Provider-initiated symptom screening for tuberculosis in Zimbabwe: diagnostic value and the effect of HIV status

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Objective To assess the diagnostic value of provider-initiated symptom screening for tuberculosis (TB) and how HIV status affects it.
Methods We performed a secondary analysis of randomly selected participants in a community-based TB–HIV prevalence survey in Harare, Zimbabwe. All completed a five-symptom questionnaire and underwent sputum TB culture and HIV testing. We calculated the sensitivity, specificity, and positive and negative predictive values of various symptoms and used regression analysis to investigate the relationship between symptoms and TB disease.
Findings We found one or more symptoms of TB in 21.2% of 1858 HIV-positive (HIV+) and 9.9% of 7121 HIV-negative (HIV–) participants ($P < 0.001$). TB was subsequently diagnosed in 48 HIV+ and 31 HIV– participants. TB was asymptomatic in 18 culture-positive individuals, 8 of whom (4 in each HIV status group) had positive sputum smears. Cough of any duration, weight loss and, for HIV+ participants only, drenching night sweats were independent predictors of TB. In HIV+ participants, cough of ≥ 2 weeks' duration, any symptom and a positive sputum culture had sensitivities of 48%, 81% and 65%, respectively; in HIV– participants, the sensitivities were 45%, 71% and 74%, respectively. Symptoms had a similar sensitivity and specificity in HIV+ and HIV– participants, but in HIV+ participants they had a higher positive and a lower negative predictive value.
Conclusion Even smear-positive TB may be missed by provider-initiated symptom screening, especially in HIV+ individuals. Symptom screening is useful for ruling out TB, but better TB diagnostics are urgently needed for resource-poor settings.

Une traduction en français de ce résumé figure à la fin de l'article. *Al final del artículo se facilita una traducción al español.* الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Symptom questionnaires provide a quick, cheap and convenient way to identify individuals at a high risk of tuberculosis (TB) disease, termed TB suspects, who then need investigation with more definitive tests such as sputum microscopy, chest radiography and, when available, TB culture. Symptom screening for TB has high sensitivity when used to define TB suspects among patients who present themselves to health-care facilities for investigation of ill-health (i.e. passive case-finding) and is a key component of the the World Health Organization's DOTS strategy for combating TB. In particular, chronic cough was found to be both highly sensitive and to have a reasonably high positive predictive value for smear-positive TB at the primary health-care level in studies in the pre-HIV era leading up to the development of the DOTS strategy.[1–3]

More recently, provider-initiated TB screening (i.e. active case-finding) has become an important part of HIV care in resource-poor settings.[4–8] Ruling out active TB is necessary both for individual patient management and for TB infection control. Symptom screening is often the only practical approach but, at least in HIV-negative (HIV–) individuals, TB symptom screening is considerably less sensitive when used for provider-initiated TB screening than when applied to patients who have self-presented for the investigation of ill health.[9–15] Evidence is mounting that this may also be true for HIV-positive (HIV+) individuals.[5–8,12–16] Screening failure can have major adverse consequences. In patients starting antiretroviral therapy, undiagnosed TB is common and carries a substantially increased risk of death or hospitalization in the first few months of treatment.[8,17] Institutional outbreaks of TB have caused high morbidity and mortality among HIV-infected outpatients, especially in South Africa.[18] Perhaps most seriously, isoniazid preventive therapy is rarely used in Africa, despite its proven effectiveness for preventing HIV-related TB: fear of the consequences of screening failure and the subsequent risk of generating drug resistance is one of the major reasons for this implementation failure.[19]

In this study, we evaluated different approaches to TB screening in participants of a population-based HIV and TB prevalence survey in Harare, Zimbabwe. A TB symptom questionnaire was administered, and all participants were screened by sputum culture (even if asymptomatic) and followed-up to confirm or exclude TB. The main aim of this study was to investigate the effect of HIV on the prevalence of TB symptoms and on the diagnostic utility of different screening strategies among survey participants not being treated for TB.

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Methods

Participants and setting

Details of recruitment into the prevalence survey have been described more fully elsewhere.[20] Briefly, a population-based survey was carried out in 2005–2006 among a random sample of adults in 46 previously enumerated neighbourhoods in the high-density suburbs of Harare. Participants were asked to answer a questionnaire, provide blood for anonymized HIV serum testing and provide two sputum specimens (one "spot" specimen and one early morning specimen) for TB culture. Voluntary HIV counselling and testing was provided separately through outreach clinics by the New Start Centre, Harare, Zimbabwe.

Definition and follow-up of TB suspects

A TB suspect was defined as an individual with any TB symptom (defined below) or who tested positive on sputum culture during screening (i.e. culture-positive). Consequently, asymptomatic culture-negative TB would not have been detected. The TB symptoms considered were: current cough of any duration or severity, haemoptysis during the previous year, self-reported fever or "hot body", night sweats and a subjective report of weight loss. Individuals who reported night sweats were asked whether they had to change their bed clothes or sheets (i.e. drenching night sweats) or not (i.e. mild night sweats). An enquiry was made about the duration (in weeks) of any reported symptoms. Cough was defined as acute if less than 2 weeks' duration and as chronic otherwise. Smoking history and alcohol intake, assessed using the Alcohol Use Disorders Identification Test questionnaire,[21] were also recorded.

