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

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OBJECTIVE: To investigate the prevalence of and evaluate screening modalities for undiagnosed tuberculosis (TB) in antiretroviral therapy (ART) eligible adults in South Africa.

METHODS: Individuals were screened for TB using symptoms, chest radiograph (CXR) and two sputum specimens for microscopy and culture, and were then followed for <6 months to determine TB diagnoses.

RESULTS: Among 361 participants (67% female, median age 38 years, median CD4 count 120 cells/mm3), 64 (18%) were sputum culture-positive; 114 (32%) fulfilled any TB case definition (culture- and/or smear-positive, or improvement on specific treatment). Symptom screening comprising any of cough, appetite loss or night sweats >2 weeks had a sensitivity and specificity of respectively 74.5% and 50.8%. Sensitivity was increased by CXR (to 96.1%), but not by smear microscopy. The World Health Organization symptom screen had a sensitivity and specificity of respectively 96.1% and 5.2% in our study population; the addition of CXR increased sensitivity to 100%. Median time to TB treatment was 8 days for diagnoses based on CXR (n = 72) vs. 37 days for diagnoses based only on sputum culture (n = 14).

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

KEYWORDS: tuberculosis; HIV infection; diagnosis; South Africa; screening

TUBERCULOSIS (TB) remains a key cause of death among people with human immunodeficiency virus (HIV) infection in sub-Saharan Africa,1 despite wider use of antiretroviral therapy (ART).2–4 Diagnosis is complicated by the high proportion of smear-negative persons,5,6 and atypical chest radiograph (CXR) findings.7

Intensified TB case finding (ICF) is recommended by the World Health Organization (WHO),8 but is poorly implemented.9 Screening prior to ART is particularly important, as risk of TB and death is high for immunosuppressed individuals.4,10 Individuals diagnosed with TB after, rather than before, ART initiation are more likely to die while on anti-tuberculosis treatment, emphasising the need for prompt diagnosis and treatment initiation.11 High TB incidence within the first few months of ART initiation suggests that cases are either missed at screening or that subclinical disease is unmasked by immunological recovery.10–12

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

METHODS

Study design and population

Between August 2007 and January 2008, we recruited ART-eligible (WHO Stage 4 or CD4 < 200 cells/mm3)13 adults (aged >17 years) into a prospective cohort study. Patients taking anti-tuberculosis treatment currently or in the previous 3 months were excluded.

Patients were referred to the clinic for ART initiation. South African guidelines at the time of this study did not specify systematic screening for TB prior to ART.13 Clinic policy was for routine CXR at enrolment, but systematic TB screening was not routine; patients were assessed by clinicians for ART eligibility and investigated as deemed appropriate. All patients with CD4 < 200 cells/mm3, or CD4 < 350 cells/mm3 and WHO Stage 2, 3 or 4 received cotrimoxazole;
isoniazid preventive therapy (IPT) was not given. Patients on anti-tuberculosis treatment started ART after 2 weeks if CD4 count < 50 cells/mm³ or if they had had another serious HIV-related illness, or after 2 months if CD4 count 50–200 cells/mm³ 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. CXRs were read by a consultant physician blinded to clinical details, using a standardised form adapted from a validated tool, 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 CXR 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 of >1.5 kg 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, TB diagnoses made outside of study visits, and evidence of clinical improvement at 2 months among those on anti-tuberculosis treatment. TB 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 BACTECTM Mycobacteria Growth Indicator Tube (MGIT)™ 960 system (BD, 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 were sputum culture-positive for Mycobacterium tuberculosis (definite PTB); sputum smear-positive, culture-negative (probable PTB); or no other cause of disease found and clinical improvement after 2 months of anti-tuberculosis treatment, or lost to follow-up or died before 2 months (possible PTB).

Patients were classified as having extra-pulmonary tuberculosis (EPTB) if they had compatible clinical features and had M. tuberculosis cultured from a relevant site (definite EPTB); other diagnostic evidence of EPTB and improvement after 2 months of anti-tuberculosis treatment (probable EPTB); or no other cause of disease was found and the patient improved after 2 months of anti-tuberculosis treatment or was lost to follow-up or died before 2 months (possible EPTB). TB episodes were considered to start on the date anti-tuberculosis treatment was started.

Prevalent TB was defined as any TB episode fulfilling case definitions within 3 months of enrolment. Only study screening tests performed on the day of enrolment were used to calculate sensitivity, specificity, and negative (NPV) and positive predictive values (PPV) for screening methods. Information from all available sources was used to assign TB case definitions.

