

Diagnostic accuracy of tuberculin skin test self-reading by HIV patients in a low-resource setting

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SUMMARY

BACKGROUND: The World Health Organization recommends tuberculin skin tests (TSTs) where feasible to identify individuals most likely to benefit from isoniazid preventive therapy (IPT). The requirement for TST reading after 48–72 h by a trained nurse is a barrier to implementation and increases loss to follow-up.

METHODS: Patients with human immunodeficiency virus (HIV) infection were recruited from a primary care clinic in South Africa and trained by a lay counsellor to interpret their own TST. The TST was placed by a nurse, and the patient was asked to return 2 days later with their self-reading result, followed by blinded reading by a trained nurse (reference).

RESULTS: Of 227 patients, 210 returned for TST

reading; 78% interpreted their test correctly: those interpreting it as negative were more likely to be correct (negative predictive value 93%) than those interpreting it as positive (positive predictive value 42%); 10/36 (28%) positive TST results were read as negative by the patient.

CONCLUSIONS: Patients with HIV in low-resource settings can be trained to interpret their own TST. Those interpreting it as positive should return to the clinic within 48–72 h for confirmatory reading and IPT initiation; those with a negative interpretation can return at their next scheduled visit and initiate IPT at that time if appropriate.

KEY WORDS: TST; IPT; tuberculosis control; self-assessment

THE WORLD HEALTH ORGANIZATION (WHO) recommends isoniazid preventive therapy (IPT) as part of the ‘three I’s’ strategy to improve tuberculosis (TB) control among people living with human immunodeficiency virus (HIV) infection in resource-limited settings.¹ A meta-analysis of randomised controlled trials showed that IPT reduces the risk of TB in HIV patients who are not receiving antiretroviral treatment (ART); however, this effect was only statistically significant in those with a positive tuberculin skin test (TST).² More recently, a randomised placebo controlled trial has shown that patients receiving ART benefit from IPT regardless of the TST result.³ The WHO recommends that although TST is not required for IPT implementation, people living with HIV who are TST-positive benefit more from IPT, and TST should be used where feasible to identify such individuals.¹

TST indurations need to be interpreted by a trained nurse 48–72 h after placement. The requirement for a return clinic visit within this time frame is impractical for many patients living in rural, low-resource settings and could potentially result in loss to

follow-up. TST is positive in HIV-positive adults if the maximum diameter of induration is ≥ 5 mm. More than 90% of readings are either >10 mm or <2 mm,^{4,5} meaning that results are rarely close to the cut-off value. It may thus be feasible to simplify the TST process by training patients to interpret their own tests at home and supply the result at their next routine clinic visit.

The aim of the present study was to determine the diagnostic accuracy of ambulant HIV-positive patients in interpreting their own TST results. Patients were given appropriate training by lay counsellors, and the results were compared to the reference standard nurse-read TST. Outcomes were accuracy, positive predictive value (PPV) and negative predictive value (NPV) of self-reading, and κ statistic for inter-observer reliability using McNemar’s test.

METHODS

Study population

Patients were recruited from a primary health care HIV and TB clinic in Khayelitsha township, located

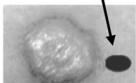
Patient study number:	
Date of TST placement:	
Date TST documentation card returned to clinic:	
Please mark or circle one answer below: Is your TST test positive?	
<p>NO</p> <p>I don't feel swelling or a bump</p>	<p>YES</p> <p>5mm hole punch in Green card</p>  <p>I do feel a swelling, and it is bigger than the hole punched in my green card</p>

Figure 1 Card given to patients to report results of TST self-reading. TST = tuberculin skin test.

30 km from Cape Town (population approximately 500 000),⁶ The 2011 antenatal HIV prevalence in Khayelitsha was estimated at 37.4%,⁷ and the TB case notification rate was at least 1500 per 100 000 population per year.⁸ Approximately 29 473 patients were on ART as of October 2014.

Patients attending the clinic for routine care were invited to participate in the study by a dedicated study nurse. Those who agreed to enter the study, including a return visit after 48 h, were screened for eligibility. Inclusion criteria were age >18 years, HIV infection, a negative WHO TB symptom screen result and eligibility for IPT according to local guidelines. Patients currently on anti-tuberculosis treatment, those with active liver disease or with active alcohol abuse were excluded.