In addition, TB suspects underwent follow-up testing, which included repeat sputum microscopy and culture and chest radiography, until TB was confirmed or excluded. A standard algorithm was used to investigate possible cases of culture-negative TB: it included analysing clinical and radiological responses to broad-spectrum antibiotics and the response to TB treatment at 1 month, where applicable.

Table 1. **Study participants' baseline characteristics, by HIV status, Zimbabwe, 2005**

Characteristic	HIV+ (*n* = 1858)	HIV– (*n* = 7121)	*P*-value
Median age in years[a] (IQR)	32 (26–38)	25 (20–35)	0.001
No. of females[b] (%)	1292 (69.6)	4202 (59.0)	< 0.001
No. of past TB treatment[c] (%)	169 (9.1)	109 (1.5)	< 0.001
No. of household TB contact in past 2 years[c] (%)	299 (16.1)	867 (12.1)	< 0.001
Alcohol (AUDIT zone score)[d]			< 0.001
I (low risk or abstinent) (%)	1491 (81.0)	6052 (85.3)	
II (in excess of low-risk intake) (%)	212 (11.5)	660 (9.3)	
III (hazardous drinking) (%)	73 (3.9)	188 (2.7)	
IV (possible alcohol dependency) (%)	76 (4.1)	197 (2.8)	
Smoking[e]			< 0.001
Never smoked (%)	1615 (86.9)	6412 (90.1)	
Current smoker (%)	196 (10.6)	589 (8.2)	
Former smoker (%)	47 (2.5)	117 (1.6)	

AUDIT, Alcohol Use Disorders Identification Test; IQR, interquartile range; TB, tuberculosis.
[a] The ages of two HIV– participants were unknown.
[b] The sexes of one HIV+ and two HIV– participants were unknown.
[c] Information on past TB treatment and household contact was missing for 1 HIV+ and 11 HIV– participants.
[d] Information on alcohol consumption was missing for 24 HIV– and 6 HIV+ participants.
[e] Information on smoking history was missing for three HIV– participants.

Table 2. **Prevalence of potential TB symptoms in study participants, by HIV status, Zimbabwe, 2005**

Symptom	Total (*n* = 8979) (%)	No. HIV+ (*n* = 1858) (%)	No. HIV– (*n* = 7121) (%)	*P*-value
Cough for less than 2 weeks	186 (2.1)	43 (2.3)	143 (2.0)	0.41
Cough for 2 weeks or more[a]	333 (3.7)	153 (8.2)	180 (2.5)	< 0.001
Haemoptysis in the last year	152 (1.7)	63 (3.4)	89 (1.3)	< 0.001
Fever	340 (3.8)	158 (8.5)	182 (2.6)	< 0.001
Mild night sweats[b]	144 (1.6)	48 (2.5)	96 (1.3)	< 0.001
Drenching night sweats	362 (4.0)	162 (8.7)	200 (2.8)	< 0.001
Weight loss	441 (4.9)	203 (10.9)	238 (3.3)	< 0.001
Any of the above	1102 (12.3)	394 (21.2)	708 (9.9)	< 0.001

TB, tuberculosis.
[a] A cough lasting 3 weeks or more was reported by 258 participants (2.9%): 129 (6.7%) HIV+ and 129 (1.8%) HIV– ($P < 0.001$).
[b] No need to change bed clothes or sheets.

Case definitions for TB disease

A case of TB disease was not diagnosed on the basis of screening results alone and subsequent evidence was required. One of the following case definitions had to be satisfied:

- definite TB: sputum culture-positive for *Mycobacterium tuberculosis* on two or more occasions (e.g. at screening and the first follow-up test);
- probable culture-positive TB: culture-positive for *M. tuberculosis* on one occasion (e.g. at screening or a follow-up test) plus the presence of a compatible clinical illness or radiological evidence of TB, failure to respond to broad-spectrum antibiotics, and a response to TB treatment at 1 month;
- probable culture-negative TB: culture-negative for *M. tuberculosis* plus radiological evidence of TB or the presence of progressive symptoms of TB, failure to respond to antibiotics, and a response to TB treatment at 1 month.

Table 3. **Prevalence of specific sputum culture and smear screening test results and TB symptoms in 79 study participants with active TB, by HIV status, Zimbabwe, 2005**

Bacteriology finding or symptom	Total (*n* = 79) (%)	No. HIV+ (*n* = 48) (%)	HIV– (*n* = 31) (%)	*P*-value
Culture[a] and smear screening test results				0.27
Culture-positive, smear-positive	31 (39)	17 (35)	14 (45)	
Culture-positive, smear-negative	23 (29)	14 (29)	9 (29)	
Culture-negative, smear-negative[b]	25 (32)	17 (35)	8 (26)	
Symptom				
Cough for less than 2 weeks	10 (13)	7 (15)	3 (10)	0.52
Cough for 2 weeks or more	37 (47)	23 (48)	14 (45)	0.81
Haemoptysis in the last year	7 (9)	7 (15)	0 (0)	0.026
Fever	28 (35)	18 (38)	10 (32)	0.63
Mild night sweats[c]	5 (6)	2 (6)	3 (6)	0.97
Drenching night sweats	30 (38)	22 (46)	8 (26)	0.073
Weight loss	37 (47)	25 (52)	12 (39)	0.64
Any of the above	61 (77)	39 (81)	22 (71)	0.29
More than one TB symptom[d]	47 (59)	32 (67)	15 (48)	0.11

TB, tuberculosis.

