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A clinical score has utility in tuberculosis case-finding among patients with HIV: A feasibility study from Bissau

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\textbf{ABSTRACT}

Background: Clinical scores are promising case-finding tools for tuberculosis (TB) among HIV-infected patients. The Bandim TBscore has been shown to increase the diagnostic yield among patients with presumed TB in general, but has not previously been tested among newly diagnosed HIV patients at high risk of TB.

Methods: HIV-infected patients were included in this cross-sectional study. A pre-post-intervention study design was used to assess the outcome of a change in practice, i.e. the application of a clinical score (TBscore) consisting of 13 signs and symptoms to assess the need for further TB diagnostics. Patients with a TBscore \( \geq 2 \) were evaluated using smear microscopy and Xpert MTB/RIF. A TB diagnosis was made based on microbiology or clinical evaluation. The sensitivity and specificity of the TBscore were compared with those of World Health Organization symptoms.

Results: The TB prevalence among newly enrolled HIV-infected patients during the study period was 13.4\% (22/164). Using the TBscore and a diagnostic algorithm, it was possible to increase the proportion of patients started on TB treatment from 2.7\% (10/367) the year before the study to 10.4\% (17/164) during the study period. Five patients diagnosed with TB were not started on TB treatment as they were lost to follow-up or died. With a cut-off value of 2, the TBscore had a sensitivity, specificity, positive predictive value, and negative predictive value of 95.5\% (21/22), 36.9\% (41/111), 23.1\% (22/118), and 97.6\% (41/42), respectively.

Conclusion: The TBscore is useful for standardized TB screening among HIV-infected individuals and may be a valuable tool to prioritize patients at high risk of TB.

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Introduction

The World Health Organization (WHO) recommends that all HIV-infected individuals are screened for active tuberculosis (TB) and given isoniazid preventive therapy if active TB is not detected (WHO, 2011). The screening and diagnosis of active TB among HIV-infected individuals is an important issue for HIV care in the countries of Sub-Saharan Africa and other low-income countries. The development of practical algorithms, both for TB screening and active case-finding, is an important aspect, and the WHO TB symptom screening algorithm is recommended for screening. This has been shown to have a good negative predictive value (NPV) for TB in antiretroviral therapy (ART)-naive patients, although specificity has been found to be low in many studies. The current WHO recommendation is to screen HIV-infected individuals for one of the following symptoms: current cough, weight loss, night sweats, or fever (WHO, 2011; World Health Organization, 2011). HIV-infected individuals may, however, show atypical signs and symptoms of TB (Burman and Jones, 2003) and it is thus a...
challenge to ensure that all newly diagnosed HIV patients are screened for TB. The expertise of health care workers (HCWs) varies, and standardized TB screening could help HCWs become aware of presumptive TB cases.

Culturing of *Mycobacterium tuberculosis* is considered the gold standard for diagnosing pulmonary TB, but it is often not possible in low-income countries (Lawn and Wood, 2011). Sputum smear microscopy is generally available, but TB cases may be overlooked when the diagnosis is only determined with this test (Rudolf et al., 2014). For HIV-infected presumptive TB cases, nucleic acid amplification analysis using the Xpert MTB/RIF test is recommended (World Health Organization, 2013). A fundamental problem for culture, sputum smear, and Xpert MTB/RIF is sputum-scarce pulmonary TB together with extrapulmonary TB. New screening methods are thus urgently needed (Corbett and MacPherson, 2013).

A number of clinical algorithms are available and a recent systematic review showed variable sensitivity and specificity, as well as a need for implementation in practice (Jensen et al., 2019). Studies evaluating the WHO symptom screening have reported sensitivity ranging between 40% and 96% and specificity ranging between 14% and 88%, and limited data are available on feasibility and implementation in practice. The TBscore, a clinical score consisting of signs and symptoms, was developed in Guinea-Bissau to monitor patients with TB receiving treatment (Wejse et al., 2008). The TBscore is a rapid and inexpensive tool, and has previously been shown to be useful for TB case-finding among adults with HIV seeking health care in Bissau (Rudolf et al., 2014).

The aim of this feasibility study was to describe the utility of the TBscore as a point-of-care case-finding tool for TB among HIV-infected patients in Guinea-Bissau, in order to increase TB detection and assess the usefulness for excluding TB.