Ethics approval was obtained from the University of Cape Town Human Research Ethics Committee, Cape Town, South Africa.

Procedure

After obtaining written consent and enrolment, the study nurse administered a standard TST by intradermal inoculation of 0.1 ml of tuberculin purified protein derivative (PPD) RT/23 (2 tuberculin units/0.1 ml dose, Litha Vaccines, Statens Serum Institut, Copenhagen, Denmark) into the volar aspect of the left forearm. Prior to leaving the clinic, a facility-based lay counsellor trained by the study nurse educated patients to read their TST result after 48–72 h using a simple written teaching aid with printed pictures of positive TST reactions. A novel approach to TST self-reading was employed: patients were instructed to place the flat tip of their fingers over the TST site and firmly rub back and forth. If no bump or swelling was noted the test was negative. If a bump or swelling was palpable, they were instructed to compare the size of the swelling, but not the colour change, to a 5 mm hole punched in their patient held medical record card. Figure 1 is an example of the

Table 1 Baseline characteristics of 227 patients enrolled in the study

Characteristics	n (%)
Female	169 (74)
Age, years, median [IQR]	35 [29–43]
On ART	125 (54)
CD4 count, median [IQR]	343 [228–498]
History of tuberculosis	81 (36)

TST = tuberculin skin test; IQR = interquartile range; ART = antiretroviral therapy.

card that was given to patients to record their TST result and return to the counsellor at 48–72 h. All instructions and study materials were translated into the predominant local language, isiXhosa.

At the return visit 48 h later, the counsellor ensured that the reporting card was marked unambiguously and prompted the patient to make an unambiguous mark if necessary; the counsellor did not read the TST him/herself. The study nurse, who was blind to the result on the card, then read the TST using the standard ball point pen and ruler technique. The cut-off for a positive TST was ≥ 5 mm induration in a transverse direction. Eligible patients were commenced on IPT according to local guidelines. The study adhered to the STARD (Standards for Reporting of Diagnostic Accuracy) guidelines for diagnostic accuracy studies.⁹ The index test consisted of self-reading of TST by patients as either 'No' (negative) or 'Yes' (positive); the reference standard was TST reading by a trained nurse.

The predicted sample size, assuming that the proportion of positive ratings was 0.70 using a two-tailed test with 90% power and a null value set at 0.60, was 199 participants. Standard accuracy measures of sensitivity, specificity, PPV, NPV and diagnostic odds ratios (ORs) were calculated, along with the κ statistic for inter-observer reliability using the McNemar's test. All statistics were performed using Stata, version 13 (StataCorp, College Station, TX, USA).

RESULTS

Of 233 patients recruited into the study from August to December 2013, 6 were ineligible to participate (3 had TB symptoms and 3 active alcohol abuse). Full data on 210/227 patients were available for evaluation, as 17 participants did not return for their follow-up visit; 10 of these returned for subsequent routine clinic visits and 7 were lost completely from clinic care. Baseline characteristics are shown in Table 1: 74% of the participants were female and 54% were on ART. Despite heterogeneity in the technique of marking the reporting card (check, circle, 'x', written words), the counsellor confirmed an ambiguously marked response by the patient on only 5/210 (2.4%) reporting cards; 36/210 (17%) tests were positive by

Table 2 Comparison of patient-read and nurse-read (reference) TST results

	Reference standard TST-positive	Reference standard TST-negative	Total
Patient self-read TST-positive	26	36	62
Patient self-read TST-negative	10	138	148
Total	36	174	210

TST = tuberculin skin test.

the reference standard; 10/36 (28%) results were read as negative by the patient (Table 2). Figure 2 shows the complete trial profile.

The κ statistic measured inter-rater reliability as 0.4, suggesting moderate agreement ($P < 0.001$). The sensitivity of self-reading was 72% (95% confidence interval [CI] 73–85), specificity 79% (95%CI 58–87), PPV 42% (95%CI 30–54) and NPV 93% (95%CI 89–97). The diagnostic OR is 9.7 (95%CI 4.41–22.55). Table 3 shows the proportion of correctly self-read TSTs and accuracy according to the result of the reference test. Patients reading their TST as negative were more likely to be correct than those reading it as positive (NPV 93%, PPV 42%).