Statistical analysis
Data were analysed using Intercooled Stata 10.0 (Stata Corporation, College Station, TX, USA). We used logistic regression to calculate unadjusted and adjusted odds ratios (ORs) for risk factors for prevalent TB and to assess the performance of symptoms for a screening tool using a gold standard of culture-positive TB. Risk factor analyses were restricted to ‘definite’ (culture-positive) cases, as a robust case definition, comparable with other studies; 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 TB, 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 ORs. We also evaluated the new WHO ICF screening tool of any of current cough, fever, weight loss or night sweats.

To estimate mortality rates pre-A RT, person-time was calculated from date of recruitment into the study until the earliest of death, ART initiation, 2 weeks after last visit date (as all patients attended monthly to collect medication), or end of study (1 July 2008). For mortality after ART start, person-time was calculated from date of ART initiation until the earliest of death, 2 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
The Figure summarises study inclusions and exclusions, losses to follow-up and TB case definitions. Among 381 participants recruited, 12 were treated for TB without fulfilling our case definitions, and a further 8 were culture-positive for non-tuberculous
High prevalence of TB prior to ART

Among 361 participants analysed, 99% were Black African, 67% were female, the median age was 38 years (interquartile range [IQR] 32–46), median CD4 was 120 cells/mm³ (IQR 72–168) and 171/305 (56%) were WHO Stage 3 or 4; 100 (28%) reported a previous episode of TB, of whom 51% were treated ≤3 years previously.

Prevalence of tuberculosis and basis of diagnosis

Of the 361 participants, 114 fulfilled our case definition for TB (definite, probable or possible), giving a prevalence of undiagnosed TB of 32% (95% confidence interval [CI] 26.8–36.6). ‘Possible’ vs. ‘definite’ cases were more likely to have more advanced WHO stage and EPTB only, but other markers of disease severity and CXR patterns did not differ (see Appendix Table A1*). Of the 114 TB patients, 99 (87%) had PTB, 5 (4%) had EPTB and 10 (9%) had both. Respectively 64 (56%), 6 (5%) and 44 (39%) were classified as definite, probable and possible TB. The prevalence of culture-proven TB was 17.7% (64/361, 95%CI 13.9–22.1). Among 360 patients with complete data, 110/113 (97%) TB patients and 236/247 (96%) patients without TB 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. Among 99 PTB cases (definite, probable and possible combined), the bases for diagnosis were clinical, radiological and micro-biological (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

Among 350 individuals with sputum results available, respectively 24 (7%) and 326 (90%) produced one or two adequate sputum specimens; 9/350 (3%) were smear-positive and 64/350 (18%) were culture-positive for M. tuberculosis, of whom 1 was culture-negative at enrolment but culture-positive subsequently, and 7 (2%) were both smear- and culture-positive. Among 300 patients with a negative or inadequate first sputum specimen, 14 (5%) had a culture-positive second specimen. Of 64 culture-positive patients, 57 (89%) were smear-negative.

Time from screening to start of treatment

Among 86 patients with definite, probable or possible TB, and for whom the basis of starting treatment was clear, the median time to starting treatment was 13 days (IQR 1–35). Of these, 72 (84%) initiated treatment based on CXR findings at median 8 days (IQR 0, 24); 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 days (IQR 11–36) after enrolment, following further review of CXR by a consultant physician. Of these 86 patients, 14 (16%) started treatment based on sputum culture result at a median of 37 days (IQR 20–49), and two (2%) patients started treatment based on sputum smear result after a median 9 days (IQR 4–13) after enrolment. Among 45 culture-confirmed TB cases, 29/45 (64%) started treatment based on CXR findings at median 1 day (IQR 0–8) vs. 35 days (IQR 20–44) for 14/45 (31%) patients started on treatment based on sputum culture result.

Eight individuals had no evidence of active TB 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 anti-tuberculosis treatment >3 months after screening (Figure).

Demographic and clinical risk factors for undiagnosed prevalent tuberculosis

Risk factor analyses were restricted to 300/361 individuals (6 ‘probable’ and 44 ‘possible’ TB cases, and 11 individuals without sputum results were excluded). In the univariable analysis (Appendix Table A2), prevalent TB was associated with male sex, more than six household members, ever having smoked and no previous history of anti-tuberculosis treatment. In the multivariable analysis, only previous anti-tuberculosis

* The Appendix is available in the online version of this article.
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 TB 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 < 10 g/dl had a similar sensitivity to CD4 count < 100 cells/mm³ (38% vs. 35%), but had better specificity (80% vs. 62%). Smear microscopy was very insensitive, particularly when compared to CXR features of active TB (11% vs. 77%), and overall only 7/300 (2%) patients were smear-positive. In a sensitivity analysis including all TB cases (definite, probable and possible), there was little change in sensitivity and specificity values (data not shown) compared to those for only culture-positive TB cases. For example, the sensitivity of CXR features of active TB was 77.4% vs. 80.4% for culture-positive vs. all TB cases.