**Methods**

**Study design and study population**

This cross-sectional study was conducted in the HIV Clinic of Hospital Nacional Simão Mendes (HNSM) in Bissau, Guinea-Bissau. The study was a feasibility study to assess the practicality of implementing the TBscore in the clinical routine for newly diagnosed HIV patients. The Xpert MTB/RIF test became available 2 years before the study period. The Bissau HIV Cohort is a clinical cohort of HIV-infected individuals initiated in 2007; this cohort has been described in detail elsewhere (Oliveira et al., 2012; Jespersen et al., 2015). Patients aged ≥15 years were included in this study between February 25 and June 30, 2014, on the same day they were enrolled into the Bissau HIV Cohort. Patients were offered participation in the study if they were not pregnant and had not started TB treatment within the last year. As a part of the usual inclusion procedure in the cohort, current symptoms were recorded, including those recommended by the WHO for symptom-based screening (cough, weight loss, fever, and night sweats). Additionally, a trained HCW interviewed patients about TB symptoms and a physical examination was performed based on the TBscore (Wejse et al., 2008; Rudolf et al., 2013a).

**TBscore**

The TBscore consists of five symptoms and six signs. The symptoms are self-reported cough, dyspnoea, night sweats, haemoptysis, and chest pain. The signs are anaemia (assessed by paleness of conjunctivae), tachycardia (pulse >90/min), positive finding on lung auscultation (any of the following findings present: crepitation, rhonchi, subdue or absent respiratory sounds), fever (axillary temperature >37.0 °C), body mass index (BMI) 16–18 kg/m² (1 point) or <16 kg/m² (2 points), and mid-upper arm circumference (MUAC) 200–220 mm (1 point) or <200 mm (2 points). All items besides lung auscultation are assessable by a trained nurse. For each positive sign or symptom, the patient is given 1 point, and the maximum possible score is 13 points (Table 1) (Rudolf et al., 2013b). We have previously found that a population of TB patients in Bissau reported weight loss even though they had objectively gained weight (Wejse et al., 2008). We chose not to further examine patients who reported weight loss as the only symptom.

**Algorithm**

During the study period, an algorithm was implemented in which newly diagnosed HIV patients with a TBscore ≥2 were asked to produce sputum if they were able to. Previously, patients had only been investigated for TB if suspected by the investigating clinician. The health care providers working in the clinic were the same over the entire observation period, and there was no difference in the level of training, experience, or motivation in the years before and during the study period. Two samples were sent to the laboratory for smear microscopy (Ziehl–Neelsen staining) and Xpert MTB/RIF (GeneXpert IV Cepheid, USA) testing for *M. tuberculosis* and rifampicin resistance; test results were available on the next working day. X-ray was available elsewhere in the hospital, and the fee for this was paid for by the study. Evaluation of the chest X-ray was also done the next working day by a physician in the HIV clinic. TB culture was unavailable at the national laboratory in Bissau during the study period. The tuberculin skin test (TST) was applied to the inside of the forearm, and patients were told to come back after 48–72 h to have it read. The TBscore was calculated for all patients, irrespective of their ability to produce sputum.

Patients who had a total TBscore ≥2 had a chest X-ray. This was also the case if the TBscore was <2 but the TST was ≥5 mm. Patients with a TBscore <2 were categorized as not likely to have TB, based on our previous finding of a NPV of 99% at this cut-off (Rudolf et al., 2014). If the X-ray showed signs of pneumonia, the patient was given a 7-day course of amoxicillin, followed by a new chest X-ray after 2 weeks. The final TB diagnosis was established based on the following: TB = sputum positive for acid-fast bacilli (AFB) OR sputum positive for Xpert OR clinical judgment OR X-ray findings not resolved after a short course of antibiotics, according to WHO guidelines (World Health Organization, 2017). If rifampicin resistance was detected by Xpert MTB/RIF, the patient was referred to the physician responsible for treating multidrug-resistant (MDR) TB. At any time, the treating physician could overrule the algorithm.

