assign tuberculosis case definitions.

Statistical analysis

Data were analysed using Intercooled Stata 10.0 (Stata Corporation, Texas, USA). We used logistic regression to calculate unadjusted and adjusted odds ratios for risk factors for prevalent tuberculosis and to assess the performance of symptoms for a screening tool using a gold standard of culture-positive tuberculosis. Risk factor analyses were restricted to "definite" (culture-positive) cases, as a robust case definition, comparable with other studies,[15,16] and probable and possible cases were excluded from these analyses. *A priori*, the multivariable model for the risk factor analysis included CD4 count and age category as established risk factors for tuberculosis, and other factors for which the P value in the univariable analysis was ≤0.2. From the multivariable model, we chose as screening criteria the three

symptoms with the highest adjusted odds ratios. We also evaluated the new WHO ICF screening tool of any of current cough, fever, weight loss or night sweats.[17]

To estimate mortality rates pre-ART, person-time was calculated from date of recruitment to the study until the earliest of death; ART initiation; two weeks after last visit date (as all patients attend monthly to collect medication), or end of study (1st July 2008). For mortality after ART start, person-time was calculated from date of ART initiation until the earliest of death; two weeks after last visit date, or end of study.

Ethical approval

The study received ethical approval from the Research Ethics Committee of the University of KwaZulu-Natal and the London School of Hygiene & Tropical Medicine. Written informed consent, or witnessed verbal consent for participants unable to read or write, was obtained for all participants.

RESULTS

Participation and demographics

Figure 1 summarises study inclusions and exclusions, losses to follow-up, and tuberculosis case definitions. Among 381 participants recruited, 12 were treated for tuberculosis without fulfilling our case definitions, and a further 8 were culture-positive for non-tuberculous mycobacteria only. Amongst 361 participants analysed, 99% were Black African, 67% were female, median age was 38 (IQR 32-46) years, median CD4 was 120 (IQR 72-168) cells/mm^3 and 171/305 (56%) were WHO stage 3 or 4. 100 (28%) reported a previous episode of tuberculosis, of whom 51% were treated ≤3 years ago.

Prevalence of tuberculosis and basis of diagnosis

114/361 participants fulfilled our case definition for tuberculosis (definite, probable or possible) giving a prevalence of undiagnosed tuberculosis of 32% (95% confidence interval [CI] 26.8-36.6%). "Possible" cases, vs. "definite", were more likely to have

more advanced WHO stage and EPTB only, but other markers of disease severity and radiographic patterns did not differ (see supplementary appendix table 1). 99/114 (87%) had PTB, 5 (4%) had EPTB, and 10 (9%) had both. Overall 64 (56%), 6 (5%), and 44 (39%) were classified as definite, probable and possible tuberculosis respectively. The prevalence of culture-proven tuberculosis was 17.7% (64/361; 95% CI 13.9-22.1%). Amongst 360 patients with complete data, 110/113 (97%) of tuberculosis patients and 236/247 (96%) of patients without tuberculosis had at least one of the following symptoms: cough, fever, drenching night sweats, self-reported weight loss, haemoptysis, dyspnoea, chest pain, loss of appetite or fatigue. Amongst 99 pulmonary tuberculosis cases (definite, probable and possible combined) the bases for diagnosis were: clinical, radiological, and microbiological (culture and/or smear) features for 39%; clinical and radiological features for 37%; clinical and microbiological features for 17%; and radiological and microbiological features for 2%.

Sputum microscopy and culture results

Amongst 350 individuals with sputum results available, 24 (7%) and 326 (90%) produced one or two adequate sputum specimens respectively. 9/350 (3%) were smear-positive and 64/350 (18%) were culture-positive for *M. tuberculosis*, of whom one was culture-negative at enrolment but culture-positive subsequently. 7/350 (2%) were both smear- and culture-positive. Amongst 300 patients with a negative or inadequate first sputum specimen, 14 (5%) had a culture-positive second specimen. 57/64 (89%) of culture-positive patients were smear-negative.

