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Tuberculin skin test results in HIV-infected patients in India: implications for latent tuberculosis treatment

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SUMMARY

OBJECTIVE: To evaluate the utility of the tuberculin skin test (TST) in detecting latent and active tuberculosis (TB) among human immunodeficiency virus (HIV) infected patients in South India.

DESIGN: TSTs and CD4 counts were collected from 631 HIV-infected individuals without active TB and 209 antiretroviral and anti-tuberculosis treatment-naïve HIV-infected patients with TB. We calculated the proportion of TST-positive individuals, as well as the sensitivity, specificity, positive predictive value (PPV) and negative predictive value of TST in the diagnosis of TB.

RESULTS: Among subjects without active TB, 28% with a CD4 count <100 cells/μl vs. 43% of the total cohort had a TST >5 mm ($P = 0.14$), while the proportions with induration >10 mm were 14% vs. 36%, respectively ($P < 0.01$). Among those with active TB, using a 5 mm cut-off, the sensitivity was 42% for those with CD4 counts <200 cells/μl compared to 70% for those with CD4 counts ⩾200 cells/μl ($P < 0.001$). The PPV for detecting active TB was 29%.

CONCLUSIONS: TST is a poor predictor of both latent and active TB in HIV-infected individuals in TB endemic countries. Programmes offering treatment for latent TB should consider including all HIV-positive patients regardless of TST status, or use other indicators, such as CD4 count.

KEY WORDS: HIV; tuberculin skin test; latent tuberculosis infection; anergy; India

WIDESPREAD TREATMENT of latent tuberculosis infection (LTBI) in developing countries was not recommended prior to the emergence of the human immunodeficiency virus (HIV) epidemic.[1] However, recent clinical trials suggest significant benefits from chemoprophylaxis for HIV-infected individuals in tuberculosis (TB) endemic countries.[2,3] The World Health Organization (WHO) currently recommends treatment of LTBI in developing countries for HIV-infected patients only if they have a positive tuberculin skin test (TST).[4] National guidelines for Thailand—one of the few TB endemic countries with an established LTBI treatment programme for HIV-infected individuals—also recommend treatment only in TST-positive cases.[5]

The TST is, however, a problematic diagnostic test in HIV-infected individuals due to cutaneous anergy and other causes of false-negative reactions, including malnutrition, acute infection and improper test administration.[6–8] This high false-negative rate may prevent LTBI treatment from being offered to many who could potentially benefit from it. Moreover, operations research from developing countries has shown that TST often complicates LTBI treatment by increasing patient loss to follow-up and by raising programme costs.[9,10] Whether to base treatment of LTBI on TST is therefore a relevant question for the development of large-scale prevention programmes in resource-limited settings.

We examine the utility of TST in diagnosing active and latent TB among HIV-infected patients in South India, and discuss the implications for programmes in treating LTBI in developing countries.

STUDY POPULATION AND METHODS

The study population consisted of participants enrolled in two different randomised clinical trials performed at the Tuberculosis Research Centre (TRC) clinics in Chennai and Madurai, India, between July 2000 and June 2005. The first trial ($n = 631$) compared the efficacy of two regimens for LTBI treatment

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—a 6-month daily regimen of isoniazid (INH) and ethambutol (EMB) vs. a 3-year course of daily INH alone (in lieu of lifelong therapy). HIV-infected individuals without evidence of active TB were recruited for this trial, regardless of baseline CD4 count or TST results. Active TB was ruled out if patients were asymptomatic with a normal chest X-ray and three negative *Mycobacterium tuberculosis* sputum cultures.

The second trial ($n = 209$) compared the efficacy of treating active pulmonary TB with a 6- vs. a 9-month course of anti-tuberculosis treatment. Antiretroviral treatment (ART) and TB treatment naïve HIV-infected patients newly diagnosed with pulmonary TB were recruited. Diagnosis of active TB was based on history, physical examination and chest X-ray, and was confirmed by an acid-fast bacilli smear or culture positive for *M. tuberculosis*. For both trials, patients fitting the above inclusion criteria were treated for either LTBI or active TB and followed up for the duration of the trial. Patients who had data on TST results as well as CD4 counts were included in the present analysis.

At the time of enrolment into either trial, a TST was performed by injecting 1 TU (tuberculin unit) of protein purified derivative (PPD) RT23 with Tween 80 into the left forearm. The induration was measured after 48–72 h. Blood was collected for confirmatory HIV testing, haematological/biochemical investigations and CD4 counts (quantified by flow cytometry). History of bacille Calmette-Guérin (BCG) vaccination was assessed based on the presence of scars.