### Table 1

<table>
<thead>
<tr>
<th>Signs and symptoms in the TBscore</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night sweats</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Haemoptysis</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Temperature &gt;37 °C (auxiliary)</td>
</tr>
<tr>
<td>Heart rate &gt;90 bpm</td>
</tr>
<tr>
<td>Anaemic eyes</td>
</tr>
<tr>
<td>Abnormal lung auscultation</td>
</tr>
<tr>
<td>MUAC &lt;220 mm</td>
</tr>
<tr>
<td>MUAC &lt;200 mm</td>
</tr>
<tr>
<td>BMI &lt;18 kg/m²</td>
</tr>
<tr>
<td>BMI &lt;16 kg/m²</td>
</tr>
</tbody>
</table>

bpm, beats per minute; MUAC, mid-upper arm circumference; BMI, body mass index.
and start patients on TB treatment if TB was diagnosed based on clinical judgement.

If the patient did not return to the clinic as planned, contact was attempted three times by telephone. If the patient still did not return to finish the algorithm for TB investigation, they were considered lost to screening (LTS).

Treatment initiation yield

Using the TB registry at the HIV clinic together with the cohort database, we compared the proportions of patients started on TB treatment in the 5 years before this study and during the study period. The previous diagnostic algorithm for TB in the HIV cohort was similar to that used in the current study, except that the TBscore was not applied, thus referral to TB diagnostics relied on clinical suspicion. The same methods were available: patients were referred for sputum microscopy or Xpert MTB/RIF (available from 2012), X-ray, and TST, and TB diagnosis was based on microbiology or clinical judgement, as described above.

HIV testing

Screening for HIV was done with a rapid test (Determine HIV-1/2 Assay; Abbott Laboratories, Tokyo, Japan). The HIV type was determined using a discriminatory HIV rapid test (Hønge et al., 2014). Depending on their availability, one of the three following tests was used: First Response HIV Card 1-2.0 (PMC Medical India Pvt Ltd), Genie III HIV-1/HIV-2 (Bio-Rad, Steenvoorde, France), or ImmunoComb HIV 12 Bispot (Organics, Yavne, Israel).

Statistical analyses

Data were analysed using Stata/MP 11.2 (StataCorp LP, College Station, TX, USA). The Chi-square test was used to assess categorical variables. Continuous variables were compared using the Wilcoxon rank-sum test (non-normal distribution). The Kruskal–Wallis test was used to compare continuous variables not normally distributed, in the case of more than two categories.

Results

The inclusion of patients in the study is described in Figure 1. Forty-seven patients were not included because enrollment stopped due to an Ebola outbreak in the neighboring country of Guinea-Conakry (Dixon et al., 2014) and for logistical reasons. Characteristics of the non-included patient were similar to those of the included patients (data not shown).

![Figure 1](#). Flow of patients. Examinations performed and categorization of patients. X-ray: chest X-ray; Amoxicillin: patients receiving amoxicillin for 7 days; No amoxicillin: patients not receiving amoxicillin; TST: tuberculin skin test; LTS: lost to screening; TB: diagnosed with tuberculosis; Non-TB: categorized as not having tuberculosis.
Table 2
Characteristics of TB patients, non-TB patients, and patients lost to screening.

<table>
<thead>
<tr>
<th></th>
<th>TB patients</th>
<th>Non-TB patients</th>
<th>Lost to screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 22</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>14/22 (63.4)</td>
<td>36/111 (32.4)</td>
<td>12/31 (38.7)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>36.5</td>
<td>37.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Civil status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married (%)</td>
<td>15/22 (68.2)</td>
<td>56/111 (50.5)</td>
<td>15/31 (48.4)</td>
</tr>
<tr>
<td>Divorced (%)</td>
<td>0/22 (0.0)</td>
<td>6/111 (5.4)</td>
<td>2/31 (6.5)</td>
</tr>
<tr>
<td>Single (%)</td>
<td>6/22 (27.3)</td>
<td>30/111 (27.0)</td>
<td>9/31 (29.0)</td>
</tr>
<tr>
<td>Widowed (%)</td>
<td>1/22 (4.6)</td>
<td>19/111 (17.1)</td>
<td>5/31 (16.1)</td>
</tr>
<tr>
<td>Went to school (%)</td>
<td>18/22 (81.8)</td>
<td>76/110 (69.1)</td>
<td>16/31 (51.6)</td>
</tr>
<tr>
<td>Literate/can read (%)</td>
<td>18/19 (94.7)</td>
<td>65/84 (77.4)</td>
<td>14/22 (60.9)</td>
</tr>
<tr>
<td>CD4 cells/μl within 30 days of enrolment (IQR)</td>
<td>183.5 (112.5–278.5)</td>
<td>300.5 (150–456.5)</td>
<td>264 (136–436)</td>
</tr>
</tbody>
</table>

TB, tuberculosis; IQR, interquartile range.

a For TB patients and non-TB patients.