Using the McNemar’s test, discrepancies between the study nurse and patient recorded test results were different in both directions, with 7% (10/148) of tests recorded by the nurse as TST-positive recorded as TST-negative by patients, and 21% (36/174) of tests recorded by the nurse as TST-negative recorded as positive by patients (OR 0.28, 95%CI 0.2–0.5). The distribution of the nurse-read TST results is shown in Figure 3A and B. In the 10 cases where a TST was recorded as negative by the patient, but positive by the nurse, the median test result was 7 mm (interquartile range [IQR] 6–9); for the 36 cases where the patient recorded the TST as positive and the nurse as negative, the median test result was 0 mm (IQR 0–2). Discordant test results were not more likely in pre-ART patients than in those on ART (20% pre-ART vs. 24% on ART, χ^2 0.52, $P = 0.47$).

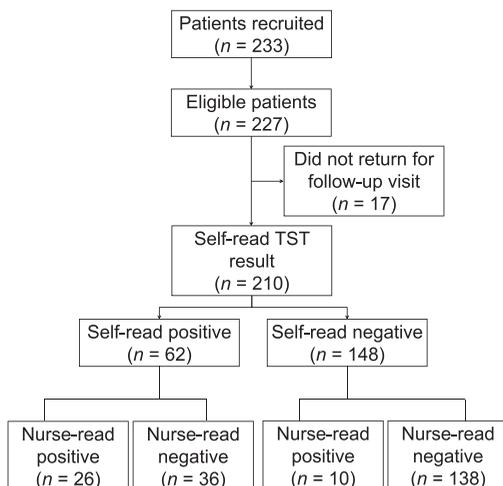


Figure 2 Trial profile. TST = tuberculin skin test.

While fewer patients with immune suppression (defined as CD4 count ≤ 200 cells/ μ l) had a negative TST reading ($n = 39$), the association between TST reading and immune status was not significant (χ^2 2.1, $P = 0.71$).

DISCUSSION

The study shows for the first time that patients from resource-limited settings can be trained to accurately interpret their own TST results when compared to the reference standard of reading by a trained nurse using the ball point pen and ruler method. Among patients who failed to self-read their TST result correctly, self-reports of positive TST were more common when the reference standard was negative. In a programmatic setting, a false-positive self-reading could prompt a return visit to the clinic for confirmation by clinic staff before initiating IPT.

More broadly, policy makers could consider including a TST self-reading algorithm within their IPT guidelines. Such an algorithm would allow nurses or counsellors to educate patients on reading their own TST after intradermal inoculation of tuberculin PPD. Patients reading their TST as negative would not need to return to the clinic until their next HIV-related appointment. Those reading a positive result would be required to return within 48–72 h for the nurse to confirm the result, and IPT could be initiated at the same visit. In our study, this strategy would have increased overall accuracy to 95% (200/210), with only 30% of patients needing to revisit the clinic. Patient education is simple to implement in low-resource settings, only requiring 2–3 min of the health worker’s time, an inexpensive paper-based teaching aid and a hole-punch to make the hole in the patient-held record.

Our data are comparable to those of studies in high-resource settings. Three studies of self-read TST results reported NPVs of 90–99% and PPVs of 55–

Table 3 Number of correctly self-read TSTs according to reference results

Reference standard	Self-reading correct/number of tests	Accuracy %
TST-positive	26/36	72
TST-negative	138/174	79
All	164/210	78

TST = tuberculin skin test.