[a] Culture refers to growth of *Mycobacterium tuberculosis* in culture.

[b] Follow-up cultures in participants who were diagnosed with TB despite being culture-negative on screening were positive in 4 (24%) HIV+ and 5 (63%) HIV– participants. All 16 participants who were consistently culture-negative were assessed for their response to TB treatment after 1 month. Of these, 14 had radiological abnormalities that did not respond to treatment with amoxicillin and erythromycin but did respond to 1 month of TB treatment (including unilateral pleural effusion in 3 patients, miliary shadowing in 2 patients and pericardial effusion confirmed by echocardiography in 2 patients) and 2 had clinical signs of TB that responded to TB treatment (namely ascites in 1 and asymmetrical cervical lymphadenopathy in 1).

[c] No need to change bed clothes or sheets.

[d] Symptoms included cough of any duration, haemoptysis in the last year, fever, night sweats and weight loss.

Laboratory methods

For participants with one or more symptoms, the two sputum specimens were processed separately for culture and sputum smears were read immediately. For asymptomatic participants, a single pooled sputum specimen was cultured and the two smears were read only if the pooled culture tested positive (hence we can not comment on the sensitivity of screening smears). Smears were made from concentrated sputum decontaminated with 4% sodium hydroxide and read by fluorescence microscopy with auramine O. All positive and 10% of negative slides were re-read by a second reader. Each positive result was confirmed using Ziehl–Neelsen staining. Culture used Löwenstein-Jensen slopes, with the residual concentrate stored at –20 °C for re-culture in the event of contamination. Species were identified using colony morphology, growth at different temperatures and growth on para-nitrobenzoic acid Löwenstein-Jensen slopes. Non-tuberculous mycobacteria were sent to the South African Institute for Medical Research in Johannesburg for further identification.

Confidential HIV serum testing was carried out with the Determine assay (Abbott Diagnostics, Johannesburg, South Africa), with all positive and 10% of negative specimens confirmed by the Unigold test (Trinity Biotech, Dublin, Ireland). For participants who were not willing to provide serum, oral mucosal transudate was collected and tested using the Vironostika assay (Vironostika, BioMérieux, Marcy l'Etoile, France).

Ethical approval

Approval was granted by the Ethics Committees of the Biomedical Research and Training Institute, Harare, Zimbabwe, the Medical Research Council of Zimbabwe, Harare, Zimbabwe, and the London School of Hygiene and Tropical Medicine, London, United Kingdom. Written informed consent was provided by all participants. Confidential HIV tests were carried out and the results were stored using dedicated laboratory numbers, with no other personal identifiers. Voluntary counselling and testing were offered to all participants.

Statistical methods

Data were captured using EpiInfo 2003 (Centers for Disease Control and Prevention, Atlanta, GE, USA) and analysed with STATA 9.0 software (STATA Corporation, College Station, TX, USA).

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of symptoms and TB culture findings were calculated using the set of TB case definitions listed above as the reference or gold standard diagnosis. The area under the receiver operating characteristic curve (AUC) was also estimated to provide a summary measure of diagnostic accuracy. A non-parametric test was used to compare different AUCs. Logistic regression analysis was used to investigate risk factors for chronic cough and, in separate analyses, the relationship between TB disease and TB symptoms. There was no significant clustering of TB disease in communities or households (only three households had multiple TB cases), so in the analysis in which TB disease was the outcome, we did not adjust for clustering effects. However, for the analysis of TB symptoms, we used robust, or sandwich, standard errors to allow for clustering.

Results

Of the 10 076 participants who consented to TB screening in the parent study, 93 were already on TB treatment (including 9 who were still culture-positive) and 1004 declined HIV-testing, leaving 8979 participants for this analysis. The participants' baseline characteristics are shown by HIV status in Table 1.

TB symptoms

As shown in Table 2, all potential TB symptoms were significantly more common in the 1858 HIV+ than the 7121 HIV– participants, except for acute cough. Overall, 21.2% of HIV+

Table 4. **ORs for TB disease among HIV– and HIV+ participants for different symptoms, recent household contact with TB and past TB treatment, as derived by unadjusted and adjusted multivariate logistic regression analysis, Zimbabwe, 2005**