Time from screening to start of treatment

Amongst 86 patients with definite, probable or possible tuberculosis, and for whom the basis of starting treatment was clear, the median time to starting treatment was 13 (IQR 1, 35) days. 72/86 (84%) initiated treatment based on chest radiograph findings at median 8 (IQR 0, 24) days; of these 31/72 (43%) were initiated on the same or next day by the clinic doctor, and the remainder started treatment at a median of 20 (IQR 11, 36) days after enrolment, following further review of chest radiograph by consultant physician. 14/86 (16%) patients started treatment based on

sputum culture result at a median of 37 (IQR 20, 49) days and two (2%) patients started treatment based on sputum smear result after median 9 (IQR 4, 13) days post enrolment. Amongst 45 culture-confirmed tuberculosis cases, 29/45 (64%) started treatment based on chest radiograph findings at median 1 (IQR 0, 8) day vs. 35 (IQR 20, 44) days for 14/45 (31%) patients started based on sputum culture result.

Eight individuals had no evidence of active tuberculosis at the time of screening (and were included in the analysis as such) but at the time of final review were observed to have started tuberculosis treatment more than three months after screening (Figure 1).

Demographic and clinical risk factors for undiagnosed prevalent tuberculosis

Risk factor analyses were restricted to 300 individuals (6 “probable” and 44 “possible” tuberculosis cases, and 11 individuals without sputum results were excluded). In the univariable analysis (see supplementary appendix table 2), prevalent tuberculosis was associated with male sex, greater than six household members, ever having smoked, and no previous history of tuberculosis treatment. In the multivariable analysis only previous tuberculosis treatment, which was protective, (adjusted OR 0.29, 95% CI 0.13-0.65) remained associated.

Sensitivity, specificity and predictive values of markers for undiagnosed prevalent tuberculosis

Using culture-positive tuberculosis as our gold standard we found that the presence of individual symptoms irrespective of duration was sensitive, but generally had low specificity, except for haemoptysis which had low prevalence (table 1). Addition of duration >2 weeks to individual symptoms reduced sensitivity, but improved specificity. Haemoglobin <10g/dl had a similar sensitivity to CD4 count<100 cells/mm^3 (38% vs. 35%), but had better specificity (80% vs. 62%). Sputum microscopy was very insensitive particularly when compared to chest radiographic features of active tuberculosis (11% vs. 77%), and overall only 7/300 (2%) patients were smear positive. In a sensitivity analysis including all tuberculosis cases (definite, probable and possible), there was little change in sensitivity and specificity values

(data not shown) compared to those for only culture-positive tuberculosis cases. For example, sensitivity of radiographic features of active tuberculosis was 77.4% vs. 80.4% for culture-positive vs. all tuberculosis cases.

The symptom, sign, and investigation with best performance in terms of sensitivity and negative predictive value were, respectively: self-reported weight loss, BMI <18.5kg/m^2, and any abnormality on chest radiograph (table 1). In terms of specificity and positive predictive value the best symptom, sign and investigation were fever >2 weeks, observed fever (although only two participants were febrile), and sputum microscopy respectively.

Combinations of screening criteria

The three symptoms with the highest adjusted odds ratios in multivariable analysis were cough>2 weeks, loss of appetite >2 weeks and night sweats >2 weeks (for details, see supplementary appendix table 3). Amongst 244 individuals with complete data the performance of these in combination was tested (table 2). A combination of any of: cough or appetite loss or night sweats for greater than two weeks (henceforth known as the symptom complex) had sensitivity, specificity, positive and negative predictive values of 75%, 51%, 29% and 88% respectively. Adding BMI <18.5kg/m^2 to our symptom complex made little difference to sensitivity and negative predictive values, in contrast to WHO clinical stage 3 or 4 which increased sensitivity and negative predictive values to 90% but halved specificity. Addition of haemoglobin <10g/dl improved the sensitivity and negative predictive value of the symptom complex to 82% and 90% respectively, and combining this with WHO stage 3 or 4 and BMI <18.5 further increased sensitivity to 90% but halved specificity.