Written informed consent was obtained from all patients. The protocols were approved by the Institutional Ethics Committee of the TRC.

To test for differences in TST positivity between patients at different CD4 count strata in the cohort without active TB, one-way analysis of variance (ANOVA) with the Bon-Ferroni multiple comparison test was used. Pearson's χ^2 test was used to examine all other relationships. A receiver operating characteristics (ROC) curve was constructed for the combined cohort to examine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the TST for the detection of active TB at 5 mm and 10 mm cut-offs. Data are expressed as mean ± standard deviation (SD) unless otherwise mentioned.

The study populations were drawn from clinics in Chennai and Madurai, the two largest cities in the Indian state of Tamil Nadu, one of the six Indian states with high HIV prevalence.[11] Tamil Nadu still has significant levels of socio-economic deprivation, as more than one fifth of its population live below the poverty line and a quarter are illiterate.[12,13] Moreover, as the government-funded clinics from which the study population is drawn provide highly subsidised health care, patients availing themselves of their services are largely of a lower socio-economic status than the general population.

RESULTS

For both cohorts, the study population largely belonged to the lowest socio-economic strata, with 70% being daily wage workers in the informal sector. Sixty-seven per cent of participants were married; 25% were illiterate and another 53% had <8 years of formal education.

For the first clinical trial, a total of 631 individuals (397 females and 234 males) without evidence of active TB were eligible for this analysis. The mean age was 30 ± 7 years (range 18–60), and the mean CD4 count was 378 ± 253 cells/μl. In this cohort, 269 (42.6%) individuals were TST-positive based on 5 mm and 227 (36%) based on 10 mm cut-offs (Table 1). Using a 5 mm cut-off, 39% of females ($n = 155$) and 48.7% of males ($n = 114$) were TST-positive, while 34.3% of females and 38.9% of males were TST-positive using a 10 mm cut-off (Table 1).

There was no significant difference in the rate of TST positivity or mean induration size between older and younger age groups. There was no significant difference in the rate of TST positivity, mean induration size or mean CD4 cell count between patients with and those without a history of BCG vaccination (Table 2). Using a 5 mm cut-off, patients with CD4 counts <100 cells/μl had a lower TST-positive rate of 27.6% (mean induration size 4.1 mm), as compared to 42–48% for those with CD4 counts >100 cells/μl (mean induration size 7.9–8.5 mm) (Table 1).

For the second trial, 209 individuals (80% male) with active pulmonary TB confirmed by positive sputum culture were included in the analysis. The mean age was 35 ± 8 years (range 18–63), and the mean CD4 count was 201 ± 214 cells/μl. TST-positive patients had a higher median CD4 count of 180 cells/μl compared to a median of 119 cells/μl for TST-negative patients ($P < 0.001$). In terms of age and BCG vaccination status, there was no significant difference in the rate of TST positivity, mean induration size or

Table 1 Tuberculin skin tests by CD4 count strata for patients without active tuberculosis disease ($n = 631$)

	Patients per strata *n*	Patients with induration ⩾5 mm %	Patients with induration ⩾10 mm %	Induration size, mm mean (±SD)
Overall cohort	631	42.6	36.0	7.8 (9.6)
CD4 cell count, cells/μl				
0–100	58	27.6	13.8	4.1 (6.8)
101–200	100	48.0	40.0	8.4 (9.4)
201–350	187	44.9	39.6	8.5 (10.1)
351–500	126	42.9	34.1	7.9 (9.3)
>500	160	41.9	38.8	7.9 (9.9)
P value		0.14	<0.01	0.04
All males	234	48.7	38.9	8.4 (9.4)
All females	397	39.0	34.3	7.5 (9.7)
P value		0.05	0.27	0.27

SD = standard deviation.

Table 2 TST vs. age and BCG vaccination status for individuals without active tuberculosis disease (n = 631)

	Patients *n*	Patients with induration ⩾5 mm %	Patients with induration ⩾10 mm %	Induration size, mm mean (±SD)	CD4 cell count, cells/μl mean (±SD)
Age, years					
<30	336	32.1	26.1	7.3 (9.2)	420 (248)
⩾30	295	42.4	35.6	7.6 (9.8)	329 (251)
P value	—	0.76	0.80	0.72	<0.001
BCG status by scar					
Vaccinated	305	46.9	41.4	8.4 (9.8)	350 (210)
Not vaccinated	326	40.0	35.2	7.3 (9.5)	377 (231)
P value	—	0.08	0.07	0.60	0.41

TST = tuberculin skin test; BCG = bacille Calmette-Guérin; SD = standard deviation.

mean CD4 cell count between older and younger age groups or between vaccinated and non-vaccinated individuals (Table 3).