Symptom or other variable	HIV– TB patients			HIV+ TB patients		
	Unadjusted OR	Adjusted OR	95% CI for adjusted OR	Unadjusted OR	Adjusted OR	95% CI for adjusted OR
No cough (reference)	1	1		1	1	
Cough for < 2 weeks	5.3	4.9	1.4–17.5	8.4	12.6	4.9–32.3
Cough for ≥ 2 weeks	34.4	19.4	7.2–52.0	11.9	6.1	2.8–13.2
Haemoptysis	2.2[a]	ND	ND	5.4	1.3	0.4–4.1
Fever	19.1	2.8	0.8–9.5	7.2	0.9	0.4–1.9
No night sweats (reference)	1	1		1	1	
Mild night sweats[b]	5.1	1.4	0.4–5.0	2.6	1.3	0.4–4.9
Drenching night sweats	12.5	1.4	0.4–5.4	10.1	3.1	1.4–7.1
Weight loss	19.2	4.0	1.5–10.7	10.0	2.8	1.3–5.7
Household TB contact in past 2 years	1.7	1.0	0.4–2.3	1.4	1.0	0.5–2.3
Past TB treatment	4.5	1.2	0.1–10.4	2.1	1.1	0.4–3.0

CI, confidence interval, ND, not determined; OR, odds ratio, TB, tuberculosis.
[a] Not significant (95% CI: 0.3–17.0), and so not included in the multivariate analysis.
[b] No need to change bed clothes or sheets.

and 9.9% of HIV– participants had at least one symptom ($P < 0.001$). The most frequent symptoms were weight loss, in 4.9% of the total, and drenching night sweats, in 4.0%. Chronic cough lasting 2 weeks or more was reported by 3.7% of participants: by 8.2% of HIV+ and 2.5% of HIV– participants.

Newly diagnosed TB disease that met one of the above case definitions was observed in 79 participants, whose sputum culture and smear results and HIV status are shown in Table 3. Symptoms differed little by HIV status (Table 3). Overall, 47 (59%) had cough, which was of 2 weeks' duration or longer in 37 (47%). The next most common symptoms were unintentional weight loss in 47% and drenching night sweats in 38%. In 18 patients (24% of HIV+ and 22% of HIV– participants with TB disease), TB was detected by screening culture alone as they denied having any symptoms at baseline. They included 8 participants who also had smear-positive disease: 4 HIV– and 4 HIV+.

Duration of symptoms

There was no significant difference in the reported duration of symptoms between participants with symptoms who had TB and those who did not, except that cough was significantly more prolonged in HIV– participants who also had TB (median: 4 weeks, interquartile range: 2–8 weeks) than in those whose cough was due to another cause (median: 2 weeks, interquartile range: 1–4 weeks; $P = 0.003$). In HIV+ participants, however, cough due to another cause was also prolonged (median: 3.5 weeks, interquartile range: 2–8 weeks) and not significantly different from cough associated with HIV-related TB (median: 4 weeks, interquartile range: 2–8 weeks; $P = 0.36$).

Multivariate analysis

In general, TB patients with symptoms tended to be polysymptomatic. Multivariate logistic regression analysis was used to identify symptoms and other variables independently associated with TB disease (Table 4). Odds ratios (ORs) adjusted for other symptoms tended to be considerably lower than unadjusted ORs. For both HIV+ and HIV– TB, acute cough (adjusted OR: 4.9 for HIV– and 12.6 for HIV+ TB), chronic cough (adjusted OR: 19.4 for HIV– and 6.1 for HIV+ TB) and weight loss (adjusted OR: 4.0 for HIV– TB and 2.8 for HIV-related TB) remained independent predictors of TB disease after adjustment. In addition, the presence of drenching night sweats was an independent predictor of HIV+ TB (adjusted OR: 3.1, 95% confidence interval: 1.4–7.1) but not of HIV– TB (adjusted OR: 1.4, 95% confidence interval: 0.4–5.4). Neither recent household contact with TB nor past TB treatment was significantly associated with TB after adjustment for symptoms.

Diagnostic utility

Measures of the utility of different screening strategies for TB disease in HIV– and HIV+ individuals are reported in Table 5. Although HIV status did not have a significant effect on either sensitivity or specificity, PPVs were considerably higher in HIV+ participants.

No screening strategy was ideal: all missed some TB patients and the highest AUC for symptom-based screening was 0.82 for HIV– TB and 0.81 for HIV+ TB.

In a pooled analysis of HIV+ and HIV– TB suspects, prolonged cough had a sensitivity of 46.8% and a specificity of 96.7% for identifying TB disease. The sensitivity increased to 59.5% for cough of any duration, with a significant increase in AUC from 0.72 for chronic cough to 0.77 ($P = 0.005$). There was a further significant increase in AUC to 0.81 ($P = 0.037$ for the comparison with any cough) for weight loss or cough (sensitivity: 69.6%). The maximum sensitivity was 77.2% for the criterion of exhibiting any one or more of the five TB symptoms used to define a TB suspect. However, there was no significant increase in AUC compared with cough or weight loss because of falls in both specificity (from 91.7% for cough or weight loss to 88.3% for any symptom) and PPV

Table 5. **Diagnostic value of different symptoms and other variables and their combination for screening for TB disease in HIV– and HIV+ individuals, Zimbabwe, 2005**