Sputum microscopy did not change the performance of the symptom complex, in contrast to chest radiography which increased sensitivity to 92% for features compatible with active tuberculosis, and 96% for any radiographic abnormality. A combination of symptom complex or any radiographic abnormality had sensitivity and negative predictive values of 96%, which was further improved by addition of CD4<100 which missed only 2% of tuberculosis cases and was our most sensitive combination (98%).

The WHO symptom screen[17] had sensitivity, specificity, positive and negative predictive values of 96%, 5%, 21% and 83% respectively in our patients. Addition of chest radiography increased sensitivity and negative predictive value to 100% for both features compatible with active tuberculosis and any radiographic abnormality.

Time to ART start and mortality

266/361 (74%) patients initiated ART by 1st July 2008, at median of 70 days from recruitment (IQR 42, 105). Among 266 patients who started ART within the study period, the median time from enrolment to ART start was shorter for those without tuberculosis (median 64 days, N=190) vs. those with tuberculosis (median 94 days, N=76). In total 26/361 patients (7.2%) died, of whom 20/26 (77%) did not initiate ART. The pre-ART mortality rate was 25.3/100 person-years (95% CI 16.3-39.1, vs. 6.8/100 person-years (95% CI 3.0-15.1) after starting ART.

Documented causes of death pre-ART (N=20) were tuberculosis (4); acute renal failure (2); 1 each of septicaemia, gastroenteritis, cryptococcal meningitis, cardiomyopathy, and pneumonia; and unknown (9; of whom three fulfilled case definitions for tuberculosis but did not start tuberculosis treatment). Documented causes of on-ART mortality (N=6) were one each of tuberculosis; cryptococcal meningitis; pneumonia and septicaemia; and unknown (3).

Among 44 patients who did not meet TB case definitions based on investigations at enrolment but were not seen at the follow-up visit, 15 were known to have died (figure 1).

DISCUSSION

One-third of our patients referred to start ART had undiagnosed tuberculosis, a major burden of morbidity with life-threatening potential;[10,11] highlighting the need to investigate all of these patients, most of whom were highly symptomatic, for tuberculosis. Our prevalence is similar to recent data from Western Cape (32%),[12] but higher than generally reported among ART-eligible adults in Africa (3%-

19%).[10,11,16,18-20] This reflects systematic screening of our patients using multiple modalities, and a broad case definition allowing diagnosis based on radiological and clinical features highlighting the 'real life' burden, and recognising that sputum culture misses some cases of disseminated tuberculosis.[21] Our 18% prevalence of culture-confirmed pulmonary tuberculosis accords with studies from Cambodia (17%),[22] KwaZulu-Natal (19%),[16] and Western Cape (17%).[15]

We found demographic and clinical data unhelpful in identifying subgroups at higher risk of undiagnosed tuberculosis. Individuals with advanced HIV disease often reach HIV care due to symptoms of tuberculosis, underscoring the need for systematic case finding. Screening for this group requires high sensitivity to avoid missing cases, but in a resource-constrained setting, this must be balanced against the high costs resulting from a test combination with poor specificity. We found sputum microscopy had very poor sensitivity, consistent with other studies,[16,19,23-25] yet this remains a key component of National Tuberculosis control programmes in resource limited settings. The WHO symptom screen[17,26] had high sensitivity (96%) in our study population. It aims primarily to rule out tuberculosis among apparently healthy individuals prior to starting isoniazid preventive therapy, requiring a high sensitivity and negative predictive value; however this is at the cost of low specificity. If all individuals identified as tuberculosis suspects, based on a symptom combination with relatively low specificity, are investigated with new rapid molecular diagnostics, such as Xpert MTB/RIF[27] at US$17 per cartridge,[28] the cost to health services may be substantial, and the cost-effectiveness of a range of algorithms for different settings needs to be investigated. 90% of our culture-proven tuberculosis cases were smear-negative, and Xpert MTB/RIF has reported sensitivities from 43%-73% for smear-negative culture-positive tuberculosis from a single sputum sample.[15, 27] An algorithm requiring Xpert-negative tuberculosis suspects to undergo further evaluation using sputum culture, trial of antibiotic and chest radiograph has potential to delay tuberculosis treatment.