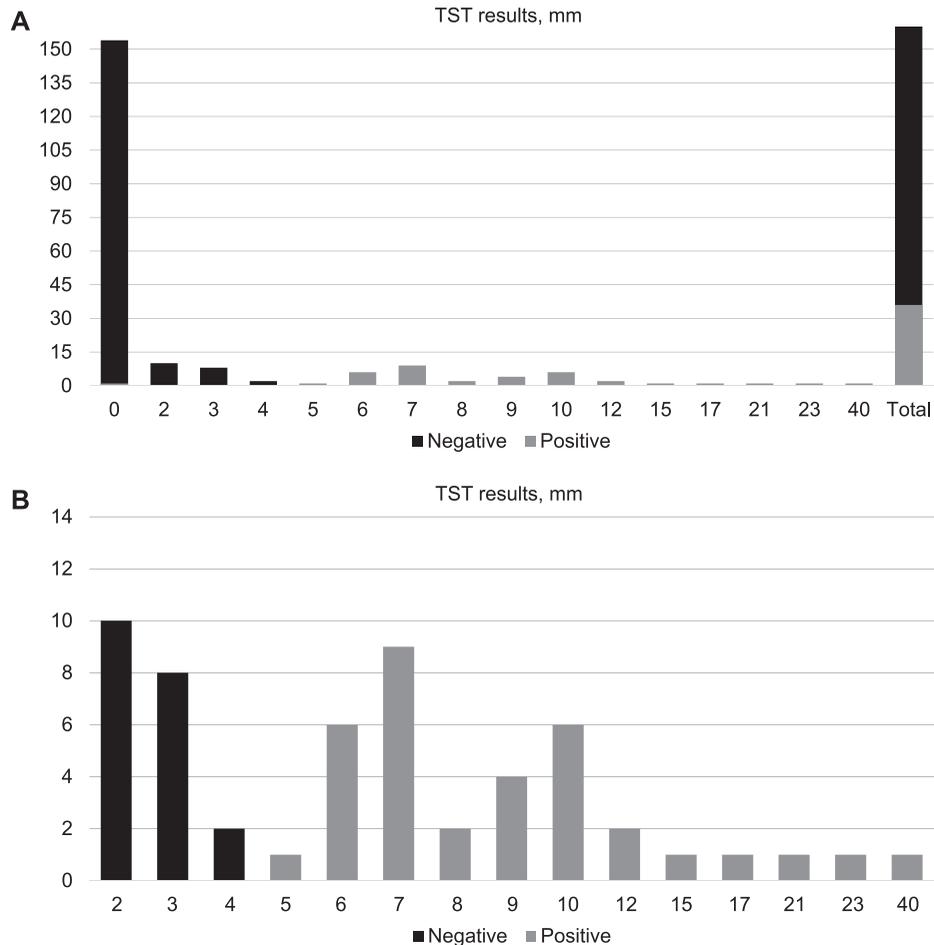


Figure 3 **A)** Distribution of TST results in mm as measured by the study nurse. **B)** Distribution of TST results in mm, excluding the zero results, as measured by the study nurse. TST = tuberculin skin test.

74%, suggesting that incorrectly interpreting TST as positive is common across different groups.^{10–12} This study is likely to be applicable to other low-resource settings: the overall rate of TST positivity was 17% compared to 22.8% found in a systematic review of TST responses in people living with HIV in under-resourced settings.¹³ There were 3.6 times more false-positive than false-negative readings in our study; in areas with considerably different prevalence, this would not be the case. Both patients on ART and ART-naïve patients were equally represented in the study.

Study strengths included the use of TST self-reading methods that can be easily replicated in other low-resource settings. There is an ongoing programmatic need for TST results despite increasing programmatic coverage of ART and the change in the criteria toward an increased CD4 count for ART initiation. Although both strategies would reduce the overall risk of active TB in HIV-positive patients, the TST will still be needed to determine the length of IPT: evidence from the study by Rangaka et al.³ indicates 12 months of IPT, regardless of TST result, while according to the

Botswana IPT clinical trial, 36 months of IPT is safe and effective in HIV-positive patients who are TST-positive.¹⁴

One weakness of the study is that it was from a single primary health care clinic with relatively small enrolment numbers. Moreover, no qualitative data were collected on patients' willingness to self-read their TST results or of their understanding. Patients appeared to understand the training on self-reading, as the majority of the response cards were marked unambiguously; however, the discordant results observed in the study indicate that training for self-reading could be improved to include repetition of instructions by the patient and response cards with 'negative/positive' rather than 'no/yes' response options.