HIV status and symptom, other variable or combination	No. of participants with defined symptoms	No. of TB cases with defined symptoms	Sensitivity	Specificity	PPV	NPV	AUC
HIV–	**(*n* = 7121)**	**(*n* = 31)**					
Cough for ≥ 2 weeks	180	14	45.2	97.7	7.8	99.8	0.71
Any cough	323	17	54.8	95.7	5.3	99.8	0.75
Either of: cough or weight loss[a]	487	20	64.5	93.4	4.1	99.8	0.79
Any of: cough, drenching night sweats or weight loss[b]	582	22	71.0	92.1	3.8	99.7	0.82
Any symptom (i.e. cough, haemoptysis, fever, night sweats or weight loss)	708	22	71.0	90.3	3.1	99.9	0.81
Any symptom or recent household TB contact	1445	22	71.0	79.9	1.5	99.8	0.75
Sputum culture-positive for TB (regardless of symptoms)	37	23	74.2	99.8	62.2	99.9	0.87
HIV+	**(*n* = 1858)**	**(*n* = 48)**					
Cough for ≥ 2 weeks	169	26	47.9	92.8	15.0	98.5	0.70
Any cough	196	30	62.5	90.8	15.3	98.9	0.77
Either of: cough or weight loss[a]	307	35	72.9	85.0	11.4	99.2	0.79
Any of: cough, drenching night sweats or weight loss[b]	354	36	75.0	82.4	10.2	99.2	0.79
Any symptom (i.e. cough, haemoptysis, fever, night sweats or weight loss)	394	39	81.3	80.4	9.9	99.4	0.81
Any symptom or recent household TB contact	609	39	81.3	68.5	6.4	99.3	0.75
Sputum culture-positive for TB (regardless of symptoms)	33	31	64.6	99.9	93.9	99.1	0.82

AUC, area under the receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value; TB, tuberculosis.

[a] In a pooled analysis of HIV+ and HIV– TB cases, the AUC for any cough or weight loss was significantly larger than for any cough alone ($P = 0.05$) and the AUC for any cough was significantly larger than for cough ≥ 2 weeks ($P = 0.006$). None of the alternative screening strategies considered performed significantly better than any cough or weight loss.

[b] Cough, drenching night sweats and weight loss were all shown to be independent predictors of TB in the multivariate analysis (Table 4).

(from 6.9% for cough or weight loss to 6.2% for any symptom).

The use of TB culture on solid culture media for screening for TB disease had a sensitivity of 68.4% and an AUC of 0.84. The specificity was just under 100% because *M. tuberculosis* grew on specimens from 16 participants, including 14 who were HIV–, in whom TB was not confirmed. Of these 16, 6 had TB symptoms, while follow-up was suboptimal in 4 (2 of whom were both symptomatic and HIV+) because they refused further investigation or relocated. The 12 participants who were followed up were known to have remained clinically stable for several months while off TB treatment. The prevalence of TB symptoms (37.5%) in culture-positive individuals in whom TB was not confirmed was significantly higher than in culture-negative individuals without TB (11.7%, $P = 0.007$). There was no other significant difference in patient characteristics between these two groups.

Discussion

This study shows that some screening failures can be anticipated when either TB symptoms alone or *M. tuberculosis* culture alone is used to screen for previously undiagnosed TB, even in HIV-infected individuals. For example, *M. tuberculosis* grew on culture of sputum specimens from 19 HIV– and 9 HIV+ participants who did not exhibit any of the five TB symptoms considered (i.e. cough, haemoptysis, fever, night sweats or weight loss) and, subsequently, 9 of the 19 HIV– and all 9 HIV+ participants had TB disease confirmed on follow-up. In addition, screening cultures were negative in 25 patients in whom TB disease was confirmed either by positive cultures on follow-up (4 HIV+ and 5 HIV– participants) or from clinical and radiological responses to TB treatment (13 HIV+ and 3 HIV– participants).

The prevalence of TB symptoms was high in HIV+ participants and the sensitivity of initial symptom screening in these individuals ranged from 47.9% when chronic cough was used to define a TB suspect to 81.3% when any of the five TB symptoms considered was used. Symptom screening was more sensitive than sputum culture on a solid medium, whose sensitivity was 64.6%. We found that the diagnostic performance of symptom screening in HIV+ participants, as assessed using the AUC, was significantly and incrementally better when acute cough of less than 2 weeks' duration and weight loss were individually added to the cardinal symptom of chronic cough lasting 2 weeks or more. Broadening the definition of a TB suspect further did not improve diagnostic performance. Nevertheless, PPVs were high for all symptoms among HIV+ participants, which supports using a less strict definition of a TB suspect in individuals known to have an HIV infection, even though specificities were suboptimal.