Patient characteristics

A total of 22 patients (13.4%) were diagnosed with TB, 111 (67.7%) were categorized as non-TB cases, and 31 (18.9%) were LTS (Figure 1). The baseline characteristics of patients in each of the three groups are shown in Table 2. A total of 132 of the 164 patients included (80.5%) had a TST applied and 82 (62.1%) came back after 48–72 hours to have it read. Of these patients, 27 (32.9%) had a TST reaction >5 mm. Sixty-five patients (39.6%) provided a sputum sample, of which four (6%) were smear-positive.

TB cases

Seventeen of the 22 (77.3%) patients diagnosed with TB had produced a sputum sample at inclusion and 13/22 (59.1%) had a positive Xpert MTB/RIF test. Two patients tested positive for rifampicin resistance. Nine of the 22 patients were diagnosed based on chest X-ray and a lack of improvement in symptoms after treatment with amoxicillin. These nine patients were given a clinical diagnosis of TB by the physicians in the HIV clinic based on the WHO criteria (World Health Organization, 2011).

TBscore

Forty-three patients (26.2%) had a TBscore <2 and 38 of these were categorized directly as not likely to be TB patients. Five had a chest X-ray performed despite a TBscore <2 (Figure 1). Three patients had a TBscore <2, but reported either a current cough, night sweats, or fever; one of these was investigated with sputum analysis.

The median TBscore for non-TB cases was 2 (interquartile range (IQR) 1–4); this was significantly lower than the median score for the TB patients, which was 5 (IQR 3–7) (p < 0.01), and the median score for the patients who were LTS, which was 4 (IQR 3–6) (p < 0.01). The median TBscore did not differ between TB patients and patients who were LTS (p = 0.21). Table 3 shows the distribution of signs and symptoms in the three groups. Among patients who were LTS, significantly fewer had an axillary temperature >37°C (p = 0.02) compared with TB cases, but patients who were LTS more often complained of night sweats (p = 0.02), cough (p = 0.03), and chest pain (p = 0.01) compared with non-TB cases. If, for the purpose of a sensitivity analysis, it was assumed that all patients who were LTS were lost because they had died of TB, the total number of TB cases would be 53/164 (32.3%).

The sensitivity and specificity for the different cut-off values of the TBscore are presented in Figure 2; patients LTS were censored from this analysis. Calculations were based on the group of TB patients and the group of non-TB patients. We used 2 as the cut-off value, which had a sensitivity of 95.5% (21/22), a specificity of 36.9% (41/111), a positive predictive value (PPV) of 23.1% (22/118), and a NPV of 97.6% (41/42). Based on this study, any one of the symptoms recommended by the WHO had a sensitivity of 100% (22/22) and a specificity of 15.3% (17/111).

Of the 164 patients, 121 (73.8%) had a TBscore >1 (cut-off value 2). If we had chosen to use a cut-off value of 1 (TBscore >0), we would have had to examine 148 (90.2%) of the patients. With a TBscore cut-off value of 3 (TBscore >2), 97 (59.1%) of the patients would have had to be examined further. A receiver operating characteristics (ROC) curve was drawn, showing optimal use for a TBscore cut-off value of 3 (TBscore >2), with an area under the ROC curve of 0.77. Eighty-eight percent of patients reported one of the four screening symptoms recommended by the WHO and 84% reported having weight loss.

Table 3
TBscore signs and symptoms in TB patients, non-TB patients, and patients lost to screening.