The symptom, sign and investigation with best performance in terms of sensitivity and NPV were respectively self-reported weight loss, body mass index (BMI) < 18.5 kg/m² and any abnormality on CXR (Table 1). In terms of specificity and PPV, the best symptom, sign and investigation were respectively fever > 2 weeks, observed fever (although only two participants were febrile) and smear microscopy.

**Combinations of screening criteria**

The three symptoms with the highest adjusted ORs in multivariable analysis were cough > 2 weeks, loss of appetite > 2 weeks and night sweats > 2 weeks (for details, see Appendix Table A3). Among 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 > 2 weeks (henceforth known as the symptom complex) had sensitivity, specificity, PPV and NPV of respectively 75%, 51%, 29% and 88%. Adding BMI <

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

<table>
<thead>
<tr>
<th>Marker</th>
<th>Prevalence of marker (N = 300)</th>
<th>Sensitivity (n = 64)</th>
<th>Specificity (n = 236)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>PPV %</td>
<td>NPV %</td>
</tr>
<tr>
<td>Symptoms</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported weight loss</td>
<td>269/299 (90.0)</td>
<td>57/63 (90.5)</td>
<td>24/10.2</td>
<td>21.2</td>
<td>80.0</td>
</tr>
<tr>
<td>Any tiredness</td>
<td>208 (69.3)</td>
<td>52/81.3</td>
<td>80/33.9</td>
<td>25.0</td>
<td>87.0</td>
</tr>
<tr>
<td>Tiredness &gt; 2 weeks</td>
<td>141 (47.0)</td>
<td>45/70.3</td>
<td>140/59.3</td>
<td>31.9</td>
<td>88.1</td>
</tr>
<tr>
<td>Any cough</td>
<td>132 (44.0)</td>
<td>44/68.8</td>
<td>148/62.7</td>
<td>33.3</td>
<td>88.1</td>
</tr>
<tr>
<td>Cough &gt; 2 weeks</td>
<td>73 (24.3)</td>
<td>28/43.8</td>
<td>191/80.9</td>
<td>38.4</td>
<td>84.1</td>
</tr>
<tr>
<td>Cough &gt; 3 weeks</td>
<td>67 (22.3)</td>
<td>27/42.2</td>
<td>196/83.1</td>
<td>40.3</td>
<td>84.1</td>
</tr>
<tr>
<td>Any loss of appetite</td>
<td>150 (50.0)</td>
<td>40/62.5</td>
<td>126/53.4</td>
<td>26.7</td>
<td>84.0</td>
</tr>
<tr>
<td>Loss of appetite &gt; 2 weeks</td>
<td>96 (32.0)</td>
<td>33/51.6</td>
<td>173/73.3</td>
<td>34.4</td>
<td>84.8</td>
</tr>
<tr>
<td>Any night sweats</td>
<td>122 (40.7)</td>
<td>38/59.4</td>
<td>152/64.4</td>
<td>31.2</td>
<td>85.4</td>
</tr>
<tr>
<td>Night sweats &gt; 2 weeks</td>
<td>86 (28.7)</td>
<td>29/45.3</td>
<td>179/75.9</td>
<td>33.7</td>
<td>83.6</td>
</tr>
<tr>
<td>Any chest pain</td>
<td>139 (46.3)</td>
<td>34/53.1</td>
<td>131/55.5</td>
<td>24.5</td>
<td>81.4</td>
</tr>
<tr>
<td>Chest pain &gt; 2 weeks</td>
<td>82 (27.3)</td>
<td>24/37.5</td>
<td>178/75.4</td>
<td>29.3</td>
<td>81.7</td>
</tr>
<tr>
<td>Any fever</td>
<td>81 (27.0)</td>
<td>23/35.9</td>
<td>178/75.4</td>
<td>28.4</td>
<td>81.3</td>
</tr>
<tr>
<td>Fever &gt; 2 weeks</td>
<td>38 (12.7)</td>
<td>16/25.0</td>
<td>214/90.7</td>
<td>42.1</td>
<td>81.7</td>
</tr>
<tr>
<td>Any haemoptysis</td>
<td>23 (7.7)</td>
<td>6/9.4</td>
<td>219/92.8</td>
<td>26.1</td>
<td>79.1</td>
</tr>
<tr>
<td>Any symptom</td>
<td>288/299 (96.3)</td>
<td>61/63 (96.8)</td>
<td>9/3.8</td>
<td>21.2</td>
<td>81.8</td>
</tr>
<tr>
<td>Signs</td>
<td>Body mass index &lt; 18.5 kg/m²</td>
<td>79/298 (26.5)</td>
<td>24/37.5</td>
<td>179/234 (76.5)</td>
<td>30.4</td>
</tr>
<tr>
<td>Temperature &gt; 37.4°C</td>
<td>2 (0.7)</td>
<td>2 (3.1)</td>
<td>236 (100)</td>
<td>100</td>
<td>74.6</td>
</tr>
<tr>
<td>Clinical investigations</td>
<td>Haemoglobin &lt; 8 g/dl</td>
<td>12/297 (4.0)</td>
<td>4/6.3</td>
<td>225/232 (96.6)</td>
<td>33.3</td>
</tr>
<tr>
<td>Haemoglobin &lt; 10 g/dl</td>
<td>70/297 (23.6)</td>
<td>24/37.5</td>
<td>187/233 (80.3)</td>
<td>34.3</td>
<td>82.4</td>
</tr>
<tr>
<td>Total lymphocyte count (10⁹/l) &lt; 1</td>
<td>66/295 (22.4)</td>
<td>18/28.1</td>
<td>183/231 (79.2)</td>
<td>27.3</td>
<td>79.9</td>
</tr>
<tr>
<td>CD4 cell count &lt; 100 cells/mm³</td>
<td>111/298 (37.2)</td>
<td>22/34.9</td>
<td>146/235 (62.1)</td>
<td>19.8</td>
<td>78.1</td>
</tr>
<tr>
<td>≥ 1 spumt AFB-positive</td>
<td>7/300 (2.3)</td>
<td>7 (10.9)</td>
<td>236 (100)</td>
<td>100</td>
<td>80.6</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>175/297 (58.9)</td>
<td>25/62.5</td>
<td>113/235 (48.1)</td>
<td>30.3</td>
<td>92.6</td>
</tr>
<tr>
<td>CXR features compatible with active TB</td>
<td>134/297 (45.1)</td>
<td>48/62.7</td>
<td>149/235 (63.4)</td>
<td>35.8</td>
<td>91.4</td>
</tr>
<tr>
<td>Clinical classification</td>
<td>WHO clinical stage 3 or 4</td>
<td>136/253 (53.8)</td>
<td>30/54 (55.6)</td>
<td>93/199 (46.7)</td>
<td>22.1</td>
</tr>
</tbody>
</table>