Although subclinical TB disease is rarely recognized in routine

clinical practice, it is often observed during provider-initiated TB testing whenever a second screening modality (e.g. radiography or diagnostic bacteriology) is combined with symptom screening.[7,9–16] Fig. 1 illustrates why the symptom and bacteriological profiles of TB patients identified through provider-initiated TB testing will tend to differ from those of patients diagnosed through routine TB clinical services, especially when a strong routine diagnosis and treatment programme is in place. In the latter case, patients with highly symptomatic disease and those with "first-line" diagnostic features, such as chronic cough or a positive smear test result, will tend to be rapidly diagnosed and treated, leaving behind a residual burden of TB patients with less clinically obvious TB and those who have not sought care. Moreover, TB patients with more severe symptoms are more likely to be smear-positive, as are those whose symptoms include chronic cough.[22,23] These factors help reconcile observations from provider-initiated prevalence surveys carried out in the pre-TB treatment era, when chronic cough had a high sensitivity for TB,[22] with observations from populations who now have access to TB diagnosis and treatment, in whom chronic cough is typically reported by only half or fewer of prevalent cases.[7,9–16]

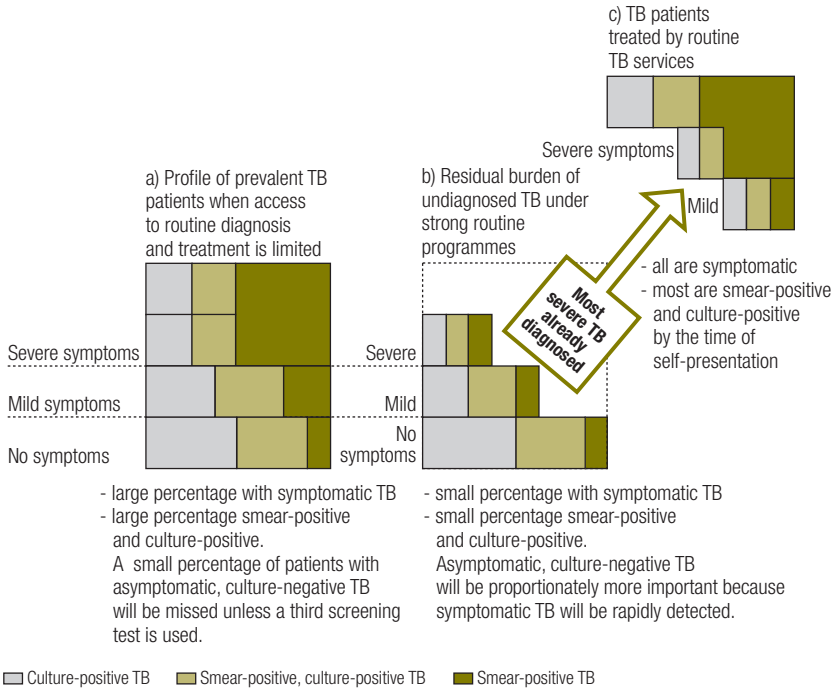
In extreme cases, provider-initiated surveys of TB in populations with very easy access to TB diagnosis and treatment have reported that all symptom combinations have very low sensitivity.[12,14] This scenario should, in fact, be the aim of most HIV care clinics, where regular provider-initiated screening based on TB symptoms is now a World Health Organization recommendation.[4] Such screening is a valuable component of individual patient management and TB infection control, but health-care providers working in these settings should not, then, be surprised by the resulting low sensitivity of TB symptoms for detecting undiagnosed TB.

In the community-based survey reported here, HIV infection was associated with a significantly increased burden of undiagnosed TB and also with a higher frequency of symptoms, including weight loss, fever, drenching night sweats and chronic cough. This higher frequency was due to increases in both TB and non-TB causes of symptoms, and so had little effect on the sensitivity or specificity of symptom screening. Neither recent household TB contact nor past TB treatment was an independent predictor of prevalent TB. Nor did these factors lead to an increase in the yield of TB detected, though their presence substantially increased the number of defined TB suspects and the cost of subsequent investigation. The value of including past TB treatment as a "screening" question may be higher in some populations, in which up to half of prevalent TB cases report past TB treatment,[24] but our results suggest that including recent household TB contact is likely to be expensive and uninformative.

One major and important difference between HIV+ and HIV– participants was that the duration of cough had limited diagnostic utility in HIV+ participants, with both acute and chronic cough having similar odds ratios for TB. In contrast, in HIV– participants, the odds ratio for chronic cough was much higher than for acute cough. This difference was mainly due to chronic cough being common in HIV+ participants without TB. Acute cough, with or without radiological changes, has been reported to have a relatively high PPV for TB in both provider-initiated screening[6] and in self-presenting patients in areas where HIV is prevalent,[25–28] and so should ideally be considered as a TB symptom in both these contexts.

The limitations of this survey are that the questionnaire used included a limited range of questions, chest radiography was not included as a third screening modality and participants were not examined for signs of extrapulmonary TB. Consequently, we will have missed some cases of asymptomatic or minimally symptomatic, culture-negative TB.[6,11,14] In addition, we used solid media for TB culture, which have a lower sensitivity than some liquid culture systems such as the Mycobacterial Growth Indicator Tube,[29] and we only examined sputum smears in symptomatic or culture-positive patients.

Fig. 1. **Effect of strong routine TB diagnosis and treatment programmes[a] on symptom and bacteriological profiles of residual TB cases that remain to be detected through provider-initiated TB screening**



TB, tuberculosis.

[a] Routine diagnosis and treatment services rely on patients with TB symptoms presenting themselves and use the smear test as the first-line investigation. Consequently, highly symptomatic and smear-positive patients are more likely to be diagnosed (part c of figure) and residual undiagnosed cases (part b of figure) will tend to have mild symptoms or none and smear-negative disease. The more effective the routine service, the greater the shift towards minimally symptomatic or asymptomatic disease. Under the World Health Organization's DOTS strategy, patients with chronic cough are particularly likely to be diagnosed, which leaves behind a higher proportion of symptomatic patients without chronic cough.