The sensitivity, specificity, PPV and NPV of the TST for detecting active TB, stratified by both 5 mm and 10 mm cut-offs and by CD4 count strata, are presented in Table 4. The overall sensitivity varied little based on the induration cut-off size used, with 51.2% of the group having TST indurations ⩾5 mm as compared to 45.9% with indurations ⩾10 mm. By contrast, the sensitivity varied significantly according to the immunological status of the patient, as assessed by CD4 count. Using a 5 mm cut-off, those with CD4 counts <200 cells/μl had a significantly lower rate of TST positivity of 42.1% (mean induration size 6.7 mm), compared to 69.6% for those with CD4 counts ⩾200 cells/μl (mean induration size 12.5 mm, $P <$ 0.001). Using a 5 mm cut-off, the overall specificity, PPV and NPV of the TST were respectively 57.4%, 28.5% and 78%.

DISCUSSION

While many studies from industrialised countries have evaluated the TST in HIV infection, ours is one of the few studies to examine this issue among HIV patients in a developing country with high TB prevalence. In the cohort without active TB, 39% of women and 49% of men were TST-positive using a 5 mm cut-off, which is the international standard for HIV-positive patients. A previous study that screened 76 011 people from the general population of the same Indian region found an LTBI prevalence of 57% in women and 66% in men using a 12 mm TST cut-off.[14] Therefore, even at higher CD4 counts, HIV-infected patients have a significantly lower TST-positive rate compared to the general population. The 5 mm cut-off is not strictly comparable to the 12 mm cut-off used for the general population; if anything, the 5 mm cut-off would tend to overestimate the TST-positive rate in the HIV-infected cohort.

Assuming HIV-infected patients have the same LTBI prevalence as the general population, we calculate that 154 men and 226 women should have LTBI in the cohort without active TB. However, only 114 men and 155 women were TST-positive using a 5 mm cut-off, making the TST only 74% and 69% sensitive in detecting LTBI in males and females, respectively. Using the 10 mm cut-off, the TST was only 60% sensitive in both males and females.

In patients with CD4 counts <100 cells/μl, the TST fails to detect more than half of those with LTBI. This trend probably represents cutaneous anergy, a phenomenon well-described in studies conducted in industrialised countries and in data from Thailand and

Table 3 TST versus age and BCG vaccination status for individuals with active tuberculosis disease (n = 209)

	Patients *n*	Patients with induration ⩾5 mm %	Patients with induration ⩾10 mm %	Induration size, mm mean (±SD)	CD4 cell count, cells/μl mean (±SD)
Age, years					
<35	107	43.0	37.6	7.1 (9.1)	212 (171)
⩾35	102	39.2	36.2	6.6 (8.8)	193 (185)
P value	—	0.60	0.52	0.42	0.68
BCG status by scar					
Vaccinated	109	52.2	48.0	9.5 (10)	211 (173)
Not vaccinated	100	54.7	52.0	9.3 (9.2)	191 (178)
P value	—	0.65	0.11	0.84	0.50

TST = tuberculin skin test; BCG = bacille Calmette-Guérin; SD = standard deviation.

Table 4 Accuracy of the TST for detection of active tuberculosis in South India (n = 840)

	Using ⩾5 mm cut-off			Using ⩾10 mm cut-off		
	CD4 cell counts <200 cells/μl (n = 295)	CD4 cell counts ⩾200 cells/μl (n = 545)	Overall cohort (all CD4 cell counts) (n = 840)	CD4 cell counts <200 cells/μl (n = 295)	CD4 cell counts ⩾200 cells/μl (n = 545)	Overall cohort (all CD4 cell counts) (n = 840)
Sensitivity	42.1	69.6	51.2	36.4	65.2	45.9
Specificity	60.0	56.5	57.4	69.0	62.4	64.0
PPV	48.8	18.8	28.5	51.5	20.1	29.7
NPV	53.4	92.8	78.0	54.6	92.5	78.1

TST = tuberculin skin test; PPV = positive predictive value; NPV = negative predictive value.

Ethiopia.[7,15] A more unique finding from our data is the significantly decreased rate of tuberculin reactivity even at CD4 counts >500 cells/μl. A Thai study similarly found decreased tuberculin reactivity even at CD4 counts >400 cells/μl.[7] This suggests that even selective TST screening of HIV-infected individuals with high CD4 counts may still miss a significant proportion of LTBI.