*Defined as patients diagnosed within 3 months of recruitment who were culture-positive for TB.
†Denominator = 300 unless otherwise indicated. All participants with probable (n = 6) or possible (n = 44) TB, 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.
WHO = World Health Organization; PPV = positive predictive value; NPV = negative predictive value; AFB = acid-fast bacilli; CXR = chest radiography; TB = tuberculosis.
18.5 kg/m² to our symptom complex made little difference to sensitivity and NPVs, in contrast to WHO Clinical Stage 3 or 4, which increased sensitivity and NPVs to 90% but halved specificity. Addition of haemoglobin < 10 g/dl improved the sensitivity and NPV of the symptom complex to respectively 82% and 90%, and combining this with WHO Stage 3 or 4, BMI < 18.5 kg/m² further increased sensitivity to 90%, but halved specificity.

Smear microscopy did not change the performance of the symptom complex, in contrast to CXR, which increased sensitivity to 92% for features compatible with active TB, and 96% for any CXR abnormality. A combination of symptom complex or any CXR abnormality had a sensitivity and NPV of 96%, which was further improved by the addition of CD4 < 100 cells/mm³, which missed only 2% of TB cases and was our most sensitive combination (98%).

The WHO symptom screen¹⁷ had a sensitivity, specificity, PPV and NPV of respectively 96%, 5%, 21% and 83% in our patients. The addition of CXR increased the sensitivity and NPV to 100% for both features compatible with active TB and any CXR abnormality.

### Table 2: Combinations of TB* screening criteria from this study and performance of WHO algorithm¹⁷ in our study population (n = 244)

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

* Defined as patients diagnosed within 3 months of recruitment who were culture-positive for TB. All participants with probable (n = 6) or possible (n = 44) TB, 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). TB = tuberculosis; WHO = World Health Organization; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; C = cough; 2w = 2 weeks; A = appetite loss; S = night sweats; BMI = body mass index (in kg/m²); HB = haemoglobin (in g/dl); AF = acid-fast bacilli; CXR = chest radiograph; F = fever; W = weight loss.