Since our prevalence survey was population-based, the HIV+ participants included probably had different patient characteristics and a lower burden of undiagnosed TB than participants in surveys based in HIV clinics. We did not investigate the possibility that antiretroviral use modified the burden of TB in HIV-infected participants, as information on HIV status and access to HIV care were both limited at the time of this survey. At baseline, we excluded nine culture-positive cases who were recently diagnosed with TB: including them would have increased the proportion of TB patients with chronic cough from 47% to 51%.

In summary, we have shown that even smear-positive TB may be missed by symptom screening in HIV+ TB patients. Although the sensitivity and specificity of symptom screening were similar for HIV+ and HIV– participants, the presence of symptoms in HIV+ participants had a higher PPV and a lower NPV. Although imperfect, three of the symptoms evaluated (i.e. cough, drenching night sweats and weight loss) were independently predictive of TB and their combination had a NPV over 99% in HIV+ participants. This suggests that symptom screening alone may be able to identify, at least in some settings, a subset of patients who are at a low risk of undiagnosed TB and in whom antiretroviral therapy or isoniazid preventive therapy can be started without further screening. This suggestion would, however, need confirmation from prospective studies ideally conducted in settings with both high and low prevalences of TB, given the limitations of the current study design. Provider-initiated TB screening is one of the many aspects of TB–HIV management in urgent need of more effective and accessible TB diagnostic tools. Unnecessary TB investigations are costly for patient and provider alike, do not always result in diagnostic certainty and delay access to life-saving antiretroviral therapy and preventive TB treatment. Consequently until better TB diagnostics for resource-poor settings become widely available, many providers of HIV care in Africa will remain in the unsatisfactory position of having to weigh the adverse consequences of potentially avoidable screening failures against those of setting unrealistically high screening standards. ■

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Résumé

Recherche des symptômes de la tuberculose à l'initiative du prestateur de services au Zimbabwe : valeur diagnostique et effet du statut VIH

Objectif Évaluer la valeur diagnostique de la recherche des symptômes de la tuberculose (TB) à l'initiative du prestateur et comment le statut VIH influe sur cette valeur diagnostique.

Méthodes Nous avons réalisé une analyse secondaire sur des participants sélectionnés au hasard parmi les sujets d'une enquête en communauté concernant la prévalence de la co-infection TB-VIH, menée à Harare, au Zimbabwe. Tous les participants ont répondu à un questionnaire portant sur cinq symptômes et ont fait l'objet d'une culture d'expectorations pour rechercher la tuberculose et d'un dépistage du VIH. Nous avons calculé la sensibilité, la spécificité et les valeurs prédictives positive et négative des différents symptômes et étudié la relation entre ces symptômes et la tuberculose maladie en utilisant l'analyse par régression.

Résultats Nous avons relevé un ou plusieurs symptômes de la tuberculose chez 21,2 % des 1858 participants positifs pour le VIH (VIH+) et chez 9,9 % des 7121 participants négatifs pour ce virus ($p < 0,001$). La tuberculose a ensuite été diagnostiquée chez 48 sujets VIH+ et chez 31 sujets VIH-. Cette maladie était présente de manière asymptomatique chez 18 individus positifs à la culture, dont 8 (4 pour chacun des statuts VIH) donnaient des frottis d'expectorations positifs. La toux, quelle que soit sa durée, la perte de poids et pour les participants VIH+ uniquement, la sudation nocturne, constituaient des facteurs prédictifs indépendants de la tuberculose. Chez les participants VIH+, la présence de toux pendant 2 semaines ou plus, chacun des symptômes et l'obtention d'une culture d'expectorations positive présentaient respectivement une sensibilité de 48, 81 et 65 %. Chez les participants VIH-, les sensibilités correspondantes valaient respectivement 45, 71 et 74 %. Les symptômes fournissaient donc une sensibilité et une spécificité similaires chez les deux types de participants, mais chez les sujets VIH+, ils avaient une valeur prédictive positive plus élevée et une valeur prédictive négative plus faible.

Conclusion La recherche des symptômes à l'initiative du prestateur peut laisser passer même des cas de tuberculose frottis positifs, en particulier chez les individus séropositifs pour le VIH. Le dépistage sur la base des symptômes est utile pour exclure la tuberculose, mais les pays démunis ont besoin d'urgence d'un meilleur outil pour diagnostiquer cette maladie.

Resumen

Cribado de síntomas de tuberculosis a instancias del profesional en Zimbabwe: valor diagnóstico y efecto de la serología VIH

Objetivo Determinar el valor diagnóstico del cribado de síntomas de tuberculosis a instancias del profesional, así como la influencia de la serología VIH en dicho cribado.

Métodos Realizamos un análisis secundario a partir de participantes seleccionados aleatoriamente en una encuesta comunitaria de prevalencia de la coinfección tuberculosis-VIH realizada en Harare, Zimbabwe. Todos ellos respondieron a un cuestionario sobre cinco síntomas y se sometieron a pruebas del VIH y de cultivo de esputo para la tuberculosis. Calculamos la sensibilidad, la especificidad y los valores predictivos positivo y negativo de los diversos síntomas y realizamos un análisis de regresión para investigar la relación entre los síntomas y la tuberculosis.

