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Tuberculin skin test conversion among HIV patients on antiretroviral therapy in Uganda

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SUMMARY

SETTING: A human immunodeficiency virus (HIV) clinic in a setting of high tuberculosis (TB) and HIV prevalence.

OBJECTIVE: To study the incidence of and factors associated with tuberculin skin test (TST) conversion in HIV patients on antiretroviral therapy (ART).

DESIGN: Prospective cohort study of TST-negative, ART-naïve HIV patients (CD4 cell count < 250 cells/μl) without active TB. TST was repeated at 2 months and, if negative, at 6 months. TST positivity was defined as an induration of $\geq$5 mm. Clinical examination, chest X-ray and CD4 cell counts were performed at baseline and follow-up. Proportions and incidence of TST conversion were calculated, and logistic regression analyses were performed.

RESULTS: Of the 142 patients, 105 (75.5%) were females. The mean age was 35.9 years (standard deviation 8.1) and the median CD4 cell count was 119 cells/μl (interquartile range 42–168). The incidence of TST conversion was 30.2/100 person years (95%CI 19.5–46.8). Conversion was not associated with clinical, CD4 cell count or chest radiography findings.

CONCLUSIONS: A high incidence of TST conversion was observed, supporting the World Health Organization recommendation to provide isoniazid preventive therapy (IPT) to all HIV patients in high TB prevalence settings. If case-control programmes choose to provide IPT only to TST-positive patients, repeat TST should be considered following initiation of ART.

KEY WORDS: tuberculin skin test; conversion; antiretroviral therapy

THE WORLD HEALTH ORGANIZATION (WHO) recommends the three 'I's (isoniazid preventive therapy [IPT], intensified case finding for active tuberculosis [TB] and TB infection control) as the main strategies to improve TB control among human immunodeficiency virus (HIV) infected persons.[1] IPT for 6–9 months reduces the risk of TB reactivation in HIV-infected persons by 40–70%, and by 92% if given for prolonged periods of up to 36 months.[2–4] The greatest benefit of IPT is observed in patients with a positive tuberculin skin test (TST).[4] A clinical trial conducted in Botswana showed that in TST-positive patients, the risk of active TB was reduced by 92%, while in TST-negative patients there was a non-statistically significant reduction of 14%.[4]

One of the challenges faced while rolling out IPT among HIV-infected persons in resource-limited settings is the lack of a sensitive test to diagnose latent tuberculosis infection (LTBI). The sensitivity of TST is markedly reduced in HIV patients due to HIV-associated anergy.[5,6] One in three HIV-positive patients are reported to be anergic to purified protein derivative (PPD)[6,7] due to HIV-associated immune deficiency. This is more common in patients with low CD4 cell counts.[8] Although HIV is the most common cause of anergy to PPD, overwhelming TB, protein energy malnutrition, cancer and use of immune suppressive drugs, such as steroids and anticancer drugs, are also associated with anergy.[9] Anergy also doubles among patients aged $\geq$65 years, and is significantly increased in patients on dialysis.[10]

Previous studies from countries with a low TB burden indicate that antiretroviral therapy (ART) use is associated with a reversal of PPD anergy as a result of immune system recovery.[11–15] The current US guidelines recommend a repeat TST for individuals whose initial TST result was negative and whose immune function has improved in response to ART.[16]

In this article, we report the proportions and incidence of TST conversion and factors associated with

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TST conversion in a prospective cohort of patients with HIV infection who were TST-negative at ART initiation.

STUDY METHODS

Design and setting

This study was nested in a prospective cohort study designed to investigate the incidence of ART-associated TB and unmasking TB-IRIS (immune reconstitution inflammatory syndrome) in patients initiating ART at the Infectious Diseases Institute clinic in Kampala, Uganda. This cohort has been described in detail elsewhere.[17]

Study eligibility

We enrolled ART-naïve HIV-infected patients aged ⩾18 years who were eligible for ART according to the Uganda Ministry of Health ART guidelines (CD4 cell count < 250 cells/μl).[18,19] Patients with active TB based on clinical criteria, smear microscopy and or chest radiography (CXR) were excluded.