<table>
<thead>
<tr>
<th>Signs and symptoms in the TBscore</th>
<th>TB patients</th>
<th>Non-TB patients</th>
<th>Lost to screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Night sweats (%)</strong></td>
<td>10/22 (45.5)</td>
<td>29/111 (26.1)</td>
<td>15/31 (48.4)</td>
</tr>
<tr>
<td><strong>Cough (%)</strong></td>
<td>15/22 (68.2)</td>
<td>31/111 (27.9)</td>
<td>15/31 (48.4)</td>
</tr>
<tr>
<td><strong>Haemoptysis (%)</strong></td>
<td>1/22 (4.6)</td>
<td>3/111 (2.7)</td>
<td>3/31 (9.7)</td>
</tr>
<tr>
<td><strong>Chest pain (%)</strong></td>
<td>14/22 (63.6)</td>
<td>47/111 (42.3)</td>
<td>21/31 (67.4)</td>
</tr>
<tr>
<td><strong>Dyspnoea (%)</strong></td>
<td>12/22 (54.6)</td>
<td>46/111 (41.4)</td>
<td>19/31 (61.3)</td>
</tr>
<tr>
<td><strong>Temperature &gt;37°C (axillary) (%)</strong></td>
<td>9/22 (40.9)</td>
<td>10/111 (9.0)</td>
<td>4/31 (12.9)</td>
</tr>
<tr>
<td><strong>Heart rate &gt;90 bpm (%)</strong></td>
<td>18/22 (81.8)</td>
<td>54/110 (49.1)</td>
<td>19/31 (61.3)</td>
</tr>
<tr>
<td><strong>Anaemic eyes (%)</strong></td>
<td>1/22 (4.6)</td>
<td>4/31 (12.9)</td>
<td>4/31 (12.9)</td>
</tr>
<tr>
<td><strong>Abnormal lung auscultation (%)</strong></td>
<td>6/22 (36.4)</td>
<td>22/109 (20.2)</td>
<td>9/31 (29.0)</td>
</tr>
<tr>
<td><strong>MUAC &lt;220 mm (%)</strong></td>
<td>12/22 (54.6)</td>
<td>31/111 (27.9)</td>
<td>14/31 (45.2)</td>
</tr>
<tr>
<td><strong>MUAC &lt;200 mm (%)</strong></td>
<td>4/22 (18.2)</td>
<td>13/111 (11.7)</td>
<td>6/31 (19.4)</td>
</tr>
<tr>
<td><strong>BMI &lt;18 kg/m&lt;sup&gt;2&lt;/sup&gt; (%)</strong></td>
<td>11/22 (50.0)</td>
<td>22/113 (19.8)</td>
<td>10/31 (32.3)</td>
</tr>
<tr>
<td><strong>BMI &lt;16 kg/m&lt;sup&gt;2&lt;/sup&gt; (%)</strong></td>
<td>3/22 (13.6)</td>
<td>10/111 (9.0)</td>
<td>4/31 (12.9)</td>
</tr>
</tbody>
</table>

TB, tuberculosis; bpm, beats per minute; MUAC, mid-upper arm circumference; BMI, body mass index.

a For TB patients and non-TB patients.
Treatment initiation yield

To evaluate the diagnostic yield of the TBscore, we compared the proportions of patients starting TB treatment in the years prior to and during the study period (Figure 3). The proportion of patients starting TB treatment increased from 2.7% (10/367) the year before the study to 10.4% (17/164) during the study (p < 0.01). During the study period, 22 patients (13.4%, 22/164) were diagnosed with TB but only 17 (10.4%, 17/164) were started on treatment, as the remaining five patients died or were lost to follow-up. During the study, 39.6% of all patients had a sputum smear performed and 23.5% of the patients starting TB treatment were smear-positive. The year before the study, 18% had a sputum smear performed and 20% of the patients starting TB treatment had a positive smear.

Discussion

It was found that systematic screening for TB among HIV-infected individuals using the TBscore resulted in a three-fold increase in the proportion of patients referred for TB diagnostics and subsequently starting on TB treatment. This increase could be explained by a higher use of diagnostic tools such as X-ray. However, the increased observation and clinical investigations needed for the TBscore may also have led to increased alertness towards TB. In a setting with a high prevalence of under-diagnosed TB, this is a simple measure to implement. Thus the study findings can be generalized to other similar HIV clinics in Africa and may carry important public health implications if more TB is uncovered and treated through implementing this low-cost clinical tool. At a cut-off value of 2 (TBscore > 1), the TBscore had a high sensitivity of 95.5% and a specificity of 36.9%. This score showed decreasing sensitivity together with increased specificity with higher cut-off values, with the ROC curve analysis indicating that a cut-off value of 3 would be optimal, although associated with a lower sensitivity.