Future research should investigate the use of self-reading of TSTs under programmatic conditions to determine whether the rate of IPT prescriptions increased following the removal of a potential barrier to implementation. A formative assessment before programmatic implementation could provide further information for training methods and reduce fears

about patients' inability to interpret their TST results. The theoretical concern that patients would deliberately record a negative result independently to avoid returning to the clinic or starting IPT would need to be considered and assessed when moving forward with implementation.

In conclusion, patients with HIV living in low-resource settings can be trained to read their own TST accurately. This form of task shifting may enable HIV treatment programmes to improve TB control in high-burden settings by the long overdue full implementation of IPT.

Acknowledgements

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Conflicts of interest: none declared.

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RESUME

CADRE : L'Organisation Mondiale de la Santé recommande le test cutané à la tuberculine (TST) quand il est faisable afin d'identifier les individus qui bénéficieront le plus du traitement préventif par isoniazide (TPI). La nécessité de lecture du TST après 48–72 h par une infirmière formée est un obstacle à sa mise en œuvre et accroît le nombre de perdus de vue.

MÉTHODE : Les patients infectés par le virus de l'immunodéficience humaine (VIH) ont été recrutés à partir d'un centre de soins de santé primaires en Afrique du Sud et formés par un conseiller de base pour interpréter leur propre TST. Le TST a été réalisé par une infirmière et le patient est revenu 2 jours plus tard avec le résultat de sa propre lecture, suivi d'une lecture aveugle par une infirmière formée (le standard de référence).

RÉSULTATS : Des 227 patients, 210 sont revenus pour

la lecture du TST : 78% ont correctement interprété leur test ; ceux qui l'ont interprété comme négatif étaient plus susceptibles d'être justes (valeur prédictive négative 93%) que ceux qui l'ont interprété comme positif (valeur prédictive positive 42%). Des 36 résultats de TST positifs, 10 (28%) ont été lus comme négatifs par les patients.

CONCLUSION : Les patients infectés par le VIH dans un contexte de ressources faibles peuvent être formés à l'interprétation de leur propre TST. Ceux qui l'interprètent comme positif doivent revenir au centre dans les 48–72 h pour une lecture de confirmation et la mise en route du TPI ; ceux qui ont fait une interprétation négative peuvent revenir à la prochaine consultation prévue et initier le TPI à ce moment si cela est approprié.

RESUMEN

MARCO DE REFERENCIA: La Organización Mundial de la Salud recomienda la prueba cutánea de la tuberculina (TST), donde sea factible, con el fin de reconocer a las personas en quienes será más útil la administración del tratamiento preventivo con isoniazida (TPI). La exigencia de una lectura del resultado en 48–72 h por parte de una enfermera capacitada representa un obstáculo a su aplicación y aumenta las pérdidas durante el seguimiento.

MÉTODOS: Se incluyeron en el estudio pacientes aquejados de infección por el virus de la inmunodeficiencia humana (VIH) que acudían a un consultorio de atención primaria en Suráfrica y un asesor lego los capacitó en la interpretación de su propia TST. El personal de enfermería iniciaba la prueba, el paciente regresaba 2 días después con el resultado de su autolectura y una enfermera capacitada practicaba la lectura de la reacción (medida de referencia), sin conocimiento de la interpretación del paciente.

RESULTADOS: De los 227 pacientes, 210 regresaron para la lectura de la prueba. De ellos, el 78% había interpretado correctamente la prueba; la probabilidad de una autolectura correcta fue mayor en los pacientes que interpretaron la prueba como negativa (valor predictivo negativo 93%) que en quienes la interpretaron como positiva (valor predictivo positivo 42%). Los pacientes leyeron como negativos 10 de los 36 resultados positivos de la TST (28%).

CONCLUSIÓN: En los entornos con escasos recursos es posible capacitar a los pacientes aquejados de infección por el VIH para interpretar su propia reacción TST. Quienes interpreten la reacción como positiva deben regresar al consultorio en 48–72 h, a fin de confirmar el resultado con una nueva lectura e iniciar el TPI; los pacientes que interpreten la prueba como negativa pueden regresar en la fecha de su siguiente cita programada e iniciar en ese momento el TPI, cuando esté indicado.