Patient assessment and follow-up

Patients were assessed at baseline and 2 weeks, monthly thereafter for 6 months, and then every 3 months up to 1 year. Recruitment started in February 2008, and follow-up ended in May 2010. Patients underwent clinical assessment at enrolment and at every follow-up visit to exclude active TB. A diagnosis of active TB was based on two positive sputum smears performed on Ziehl-Neelsen or fluorescent microscopy, and/or a positive mycobacterial culture on Löwenstein-Jensen media, or the presence of TB symptoms and CXR suggestive of active TB (interpreted by a radiologist) plus clinical improvement on anti-tuberculosis treatment. In all patients, a CXR was performed before enrolment and repeated during follow-up if clinically indicated. Other tests performed on clinical indication included abdominal ultrasound, fine-needle lymph node aspirate for TB microscopy and TB blood culture.

CD4 cell count measurement (FACSCalibur, BD, Sparks, MD, USA) was performed at enrolment and at the 6-month follow-up visit.

The TST was performed as follows: the area was swabbed with alcohol and allowed to dry before injection, then 0.1 ml of PPD (RT-23 SSI 2TE; Statens Serum Institute, Copenhagen, Denmark) was injected into the volar aspect of the left arm. Patients were instructed to return after 2–3 days for reading of the test. The TST results were recorded in the patient's study file. A skin induration of ⩾5 mm was considered positive. Patients TST-negative at enrolment were tested at 2 months, and then again at 6 months if they were negative at month 2. A diagnosis of active TB during follow-up was not an exclusion criterion for repeat TST.

All TST-positive patients whose CXR showed no evidence of active TB and who were culture-negative were offered IPT.

Patients were considered to have entered follow-up if their baseline TST was negative. Patients who returned for a TST at 2 months follow-up and tested positive were considered to have completed follow-up. TST-negative patients at 2 months follow-up underwent TST again at month 6 of follow-up. All patients with a TST result at 6 months were classified as having completed follow-up. Patients who did not undergo TST testing at 2 months, but returned for TST testing at 6 months follow-up were also classified as having completed follow-up.

Data analysis

Data were collected with piloted clinical review forms, double-entered into EpiData, version 3.1 (EpiData Association, Odense, Denmark) and exported to STATA, version 11 (Stata Corp, College Station, TX, USA) for analysis. Descriptive statistics were used to summarise demographic, clinical and laboratory data. We calculated proportions of TST-positive patients at baseline and 2 and 6 months after commencing ART. Follow-up time was calculated as follows: for patients who underwent TST conversion, it was calculated from the time the baseline TST was performed to the time the patient became TST-positive. For patients who remained TST-negative throughout follow-up, it was calculated from the time of the baseline TST to 6 months follow-up. Patients who were lost to follow-up were not included in the calculation of the incidence. Total follow-up time was calculated by summing each patient's follow-up time. The incidence of TST conversion in the cohort was then calculated by dividing the total number of TST conversions by the total follow-up time. Logistic regression was used to examine predictors of TST conversion at univariate analysis. All *P* values were two-sided.

Ethics

The study was approved by the scientific review committee of the Infectious Diseases Institute, Kampala; the institutional review boards of Makerere College of Health Sciences and the University of Antwerp, Belgium; and by the Uganda National Council of Science and Technology. All participants provided written informed consent; patients who did not consent to participate continued to receive standard care from the clinic. Patients were free to withdraw consent. Patients who developed active TB were treated according to the Uganda National TB and Leprosy Programme guidelines.

RESULTS

Of the 219 patients eligible for ART, 204 underwent a TST. Among those tested, 62 (30.4%) were

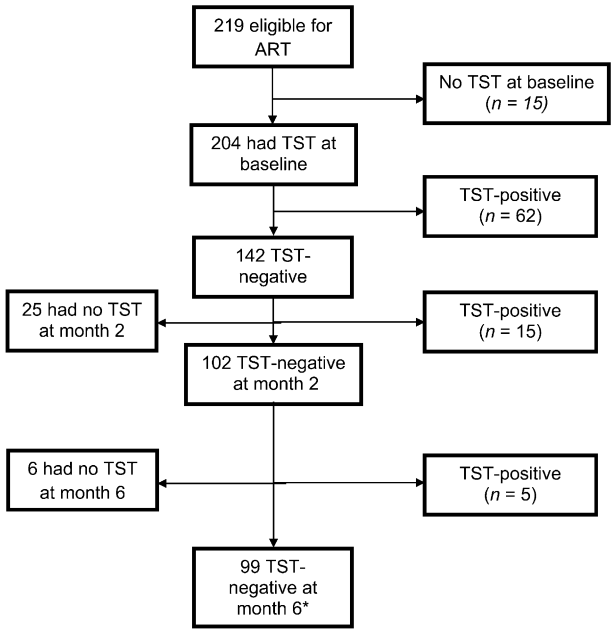

Figure Patients evaluated at the different study points. *Number greater than expected as eight patients not tested at month 2 returned at month 6 for testing. ART = antiretroviral therapy; TST = tuberculin skin test.