Chest radiography improved sensitivity of our symptom screening complex substantially, consistent with our earlier data from South African gold miners with less advanced HIV disease.[23] Use of chest radiography to augment the WHO symptom screen in high tuberculosis prevalence settings is supported by a recent meta-

analysis[26] and WHO guidance,[17] and in our study population increased sensitivity and negative predictive value to 100%. Our data show that chest radiography facilitates prompt tuberculosis treatment initiation. Although implementation of chest radiography can be challenging,[29,30] we suggest it should be done where possible. In high prevalence settings systematic sputum culture for all patients prior to ART has also been suggested, but presents the same challenges of access.[12,16] In our study, most culture-positive patients started tuberculosis treatment based on clinical and radiological features prior to availability of culture results; even with liquid culture, the median time to tuberculosis treatment start based on a positive culture was 37 days. Chest radiography provides a basis for rapid initiation of tuberculosis treatment both to reduce individual risk of death and also reduce risk of onward transmission in both clinic and community, and procedures must be in place to ensure follow-up of tuberculosis suspects.[30] The cost per chest radiograph has been estimated at only US$2.[30] The reported sensitivity of Xpert MTB/RIF among smear-negative tuberculosis cases (most ART-eligible patients will be smear-negative) is lower than chest radiography in this study, but it has much higher specificity.[27] Implementation of Xpert MTB/RIF should similarly reduce time to tuberculosis treatment start, but cost is likely to limit its wide use at peripheral health facilities, and effective low-cost point-of-care diagnostic tools remain a pressing need.

A low haemoglobin level is an independent predictor for mortality amongst patients commencing antiretroviral therapy[31-33] and may reflect undiagnosed tuberculosis. Adding anaemia to our symptom complex increased sensitivity, and supports the clinical practice of investigating all anaemic patients for tuberculosis prior to initiation of ART.

A major strength of our study was our longitudinal follow-up period, which is lacking from many screening studies,[19] minimising the number of tuberculosis cases missed and ensuring a robust case definition for possible tuberculosis. One-third of participants without a review visit are known to have died, underscoring how ill individuals were at enrolment. Tuberculosis cannot be excluded as cause of death amongst all; hence we may have underestimated the true tuberculosis prevalence. The study setting in a large public sector clinic is relatively typical of antiretroviral roll out sites, although better resourced than many in sub-Saharan Africa. We had

access to routine radiographs, read by an experienced physician, and mycobacterial cultures, and good patient retention in the study. Our screening procedure was straightforward to operationalise and did not appear to delay initiation of ART; the typical time from first visit to ART initiation in this clinic was 60-90 days (personal communication, E Variaiva).

In conclusion we found a very high prevalence of undiagnosed tuberculosis among patients presenting for ART to a public sector HIV clinic. These patients need routine systematic investigation for tuberculosis. Until accurate point-of-care diagnostic tests are available, our results suggest that chest radiography is a useful addition to routine screening which allows rapid initiation of tuberculosis treatment. Given the high mortality of patients awaiting investigation results,[2,4,34] presumptive tuberculosis treatment for high-risk individuals also needs to be evaluated.[35]