≥ Time to ART start and mortality

Of 361 patients, 266 (74%) initiated ART by 1 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 TB (median 64 days, n = 190) vs. those with TB (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 TB (n = 4), acute renal failure (n = 2), 1 each of septicaemia, gastroenteritis, cryptococcal meningitis, cardiomypathy and pneumonia; and unknown (n = 9), of whom three fulfilled case definitions for TB but...
did not start anti-tuberculosis treatment). Documented causes of on-ART mortality \( (n = 6) \) were one each of TB, cryptococcal meningitis, pneumonia and septicaemia, and unknown \( (n = 3) \).

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).

**DISCUSSION**

One third of our patients referred to start ART had undiagnosed TB, 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 TB. 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 TB.\(^{21}\) Our 18% prevalence of culture-confirmed PTB 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 TB. Individuals with advanced HIV disease often reach HIV care due to symptoms of TB, underscores 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 that smear microscopy had very poor sensitivity, consistent with other studies;\(^{15,19,23–25}\) however, 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 TB among apparently healthy individuals prior to starting IPT, requiring a high sensitivity and NPV; however, this is at the cost of low specificity. If all individuals identified as TB suspects, based on a symptom combination with relatively low specificity, are investigated with new rapid molecular diagnostics, such as Xpert\(^ {27} \) MTB/RIF \( \text{Cepheid, Sunnyvale, CA, USA} \) at US$17 per cartridge,\(^ {28} \) the cost to health services may be substantial; the cost-effectiveness of a range of algorithms for different settings needs to be investigated. Ninety per cent of our culture-proven TB cases were smear-negative, and Xpert MTB/RIF has reported sensitivities from 43% to 73% for smear-negative, culture-positive TB from a single sputum sample.\(^ {15,27} \) An algorithm requiring Xpert-negative TB suspects to undergo further evaluation using sputum culture, trial of antibiotic and CXR will potentially delay anti-tuberculosis treatment.

CXR improved the 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 CXR radiography to augment the WHO symptom screen in high TB prevalence settings is supported by a recent meta-analysis\(^ {26} \) and WHO guidance,\(^ {17} \) and in our study population it increased sensitivity and NPV to 100%. Our data show that CXR facilitates the prompt initiation of anti-tuberculosis treatment. Although implementation of CXR 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 anti-tuberculosis treatment based on clinical and radiological features prior to the availability of culture results; even with liquid culture, the median time to treatment start based on positive culture was 37 days. CXR provides a basis for rapid initiation of anti-tuberculosis treatment, both to reduce individual risk of death and also reduce risk of onward transmission in both clinic and community, and procedures should be in place to ensure follow-up of TB suspects.\(^ {30} \) The cost per CXR has been estimated at only US$2.\(^ {30} \) The reported sensitivity of Xpert MTB/RIF among smear-negative TB cases \( \text{most ART-eligible patients will be smear-negative} \) is lower than CXR in this study, but it has much higher specificity.\(^ {27} \) Implementation of Xpert MTB/RIF should similarly reduce time to 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 among patients commencing ART,\(^ {31–33} \) and may reflect undiagnosed TB. Adding anaemia to our symptom complex increased sensitivity, and supports the clinical practice of investigating all anaemic patients for TB 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 TB cases missed and ensuring a robust case definition for possible TB. One third of participants without a review visit are known to have died, underscoring how ill individuals were at enrolment. TB cannot be excluded as cause of death among all patients; hence, we may have underestimated true TB 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 CXR, 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 TB among patients presenting for ART to a public sector HIV clinic. These patients need routine systematic investigation for TB. Until accurate point-of-care diagnostic tests are available, our results suggest that CXR is a useful addition to routine screening, which allows rapid initiation of anti-tuberculosis treatment. Given the high mortality of patients awaiting investigation results,2,4,34 presumptive anti-tuberculosis treatment for high-risk individuals also needs to be evaluated.35

Acknowledgements

The authors thank the study participants; the nursing and medical staff of Tshepong Hospital Health Services, South Africa; the staff of National Health Laboratory Services, Tshepong Hospital, South Africa; and the staff of Aurum Institute for their essential contributions to this study.

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ADG was supported by a UK Department of Health Public Health Career Scientist award. Sources of support in form of grants, gifts, equipment and/or drugs: partial costs of staff provided by PEPFAR. EV and BL received TB-HIV research training funded by the Fogarty International Center (two grants RTW007370/3).