TST-positive and 142 were TST-negative at baseline. Twenty-five patients with negative baseline TST did not undergo TST at 2 months follow-up. Eight of these 25 patients underwent TST at 6 months follow-up. Of the 102 patients who were TST-negative at the 2 month follow-up visit, six did not undergo TST at 6 months. The main reasons for failure to complete follow-up TST were patients declining repeat TST and loss to follow up (Figure). Overall, 119 patients completed the TST schedule as required after ART initiation.

Baseline patient characteristics

Of the 142 TST-negative patients enrolled, 105 (73.9%) were females. The mean age was 35.9 years (standard deviation ± 8.1) and the median CD4 cell count at baseline was 119 cells/μl (interquartile range [IQR] 42–168). Eighty-one patients (57.4%) had a visible bacille Calmette-Guérin (BCG) scar; in 12 patients BCG scar status could not be confirmed. Among the 126 patients who underwent CXR, 14 (9.5%) had CXR suggestive of TB. The remaining baseline patient characteristics are shown in Table 1. Compared to patients who underwent TST after initiation of ART, patients who did not were more likely to have lower haemoglobin ($P = 0.008$), lower body mass index (BMI, $P = 0.012$) and lower CD4 cell count ($P = 0.001$, Table 2).

Table 2 Comparison of the baseline characteristics of patients who completed the TST schedule and those who did not

Variable	Completed TST ($n = 119$) n (%) or mean ± SD	Did not complete TST ($n = 23$) n (%) or mean ± SD	P value
Female sex	93 (78.2)	14 (60.9)	0.078
Age, years	35.9 ± 8.0	36.2 ± 9.3	0.902
BCG scar present	69 (63.9)	13 (59.1)	0.671
BMI, kg/m^2	24.2 ± 7.1	20.3 ± 3.2	0.012
Any TB symptom present	22 (18.2)	8 (34.8)	0.072
Haemoglobin, g/dl	12.3 ± 1.8	11.2 ± 2.1	0.008
CD4 cell count, cells/μl	136 ± 114	35 ± 106	0.001
Baseline temperature, °C	36.3 ± 0.5	36.4 ± 0.9	0.324

TST = tuberculin skin test; SD = standard deviation; BCG = bacille Calmette-Guérin; BMI = body mass index; TB = tuberculosis; IQR = interquartile range.

Tuberculin skin test conversion

At 6 months, 20 of the 119 (16.8%) TST-negative patients who underwent TST after initiation of ART became TST-positive. Fifteen of these conversions (75.0%) occurred after 2 months of ART. The median follow-up time was 190 days (IQR 180–201). The overall cohort TST conversion incidence rate was 30.2/100 person years (py; 95% confidence interval [CI] 19.5–46.8/100 py). All TST converters had 0 mm induration at baseline. At the time of TST conversion, the lowest induration size was 12 mm and the maximum was 28 mm, with an average induration size of 19 mm.

Table 1 Baseline cohort characteristics comparing TST converters and non-converters

Variable	All (n =142) n (%) or mean ± SD	Converters (n = 20) n (%) or mean ± SD	Non-converters (n = 99) n (%) or mean ± SD
Female sex	105 (73.9)	15 (75)	77 (77.8)
Age, years	35.9 ± 8.1	36.3 ± 8.2	35.8 ± 7.5
BCG scar present	81 (57.4)	12 (54.5)	75 (64.1)
Any TB symptom present	25 (18.0)	3 (13.6)	25 (21.4)
BMI, kg/m^2, median [IQR]	22.4 [20.5–25.3]	21.8 [21.1–23.8]	22.8 [20.5–26.4]
Haemoglobin, g/dl	12.1 ± 1.8	12.2 ± 1.5	12.1 ± 1.9
CD4 cell count, cells/μl, median [IQR]	119 [42–168]	134 [35–176]	112 [49–164]
Temperature, °C	36.4 ± 0.6	36.4 ± 0.4	36.4 ± 0.6

TST = tuberculin skin test; SD = standard deviation; BCG = bacille Calmette-Guérin; TB = tuberculosis; BMI = body mass index; IQR = interquartile range.