Resultados Detectamos uno o más síntomas de tuberculosis en el 21,2% de 1858 pacientes VIH-positivos (VIH+) y el 9,9% de 7121 participantes VIH-negativos (VIH-) ($p < 0,001$). Posteriormente se diagnosticó tuberculosis en 48 participantes VIH+ y 31 participantes VIH-. Sufrían tuberculosis asintomática 18 personas con cultivo positivo, 8 de las cuales (4 en cada grupo serológico) presentaron esputo positivo. La tos de cualquier duración, la pérdida de peso y, sólo en el caso de los participantes VIH+, la presencia de sudores nocturnos, fueron factores predictivos independientes de la tuberculosis. En las personas VIH+, la tos de más de 2 semanas de duración, la presencia de cualquiera de los síntomas y un cultivo de esputo positivo tuvieron una sensibilidad del 48%, 81% y 65%, respectivamente; entre los participantes VIH-, la sensibilidad fue del 45%, 71% y 74%, respectivamente. Los síntomas presentaron una sensibilidad y especificidad similares en los pacientes VIH+ y VIH-, pero en los primeros tenían un mayor valor predictivo positivo y un menor valor predictivo negativo.

Conclusión Incluso la tuberculosis con baciloscopia positiva puede pasar desapercibida en el cribado de los síntomas realizado a instancias del profesional, especialmente en las personas VIH+. El cribado de los síntomas es útil para descartar la tuberculosis, pero se necesitan urgentemente mejores medios de diagnóstico de esta enfermedad para los entornos con recursos escasos.

مخلص

مبادرة مقدمي الرعاية في التحري عن أعراض السل في زيمبابوي: القيمة التشخيصية وتأثير حالة العدوى بفيروس الإيدز

الغرض: قياس القيمة التشخيصية لمبادرة مقدمي الرعاية في التحري عن أعراض السل وكيف تؤثر حالة العدوى بفيروس الإيدز في ذلك.

الطريقة: قام الباحثون بتحليل ثانوي لمشاركين جرى انتقاؤهم عشوائياً في مسح مجتمعي-المرتكز لقياس انتشار العدوى المشتركة بالسل وفيروس الإيدز في مدينة هراري بزيمبابوي. وأكمل جميع المشاركين استبياناً يضم خمسة أعراض، وأجري لهم مزرعة لعصيات السل في البلغم، واختبار لتشخيص العدوى بفيروس الإيدز. وحسب الباحثون الحساسية والنوعية، والقيم الإيجابية والسلبية لمختلف الأعراض، واستخدموا تحليل التحوف لتقصي العلاقة بين الأعراض ومرض السل.

الموجودات: اكتشف الباحثون عرضاً واحداً أو أكثر للسل في 21.2% من 1858 شخصاً من المشاركين كانوا إيجابيين للعدوى بفيروس الإيدز، وفي 9.9% من 7121 شخصاً كانوا سلبيين للعدوى بفيروس الإيدز (P أقل من 0.001). وجرى تشخيص السل لاحقاً في 48 شخصاً من المشاركين كانوا إيجابيين للعدوى بفيروس الإيدز، وفي 31 شخصاً كانوا سلبيين للعدوى بفيروس الإيدز. اكتُشف السل عديم الأعراض في 18 شخصاً وكانت مزرعة البلغم لديهم إيجابيةً، ثمانية أشخاص منهم (كل أربعة منهم يقع في مجموعة مختلفة حسب حالة الإيدز) كانت لطاخة البلغم لديهم إيجابية. كان السعال لأي مدة، وفقدان الوزن، و غزارة التعرق الليلي بالنسبة للإيجابيين للعدوى بفيروس الإيدز فقط منبئات مستقلة للإصابة بالسل. وبالنسبة للمشاركين الإيجابيين للعدوى بفيروس الإيدز، كان للسعال لمدة أكبر من أو تساوي أسبوعين، وأي عرض، وإيجابية مزرعة البلغم حساسيات قدرها 48%، 81%، 65% بالترتيب؛ وبالنسبة للمشاركين السلبيين للعدوى بفيروس الإيدز، كانت الحساسيات قدرها 45%، 71%، 74% بالترتيب. وكان للأعراض حساسية ونوعية متشابهة بالنسبة للمشاركين الإيجابيين والسلبيين للعدوى بفيروس الإيدز، ولكن كان للإيجابيين لفيروس الإيدز قيمة تنبؤية إيجابية أعلى وقيمة سلبية أدنى.

الاستنتاج: حتى بالنسبة لمرضى السل الإيجابيين للطاخة، يمكن تعذر اكتشاف الأعراض لديهم عند مبادرة مقدمي الرعاية بالتحري عن أعراض السل، ولاسيما الإيجابيين للعدوى بفيروس السل. ويفيد التحري عن الأعراض في استبعاد السل، ولكن هناك حاجة ملحة لتوفير تشخيص أفضل في المواقع الفقيرة الموارد.

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