To our knowledge, this is only the second study to evaluate TST in HIV-infected individuals with active TB. We found a low sensitivity of TST of 51% among HIV-infected patients with pulmonary TB, as compared to 94% among 708 HIV-negative patients with pulmonary TB (unpublished data from our clinic). The PPV of the TST for detecting active TB is low in TB-endemic areas (29% in this study). While the NPV was high at higher CD4 counts, it was poor in immunosuppressed individuals. Many doctors in India and other countries still rely on TST as part of their diagnostic workup for active TB. These data show that TST should not be used in this manner, especially in HIV-infected individuals.

Cobelens et al. suggest that there are limited benefits in using a 5 mm induration cut-off to define a positive TST in HIV-positive patients as compared to the 10 mm cut-off used in non-HIV-infected patients.[16] Our data support this finding for HIV-infected patients at most CD4 count strata, as the difference between positivity rates using a 5 mm vs. 10 mm cut-off for detection of either latent or active TB was minimal. However, at CD4 counts <100 cells/μl, the 5 mm cut-off detected twice as many cases of LTBI (28% vs. 14%) as the 10 mm cut-off. The more sensitive 5 mm cut-off may therefore still be beneficial in this subset of severely immunosuppressed patients.

Current WHO guidelines recommend LTBI treatment in HIV-infected patients only if they have a positive TST.[4] However, debate remains as to whether treatment of LTBI benefits TST-negative patients. While some studies show statistically significant benefits from treating LTBI in TST-negative individuals,[17,18] two major meta-analyses support the WHO position by showing milder benefits that did not reach statistical significance.[19,20] In contrast, our data suggest that a large proportion of HIV-infected individuals in this TB-endemic area are likely to have LTBI despite being TST-negative, suggesting many TST-negative patients would benefit from LTBI treatment. This finding is supported by similar data from Thailand[7] and a previous study of HIV-infected patients in South India, which found that TST-positive and -negative patients developed active TB at similar incidence rates of respectively 7.1 and 6.7 cases per 100 person-years.[21]

While we can only speculate on the reasons for this discrepancy between our own findings and those of prior meta-analyses, this incongruity may partly be due to the inclusion in these meta-analyses of data from diverse geographical regions (i.e., sites in the US vs. sites in Africa), which may have very different prevalences of LTBI in the general population. In low TB prevalence settings such as the US, most TST-negative HIV-infected individuals are unlikely to have been exposed to TB (i.e., the TST has a higher NPV due to low TB prevalence). Treatment of TST-negative patients in this context is therefore unlikely to produce a significant decrease in the rate of reactivation TB.

By contrast, in South India, where nearly two thirds of the population is latently infected with TB, the TST has a low NPV and 'misses' a larger proportion of LTBI. Treatment of TST-negative HIV-infected individuals is therefore likely to have a more favourable risk-benefit ratio. More benefit in TST-negative individuals may be expected in places with even higher TB prevalence, such as the South African gold mines, which have a remarkably high TB rate due to pervasive silica dust exposure and HIV infection.[3] Therefore, rather than endorsing a one-size-fits-all answer to the question of whether TST screening should be used in programmes that treat LTBI in HIV-infected populations, we believe that this decision should be based partly on the local LTBI prevalence in the general population, as well as on local data assessing the efficacy of treating TST-negative individuals.

Finally, operations research also provides mixed evidence as to whether the TST should be used in LTBI treatment programmes. While one study from Uganda suggests that use of the TST is cost-effective,[22] other studies from Thailand and Uganda found that TST screening is associated with higher patient drop-out rates before treatment initiation.[9,10] The Ugandan study found that 19% of patients who had a TST placed

did not return at the appropriate time for follow-up test reading.[10] Another Thai study found that 86% of physicians providing LTBI treatment did not routinely perform TST despite its being part of the national guidelines.[5]

Other factors that we examined, such as age and BCG vaccination status, did not have a statistically significant influence on the operational characteristics of TST. The lack of influence of BCG vaccination is supported by a recent meta-analysis finding only a 1% false-positive rate attributable to BCG.[23] As the majority of our patients belonged to the lowest socio-economic group, we were not able to perform a meaningful analysis of the impact of socio-economic factors on the TST.