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the CDC.

References


### APPENDIX

#### Table A1: Demographic and clinical characteristics of patients with definite and possible prevalent undiagnosed active TB*

<table>
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<tr>
<th>Characteristic</th>
<th>Definite TB</th>
<th>Possible TB</th>
<th>P value</th>
<th>Characteristic</th>
<th>Definite TB</th>
<th>Possible TB</th>
<th>P value</th>
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*Probable cases (n = 6) not shown.
†Denominator = 64 unless otherwise indicated.
‡Denominator = 44 unless otherwise indicated.
§χ² test.
¶Fisher’s exact test.
#US$1 = 8.1 ZAR (as of 14 May 2012).
TB = tuberculosis; ZAR = South African Rand; WHO = World Health Organization; CXR = chest radiography; PTB = pulmonary TB; EPTB = extra-pulmonary TB.
## Table A2  Characteristics of study population and risk factors for undiagnosed prevalent active TB*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 300)†</th>
<th>Active TB prevalence (n = 64/300)</th>
<th>Unadjusted OR (95%CI)</th>
<th>Adjusted OR (95%CI)‡</th>
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<td>n/N (%)</td>
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<td>202 (67.3)</td>
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<td>11/51 (21.6)</td>
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<td>30–39</td>
<td>122 (40.7)</td>
<td>29/122 (23.8)</td>
<td>1.13 (0.52–2.49)</td>
<td>1.04 (0.44–2.46)</td>
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<td>40–49</td>
<td>80 (26.7)</td>
<td>17/80 (21.3)</td>
<td>0.98 (0.42–2.31)</td>
<td>0.91 (0.36–2.31)</td>
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<tr>
<td>&gt;50</td>
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<td>7/47 (14.9)</td>
<td>0.64 (0.22–1.81)</td>
<td>0.58 (0.19–1.75)</td>
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<td>40/176 (22.7)</td>
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<td>Average monthly income per household member, ZAR/person§</td>
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<td>263 (87.7)</td>
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<td>1.85 (0.89–3.83)</td>
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<tr>
<td>Alcohol status</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Never drank</td>
<td>148 (49.3)</td>
<td>26/148 (17.6)</td>
<td>1.0</td>
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</tr>
<tr>
<td>Former</td>
<td>83 (27.7)</td>
<td>22/83 (26.5)</td>
<td>1.69 (0.89–3.23)</td>
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</tr>
<tr>
<td>Current (last 1 year)</td>
<td>69 (23.0)</td>
<td>16/69 (23.2)</td>
<td>1.42 (0.70–2.86)</td>
<td></td>
</tr>
<tr>
<td>Contact with TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>179 (59.7)</td>
<td>38/179 (21.2)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>121 (40.3)</td>
<td>26/121 (21.5)</td>
<td>1.02 (0.58–1.78)</td>
<td></td>
</tr>
<tr>
<td>History of TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>216 (72.0)</td>
<td>56/216 (25.9)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>84 (28.0)</td>
<td>8/84 (9.5)</td>
<td>0.30 (0.14–0.66)</td>
<td>0.29 (0.13–0.65)</td>
</tr>
<tr>
<td>WHO stage at enrolment (n = 253)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32 (12.6)</td>
<td>10/32 (31.3)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>85 (33.6)</td>
<td>14/85 (16.5)</td>
<td>0.43 (0.17–1.11)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>121 (47.8)</td>
<td>28/121 (23.1)</td>
<td>0.66 (0.28–1.56)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15 (5.9)</td>
<td>2/15 (13.3)</td>
<td>0.34 (0.06–1.79)</td>
<td></td>
</tr>
<tr>
<td>CD4 at enrolment, cells/mm³ (n = 298)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>40 (13.6)</td>
<td>8/40 (20.0)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>50–99</td>
<td>71 (23.3)</td>
<td>14/71 (19.7)</td>
<td>0.98 (0.37–2.60)</td>
<td>1.12 (0.39–3.18)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>187 (63.1)</td>
<td>41/187 (21.9)</td>
<td>1.12 (0.48–2.62)</td>
<td>1.16 (0.47–2.84)</td>
</tr>
</tbody>
</table>

* Defined as patients diagnosed within 3 months of recruitment who were culture-positive for TB.
1Denominator = 300 unless otherwise indicated. All participants with probable (n = 6) or possible (n = 44) TB, and those without sputum culture results (n = 11) have been excluded.
2Adjusted for sex, age category, number of household members, smoking status, history of TB and CD4 at enrolment.
3US$1 = 8.1 ZAR (as of 14 May 2012).
4TB = tuberculosis; OR = odds ratio; CI = confidence interval; ZAR = South African Rand; WHO = World Health Organization.
Table A3  Multivariable logistic regression analysis for associations between symptoms and prevalent undiagnosed active TB*