We found that a large proportion of patients at the clinic presented with a wide variety of symptoms. This makes it difficult to screen patients by asking about only a few symptoms, as a very large group who should undergo further examination for TB would be excluded. The TBscore provides a systematic approach that needs more effort than just asking about the presence of the four WHO symptoms, but refers fewer for testing. This may limit the use
of expensive diagnostics without losing much sensitivity and could therefore be a simple tool to apply to HIV clinics in high TB incidence areas. However, this was not a head-to-head comparative study of the WHO symptom screening approach versus the TBscore approach to exclude TB; a trial with this purpose is therefore warranted.

Many studies have been performed in Africa to investigate the prevalence of HIV among TB patients (Corbett and MacPherson, 2013); however, data on TB prevalence among HIV-infected individuals are not available in some Sub-Saharan settings, including Bissau. The present study suggests that TB prevalence is likely to be at least 13.4% and that more TB cases may be identified with more intensified case-finding (Bjerregaard-Andersen et al., 2010). Studies from South Africa, Nigeria, and Senegal have reported TB prevalence of between 5% and 17.3% (Wood et al., 2007; Lawn et al., 2012; Illyasu and Babashani, 2009; Etard et al., 2009) among HIV-infected individuals.

Most data on TB describe cases of active infection. A less researched topic is the diagnostic pathway and the symptoms of presumptive TB, in particular in low-resource settings. Previous studies on presumptive TB performed by a group in Zimbabwe (MacPherson et al., 2011) and our group in Bissau (Rudolf et al., 2014; Porskrog et al., 2011; Rabna et al., 2009; Rudolf et al., 2017) have shown a high active TB prevalence of up to 98% among health care-seeking presumptive TB cases in the general population in Bissau (Rudolf et al., 2014). Yet, the body of literature on TB case-finding, in particular among HIV-infected individuals, is considerable, and we have reviewed this in a previous article (Jensen et al., 2019), demonstrating that a number of diagnostic algorithms are available, with and without biomarkers.

We have previously shown that HIV-infected patients may be lost to follow-up at all stages of HIV care in Bissau (Henge et al., 2013). Standardizing screening and diagnostic work-up are thus useful to ensure patients are followed through. The present study suggests that the TBscore can be used to identify those HIV-infected patients who are more likely to suffer from TB co-infection and ensure that they are referred for additional testing. This may indeed be possible to roll out, and almost as simple as a symptom-based screening tool, since it only involves a standardized approach for TB in clinics managing patients with presumed TB, where all symptoms and signs are noted systematically and scored. It is indeed manageable to ensure the investigation of patients with presumed TB from evidence-based algorithms instead of random referrals for further diagnostics. Despite the need for training of staff and implementation of procedures, it would probably be possible to do this at lower cost when compared to scaling up advanced microbiological diagnostics such as Xpert MTB/RIF in peripheral settings (Wejse, 2019).

(Getahun et al., 2011) found that screening for TB among HIV-infected individuals using any of the symptoms recommended by the WHO had an overall sensitivity of 78.9% and a specificity of 49.6%. For the symptoms described in the WHO recommendations, we found a sensitivity of 100% and a specificity of 15.3%. The present study suggests that a TBscore cut-off value of 2 has a sensitivity of 95.5% and a specificity of 36.9%.

Based on the study results, it is assumed that we did not overlook more TB patients than we would have done using the screening symptoms recommended by the WHO, taking into consideration that reported weight loss is not a good screening parameter in this setting. To support the assumption that we found most of the TB cases by using a TBscore cut-off of 2, a previous study showed that a TBscore cut-off of 3 had a sensitivity for TB of 92.6% and a specificity of 11.7% among HIV-infected individuals (Rudolf et al., 2014). Chest X-ray as a screening tool alone among HIV-infected individuals is problematic, because TB findings on X-rays depend on the disease stage of the HIV infection (Getahun et al., 2011; Reid and Shah, 2009); therefore it was decided to further examine only symptomatic patients and patients with a TST > 5 mm. The TST is not generally recommended for the investigation of active TB; it has low sensitivity in immunosuppressed persons and can be false-negative in active TB. It was commonly used by clinicians in the HIV clinic at the time of the study, which we therefore chose to report, as this had an impact on some of the diagnostic pathways.