In summary, our data suggest that TST underestimates the extent of LTBI in HIV-infected individuals in South India, with a sensitivity of only 69–74% even among patients with less advanced HIV. Guidelines in developing countries basing LTBI treatment in HIV-positive individuals on a positive TST may prevent therapy from being offered to many who could benefit from it, apart from increasing costs and patient drop-out rates. Programmes offering LTBI treatment should partly base the decision to implement TST screening on the local prevalence of LTBI in the general population. Programmes in high TB prevalence settings should consider including all HIV-infected patients, regardless of TST status, or use other treatment indicators, such as CD4 count or total lymphocyte count.[24,25] Current WHO guidelines recommend initiation of ART in asymptomatic HIV-infected individuals only at CD4 counts <200 cells/μl.[26] As a significant proportion of HIV-infected individuals in TB endemic settings experience an episode of active TB even at CD4 counts >200 cells/μl,[24] liberalisation of current CD4 count guidelines for initiation of ART may be an additional approach for preventing TB among individuals living with HIV in developing countries.

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RÉSUMÉ

OBJECTIF : Evaluer l'utilité du test cutané tuberculinique (TST) pour la détection de la tuberculose (TB) latente et active chez les patients infectés par le virus de l'immunodéficience humaine (VIH) en Inde du Sud.
SCHÉMA : On a examiné le TST et le décompte de CD4 chez 631 individus infectés par le VIH et sans TB active ainsi que chez 209 patients infectés par le VIH et atteints de TB mais sans traitement antirétroviral ou antituberculeux. Nous avons calculé le pourcentage d'individus à TST positif ainsi que la sensibilité, la spécificité, la valeur prédictive positive (VPP) et la valeur prédictive négative du TST pour le diagnostic de la TB.
RÉSULTATS : Parmi les sujets sans TB active, 28% des patients dont le décompte de CD4 était <100 cellules/μl versus 43% de la cohorte totale avaient un TST >5 mm ($P = 0,14$), alors que les proportions avec une induration >10 mm ont été respectivement de 14% vs. 36% ($P < 0,01$). Parmi les sujets atteints de TB active, l'utilisation d'une limite de 5 mm a donné une sensibilité de 42% pour ceux dont les décomptes de CD4 étaient <200 cellules/μl, par comparaison avec 70% pour ceux dont les décomptes étaient ⩾200 cellules/μl ($P < 0,001$). La VPP pour la détection d'une TB active a été de 29%.
CONCLUSIONS : Chez les individus infectés par le VIH et vivant dans des pays où la TB est endémique, le TST est un facteur prédictif médiocre tant de la TB latente que de la TB active. Les programmes offrant un traitement pour la TB latente devraient considérer d'y inclure tous les patients séropositifs pour le VIH, quel que soit leur statut de TST, ou encore utiliser d'autres indicateurs comme le décompte des CD4.

RESUMEN

OBJETIVO : Evaluar la utilidad de la prueba cutánea de la tuberculina (TST) en la detección de tuberculosis (TB) latente y activa en pacientes infectados por el virus de la inmunodeficiencia humana (VIH) en el sur de la India.
MÉTODO : Se recogieron datos de los resultados de la TST y del recuento de linfocitos CD4 de 631 pacientes con infección por el VIH, sin TB activa y 209 infectados por el VIH, con TB y sin antecedentes de tratamiento antirretrovírico ni antituberculoso. Se calculó el porcentaje de reacción positiva a la TST y la sensibilidad, especificidad, valor de predicción positiva (VPP) y valor de predicción negativa de la TST en el diagnóstico de TB.
RESULTADOS : En la cohorte de pacientes sin TB activa, se observó una reacción cutánea a la TST de >5 mm en 28% de los pacientes con recuentos de CD4 <100 células/μl y en 43% de los pacientes con recuentos superiores ($P = 0,14$) ; la induración de >10 mm estuvo presente en 14% de aquellos con <100 células CD4/μl y en 36% de quienes tuvieron recuentos más altos ($P < 0,01$). En la cohorte de pacientes con TB activa el umbral de 5 mm tuvo una sensibilidad de 42% en pacientes con recuento de CD4 <200 células/μl y de 70% en aquellos con recuentos ⩾200 células/μl ($P < 0,001$). El VPP de TB activa fue 29%.
CONCLUSIÓN : La TST es un débil indicador de TB latente y activa en individuos infectados por el VIH en países endémicos. Los programas que ofrecen tratamiento de la TB latente deberían contemplar la inclusión de todos los pacientes con serología positiva para el VIH, sin tener en cuenta el resultado de la TST ni otros indicadores como el recuento de CD4.