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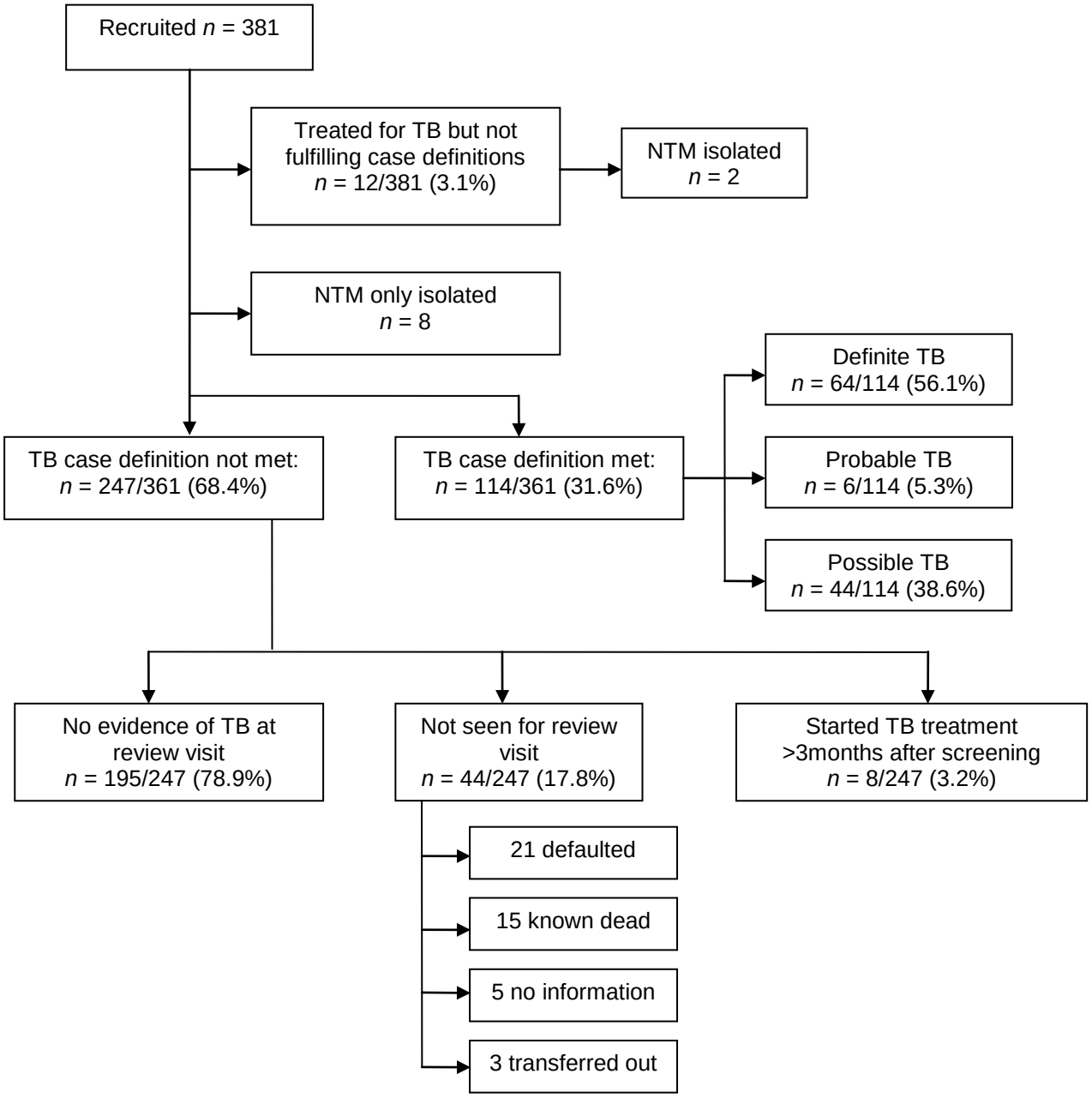
FIGURE LEGEND

Figure 1 Study inclusions, exclusions, case definitions and basis for diagnosis

Figure 1: Study inclusions, exclusions, case definitions and basis for diagnosis



TB = tuberculosis; NTM = non-tuberculous mycobacteria

Table 1: Performance of symptoms, signs, investigations and WHO stage as markers for undiagnosed prevalent tuberculosis*