An important weakness of this study is that TB diagnosis was not culture-confirmed and we could have missed TB cases in patients categorized as non-TB cases (Porskrog et al., 2011). A study by (Wood et al. (2007)) found that 5% of HIV-infected individuals had undiagnosed TB. All patients were screened using sputum analyses, and several TB patients co-infected with HIV showed none of the typical symptoms of TB. This suggests that it may be necessary to screen all HIV-infected individuals with sputum analyses regardless of reported symptoms. If not able to produce sputum, individuals with a TBscore of 0 or 1 were categorized as non-TB cases without further examination. We may therefore have missed sputum-scarse and asymptomatic patients who actually had TB. We may also have over-diagnosed TB, because although TB is the major opportunistic infection among HIV-positive persons in Sub-Saharan Africa, other conditions may present similarly and may be misinterpreted as TB. This may account for some of the TB diagnoses made on clinical evaluation.

The increase in diagnostic yield may have resulted from the increase in diagnostic samples being obtained. This may certainly be a part of the explanation, since the proportion providing a sputum sample doubled, and if the same proportion were smear-positive, it would be fair to assume that a random doubling of smears would double the yield. A five-fold increase in the yield was found in the present study, which is an indicator that relevant patients were sampled and that the increase in yield was not only because of increased sampling.

A limitation of the study is that the impact of the TBscore on diagnostic yield is not completely known. The full TB diagnostic evaluation and cascades of care for the time period before the study period were unfortunately not available. The number and proportion of patients eligible for TB evaluation referred for diagnostic evaluation, diagnosed with TB, and started on treatment should have been assessed, but the historic data used did not allow this. It is possible that more TB cases were present in the group of patients LTS who presented with a high prevalence of symptoms; this would cause the TB prevalence to be underestimated. A limitation of the current data presentation of sensitivity and specificity is that these were calculated without the LTS patients. Two LTS patients were diagnosed with TB at first sputum sample analysis, but were then lost, and treatment was thus not started. Adding these LTS patients with a TB diagnosis to the LTS group would decrease the sensitivity, as would adding the initially TB-negative LTS patients to the non-TB group. Another limitation is that this was an observational study, thus caution should be applied when interpreting the results, in particular in relation to the bias introduced by the increased use of diagnostics with a TBscore > 2. Furthermore, the awareness of patients having multiple symptoms and signs suggestive of TB may have led to an increased diagnosis of TB based on clinical judgement. However, comparing the different score levels and calculating the sensitivity and specificity has validity, with the caveat that it introduced a bias towards a higher probability of TB diagnosis for scores > 1 compared with an algorithm in which none or only those having an X-ray were referred. Likewise this strategy would lead to a bias towards fewer TB diagnoses compared with a situation where all were referred. This can only be resolved in a strictly randomized trial design. This was not possible in the current study, which only claims to be observational with the inherent weaknesses of such a
design. We are currently testing implementation of the TBscore in a randomized study (Trial ID: PACTR20161001838365).

In conclusion, the results of this study suggest that the TBscore can be used to screen patients and prioritize those patients who require further examination for TB. A simple clinical tool may alert overburdened staff of the need for increased testing specifically directed towards those in most need, and may hence increase the TB treatment initiation yield among newly diagnosed HIV patients. Further studies are needed to compare the performance of the TBscore with other screening tools and to test our findings in settings where TB cases are culture-confirmed.

Author contributions
JWA, FR, ISJ, and CW conceived the study idea and drafted the protocol. JWA, BLH, SJ, CM, and FGC enrolled patients and supervised the clinical data collection. JWA, BLH, and CW undertook the data analysis. JWA wrote the first draft of the manuscript, with a major revision by CW; the manuscript was subsequently revised by all authors. The final version was approved by all authors.

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Ethical approval
The study was approved by the National Ethics Committee of Guinea-Bissau, UCEPS (N. ref. 0659/CNES/INASA/2013). Informed consent was given by the participants, with a signature or fingerprint if they were illiterate.

Conflict of interest
The authors all declare that there are no conflicts of interest.

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