<table>
<thead>
<tr>
<th>Marker</th>
<th>Active TB prevalence (n/N = 64/300)</th>
<th>Unadjusted OR (95%CI; n = 300)</th>
<th>P value</th>
<th>Adjusted OR (95%CI; n = 300)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cough</td>
<td>20/168 (11.9)</td>
<td>1.0</td>
<td>&lt;0.0001</td>
<td>1.0</td>
<td>0.0009</td>
</tr>
<tr>
<td>Cough &lt;2 weeks</td>
<td>16/59 (27.1)</td>
<td>2.75 (1.31–5.77)</td>
<td>3.61 (1.51–8.64)</td>
<td>3.46 (1.62–7.41)</td>
<td></td>
</tr>
<tr>
<td>Cough &gt;2 weeks</td>
<td>28/73 (38.6)</td>
<td>4.60 (2.37–8.94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No fever</td>
<td>41/219 (18.7)</td>
<td>1.0</td>
<td>0.007</td>
<td>1.0</td>
<td>0.79</td>
</tr>
<tr>
<td>Fever &lt;=2 weeks</td>
<td>7/43 (16.3)</td>
<td>0.84 (0.35–2.03)</td>
<td>1.03 (0.37–2.88)</td>
<td>1.35 (0.57–3.18)</td>
<td></td>
</tr>
<tr>
<td>Fever &gt;2 weeks</td>
<td>16/38 (42.1)</td>
<td>3.16 (1.52–6.54)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No night sweats</td>
<td>26/178 (14.6)</td>
<td>1.0</td>
<td>0.002</td>
<td>1.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Night sweats &lt;=2 weeks</td>
<td>9/36 (25.0)</td>
<td>1.95 (0.82–4.61)</td>
<td>2.40 (0.87–6.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night sweats &gt;2 weeks</td>
<td>29/86 (33.7)</td>
<td>2.97 (1.62–5.48)</td>
<td>1.89 (0.93–3.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No tiredness</td>
<td>12/92 (13.0)</td>
<td>1.0</td>
<td>0.0001</td>
<td>1.0</td>
<td>0.23</td>
</tr>
<tr>
<td>Tiredness &lt;=2 weeks</td>
<td>7/67 (10.5)</td>
<td>0.78 (0.29–2.09)</td>
<td>0.47 (0.13–1.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiredness &gt;2 weeks</td>
<td>45/141 (31.9)</td>
<td>3.13 (1.55–6.31)</td>
<td>1.30 (0.51–3.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No loss of appetite</td>
<td>24/150 (16.0)</td>
<td>1.0</td>
<td>0.001</td>
<td>1.0</td>
<td>0.30</td>
</tr>
<tr>
<td>Loss of appetite &lt;=2 weeks</td>
<td>7/54 (13.0)</td>
<td>0.78 (0.32–1.94)</td>
<td>0.64 (0.19–2.10)</td>
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</tr>
<tr>
<td>Loss of appetite &gt;2 weeks</td>
<td>33/96 (34.4)</td>
<td>2.75 (1.50–5.04)</td>
<td>1.60 (0.72–3.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chest pain</td>
<td>30/161 (18.6)</td>
<td>1.0</td>
<td>0.13</td>
<td>1.0</td>
<td>0.94</td>
</tr>
<tr>
<td>Chest pain &lt;=2 weeks</td>
<td>10/57 (17.5)</td>
<td>0.93 (0.42–2.04)</td>
<td>0.87 (0.33–2.33)</td>
<td></td>
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</tr>
<tr>
<td>Chest pain &gt;2 weeks</td>
<td>24/82 (29.3)</td>
<td>1.81 (0.97–3.36)</td>
<td>0.89 (0.43–1.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No difficulty breathing</td>
<td>53/261 (20.3)</td>
<td>1.0</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty breathing &lt;=2 weeks</td>
<td>3/14 (21.4)</td>
<td>1.07 (0.29–3.97)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty breathing &gt;2 weeks</td>
<td>8/25 (32.0)</td>
<td>1.85 (0.76–4.51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No haemoptysis</td>
<td>58/277 (20.9)</td>
<td>1.0</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoptysis reported</td>
<td>6/23 (26.1)</td>
<td>1.33 (0.50–3.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported weight loss (n = 299)</td>
<td>57/269 (21.2)</td>
<td>1.08 (0.42–2.76)</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reported weight loss</td>
<td>6/30 (20.0)</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Defined as patients diagnosed within 3 months of recruitment who were culture-positive for TB.