Marker	Prevalence of marker (N=300)† % (n)	Sensitivity (N=64) % (n)	Specificity (N=236) % (n)	PPV %	NPV %
SYMPTOMS					
Reported weight loss	90.0 (269/299)	90.5 (57/63)	10.2 (24)	21.2	80.0
Any tiredness	69.3 (208)	81.3 (52)	33.9 (80)	25.0	87.0
Tiredness > 2 weeks	47.0 (141)	70.3 (45)	59.3 (140)	31.9	88.1
Any cough	44.0 (132)	68.8 (44)	62.7 (148)	33.3	88.1
Cough > 2 weeks	24.3 (73)	43.8 (28)	80.9 (191)	38.4	84.1
Cough > 3 weeks	22.3 (67)	42.2 (27)	83.1 (196)	40.3	84.1
Any loss of appetite	50.0 (150)	62.5 (40)	53.4 (126)	26.7	84.0
Loss of appetite > 2 weeks	32.0 (96)	51.6 (33)	73.3 (173)	34.4	84.8
Any night sweats	40.7 (122)	59.4 (38)	64.4 (152)	31.2	85.4
Night sweats > 2 weeks	28.7 (86)	45.3 (29)	75.9 (179)	33.7	83.6
Any chest pain	46.3 (139)	53.1 (34)	55.5 (131)	24.5	81.4
Chest pain > 2 weeks	27.3 (82)	37.5 (24)	75.4 (178)	29.3	81.7
Any fever	27.0 (81)	35.9 (23)	75.4 (178)	28.4	81.3
Fever > 2 weeks	12.7 (38)	25.0 (16)	90.7 (214)	42.1	81.7
Any haemoptysis	7.7 (23)	9.4 (6)	92.8 (219)	26.1	79.1
Any symptom‡	96.3 (288/299)	96.8 (61/63)	3.8 (9)	21.2	81.8
SIGNS:					
Body Mass Index <18.5 kg/m^2	26.5 (79/298)	37.5 (24)	76.5 (179/234)	30.4	81.7
Temperature >37.4 ˚C	0.7 (2)	3.1 (2)	100 (236)	100	74.6
INVESTIGATIONS:					
Haemoglobin <8 g/dl	4.0 (12/297)	6.3 (4)	96.6(225/233)	33.3	79.0
Haemoglobin <10 g/dl	23.6 (70/297)	37.5 (24)	80.3(187/233)	34.3	82.4
Total lymphocyte count (10^9/l) <1	22.4 (66/295)	28.1 (18)	79.2(183/231)	27.3	79.9
CD4 cell count <100 cells/mm^3	37.2 (111/298)	34.9 (22/63)	62.1(146/235)	19.8	78.1
≥1 Sputum AFB Positive	2.3 (7/300)	10.9 (7)	100 (236)	100	80.6
Abnormal CXR	58.9 (175/297)	85.5 (53/62)	48.1(113/235)	30.3	92.6
CXR compatible with active TB	45.1 (134/297)	77.4 (48/62)	63.4(149/235)	35.8	91.4
Clinical classification					
WHO clinical stage 3 or 4	53.8 (136/253)	55.6 (30/54)	46.7 (93/199)	22.1	79.5

* Tuberculosis case defined as patients diagnosed within three months of recruitment who were culture-positive for tuberculosis; † denominator =300 unless otherwise indicated (all participants with probable [n=6] or possible [n=44] tuberculosis, and those without sputum culture results [n=11] have been excluded); ‡ any of the following irrespective of duration: cough, sputum production, night sweats, self-reported weight loss, fever, haemoptysis, dyspnoea, chest pain, loss of appetite or fatigue; CXR = Chest radiograph; PPV= positive predictive value; NPV=negative predictive value; AFB = Acid-fast bacilli; HIV = human immunodeficiency virus; MTB = *M. tuberculosis*; WHO = World Health Organization

Table 2: Combinations of tuberculosis* screening criteria from this study and performance of WHO algorithm [17] in our study population (N=244)

Screening criteria: at least one of	Present overall n=244 (%)	Sensitivity % n=51 (95% CI)	Specificity % n=193 (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Symptoms only					
C>2w, A>2w, S>2w	133 (54.5)	74.5 (69.0, 80.0)	50.8 (44.5, 57.1)	28.6 (22.9, 34.2)	88.3 (84.3, 92.3)
Addition of clinical features					
C>2w, A>2w, S>2w, WHO 3/4	190 (77.9)	90.2 (86.5, 93.9)	25.4 (19.9,30.9)	24.2 (18.8, 29.6)	90.7 (87.1, 94.4)
C>2w, A>2w, S>2w, BMI<18.5	151 (61.9)	78.4 (73.3, 83.6)	42.5 (36.3, 48.7)	26.5 (21.0,32.0)	88.2 (84.1,92.2)
C>2w, A>2w, S>2w, WHO 3/4, BMI<18.5	199 (81.6)	90.2 (86.5, 93.9)	20.7 (15.6, 25.8)	23.1 (17.8, 28.4)	88.9 (85.0, 92.8)
Addition of basic laboratory tests					
C>2w, A>2w, S>2w, Hb <10	151 (61.9)	82.4 (77.6, 87.1)	43.5 (37.3, 49.7)	27.8 (22.2, 33.4)	90.3 (86.6, 94.0)
C>2w, A>2w, S>2w, Hb<10, BMI<18.5	166 (68.0)	84.3 (79.8, 88.9)	36.3 (30.2, 42.3)	25.9 (20.4, 31.4)	89.7 (85.9, 93.6)
C>2w, A>2w, S>2w,WHO 3/4, Hb<10, BMI<18.5	204 (83.6)	90.2 (86.5, 93.9)	18.1 (13.3, 23.0)	22.6 (17.3, 27.8)	87.5 (83.4, 91.7)
Addition of sputum microscopy					
C>2w, A>2w, S>2w, Sputum AFB-positive	135 (55.3)	78.4 (73.3, 83.6)	50.8 (44.5, 57.1)	29.6 (23.9, 35.4)	89.9 (86.1, 93.7)
Addition of CXR					
C>2w, A>2w, S>2w,any CXR abnormality	195 (79.9)	96.1 (93.6, 98.5)	24.4 (19.0, 29.7)	25.1 (19.7,30.6)	95.9 (93.4, 98.4)
C>2w, A>2w, S>2w,CXR compatible with active TB	179 (73.4)	92.2 (88.8, 95.5)	31.6 (25.8, 37.4)	26.3 (20.7, 31.8)	93.9 (90.8, 96.9)
Addition of CD4 count					
C>2w, A>2w, S>2w,CD4<100	171 (70.8)	82.4 (77.6, 87.1)	33.2 (27.3, 39.1)	24.6 (19.2, 30.0)	87.7 (83.6, 91.8)
Addition of CXR and CD4					
C>2w, A>2w, S>2w,any CXR abnormality, CD4<100	211 (86.5)	98.0 (96.3, 99.8)	16.6 (11.9, 21.3)	23.7 (18.4, 29.0)	97.0 (94.8, 99.1)
C>2w, A>2w, S>2w,CXR compatible with active TB, CD4<100	199 (81.6)	94.1 (91.2, 97.1)	21.8 (16.6, 26.9)	24.1 (18.8, 29.5)	93.3 (90.2, 96.5)
WHO screening algorithm [17]					
C, F, W, S	232 (95.1)	96.1 (93.6, 98.5)	5.2 (2.4, 8.0)	21.1 (16.0, 26.2)	83.3 (78.7, 88.0)
C, F, W, S, any CXR abnormality	240 (98.3)	100 (100,100)	2.1 (0.3, 3.9)	21.3 (16.1, 26.4)	100 (100, 100)

*Tuberculosis case defined as patients diagnosed within three months of recruitment who were culture-positive for tuberculosis. All participants with probable [n=6] or possible tuberculosis [n=44] and those without sputum culture results [n=11] have been excluded. Participants with missing data have also been excluded: WHO clinical stage [n=47], haemoglobin [n=3], chest radiograph [n=3], BMI [n=2], and reported weight loss [n=1].

A, appetite loss; C, cough; F, fever; S, night sweats; W, weight loss

PPV= positive predictive value; NPV=negative predictive value; 2w=2 weeks; WHO = World Health Organization clinical stage; BMI=Body mass index (kg/m^2); Hb=Haemoglobin g/dl; AFB = Acid-fast bacilli; CXR = Chest radiograph; CD4 = CD4 cell count (cells/mm^3); TB=tuberculosis