Denominator = 300 unless otherwise indicated. All participants with probable (n = 6) or possible (n = 44) TB, and those without sputum culture results (n = 11) have been excluded.

TB = tuberculosis; OR = odds ratio; CI = confidence interval.
CONTEXTE : En Afrique du Sud, nous avons investigué la prévalence du dépistage et évalué ses modalités dans les cas de tuberculose (TB) non diagnostiquée chez les adultes éligibles pour le traitement anti-rétroviral (ART).

MÉTHODES : On a dépisté la TB chez les individus au moyen des symptômes, du cliché thoracique (CXR) et de deux échantillons de crachats pour examen microscopique et culture et on les a suivis pendant moins de 6 mois pour déterminer les diagnostics de TB.

RÉSULTATS : Parmi 361 participants (67% de femmes, âge médian 38 ans, décompte médian des CD4 120 cellules/mm³), la culture des crachats a été positive chez 64 participants (18%). La réponse a été positive à n’importe quelle définition des cas de TB chez 114 participants (32%) (positifs à la culture et/ou au frottis ; ou amélioration sous traitement spécifique). Un dépistage des symptômes comportant n’importe lequel des symptômes suivants : toux, inappétence ou sueurs nocturnes pendant > 2 semaines a une sensibilité de 74,5% et une spécificité de 50,8%. La sensibilité est accrue par le CXR (jusqu’à 96,1%) mais non par l’examen microscopique des crachats. La sensibilité du dépistage par symptôme préconisée par l’Organisation Mondiale de la Santé a été de 96,1% et la spécificité de 5,2% dans la population de notre étude ; l’adjonction du CXR a augmenté la sensibilité jusqu’à 100%. La durée médiane avant la mise en route du traitement TB a été de 8 jours pour les diagnostics basés sur le CXR (n = 72) vs. 37 jours pour les diagnostics basés sur la seule culture des crachats (n = 14).

CONCLUSIONS : La prévalence très élevée de TB non diagnosticée chez les patients se présentant pour l’ART impose une investigation de routine. Les CXR augmentent la sensibilité de manière substantielle, permettent une mise en route rapide du traitement et devraient être exécutés en routine lorsqu’ils sont disponibles dans l’espoir d’une amélioration du diagnostic sur le site de soins.

RESUMEN

MARCO DE REFERENCIA: Se investigó la prevalencia de casos de tuberculosis (TB) no diagnosticada y se evaluaron las modalidades de búsqueda de los mismos en los adultos aptos para recibir el tratamiento antirretrovírico (ART) en Suráfrica.

MÉTODOS: Se llevó a cabo una detección sistemática de la TB con base en los síntomas, la radiografía de tórax (CXR) y dos muestras de esputo para microscopía y cultivo y un seguimiento hasta de 6 meses, con el objeto de establecer el diagnóstico.

RESULTADOS: En los 361 participantes (67% mujeres, con una mediana de la edad de 38 años y de recuento de células CD4 de 120 células/mm³), se encontró un cultivo de esputo positivo en 64 casos (18%). Ciento catorce personas (32%) cumplieron con alguna definición de caso de TB (cultivo o baciloscopia positiva o mejora con un tratamiento de prueba). Una estrategia de detección por síntomas que incluyese tos, pérdida de apetito o sudores nocturnos durante más de 2 semanas ofreció una sensibilidad de 74,5% y una especificidad de 50,8%.

La CXR aumentó la sensibilidad a 96,1%, pero la baciloscopia del esputo no produjo ningún efecto. La estrategia de la Organización Mundial de la Salud de detección de la TB mediante los síntomas presentó una sensibilidad de 96,1% y una especificidad de 5,2% en la población estudiada; la adición de la CXR aumentó la sensibilidad a 100%. La mediana del lapso hasta el comienzo del tratamiento antituberculoso fue 8 días en los casos con diagnóstico basado en la CXR (n = 72), comparada con 37 días en los casos basados solo en el cultivo de esputo (n = 14).

CONCLUSIÓN: La prevalencia muy alta de TB no diagnosticada en las personas que reciben el ART exige una investigación sistemática de la TB en estos pacientes. La CXR mejoró de manera considerable la sensibilidad del diagnóstico, favoreció el inicio rápido del tratamiento y se debería practicar de rutina, siempre que esté al alcance, mientras no se cuente con mejores medios diagnósticos de la TB en el lugar de la consulta.