Table 3 Univariate analysis of factors associated with TST conversion

Variable	OR (95%CI)	*P* value
Sex		
Female	0.75 (0.26–2.14)	0.59
Male	1	
Age, years		
<39	0.89 (0.34–2.33)	0.82
⩾39	1	
BCG scar		
Present	1.02 (0.50–2.06)	0.97
Absent	1	
BMI, kg/m^2		
⩾18.5	0.94 (0.18–4.78)	0.94
<18.5	1	
Haemoglobin, g/dl		
⩾12.5	0.81 (0.31–2.11)	0.67
<12.5	1	
Baseline CD4 cell count, cells/μl		
⩾50	0.47 (0.17–1.34)	0.16
<50	1	
CD4 cell count increase, cells/μl		
⩾100	1.10 (0.42–2.92)	0.84
<100	1	
Baseline temperature, °C		
⩾37.2	1.02 (0.11–9.61)	0.98
<37.2	1	
Development of active TB		
Yes	1.25 (0.13–11.78)	0.85
No	1	

TST = tuberculin skin test; OR = odds ratio; CI = confidence interval; BCG = bacille Calmette-Guérin; BMI = body mass index; TB = tuberculosis.

Factors associated with tuberculin skin test conversion

The median CD4 cell count increase after 6 months of ART was 109 cells/μl (IQR 58–183). There was no association between CD4 cell count increase and baseline CD4 cell count and TST conversion. In addition, none of the demographic, clinical or radiological characteristics were found to be associated with TST conversion (Table 3).

Five patients developed active TB during follow-up; one of these converted to a positive TST. Development of active TB was not associated with TST conversion (odds ratio 1.25, 95%CI 0.13–11.78, $P = 0.85$).

DISCUSSION

Over a period of 6 months after initiating ART, 20/119 (16.8%) TST-negative patients who underwent repeat TST experienced TST conversion, an incidence rate of 30.2/100 py. These conversions could be due to reversal of anergy following ART, as previously reported.[11–15] However, neither baseline CD4 cell count nor CD4 increase following ART was found to be associated with TST conversion, contrary to previous reports (Table 4).[12,13] One reason could be because the study was underpowered to detect this association. The lack of significant association between TST conversion and the predictor variables investigated could also be due to the fact that some patients did not complete the TST schedule as planned. These patients had more advanced HIV disease, as evidenced by lower CD4 cell counts, haemoglobin and BMI compared to those who completed TST as planned. It is therefore likely that these patients missed TST visits due to poor health or that they had died, as many of these factors have previously been associated with early mortality.[20–22]

In repeat TST studies, conversions may also be due to a booster phenomenon, incident TB infection, change in method of administration or inter-/intra-reader variability at different testing time points. A booster phenomenon is unlikely to have played a major role in our study, as boosting mostly occurs if repeat testing is performed within 1–5 weeks.[23–25] In this study, testing was repeated after 8 weeks. We used the Mantoux method, which has less variability than the Tine method, at all testing time points.[26] Throughout the study, the same nurse administered the TST and read the results. Furthermore, the observed indurations at repeat testing were much larger than those attributed to inter-reader variability.[27] We observed an average TST induration of 19 mm at repeat testing, which is greater than the size usually attributed to inter-reader variability (2.5 mm).[28]

The TST conversions may have been due to new TB infection during follow-up, as the study was conducted in a high TB transmission setting and it is well known that HIV-positive patients have an increased risk of infection following exposure to TB.[29,30] Subclinical active TB at the time of ART initiation is reported to be high in HIV patients, especially those with advanced immunodeficiency, as was the case in this cohort.[31] However, in this study only one of the five patients diagnosed with active TB during the 6 months of follow-up was TST-positive.

Non-tuberculous mycobacteria (NTM) are ubiquitous in the Ugandan environment.[32] However, in

Table 4 Studies reporting TST conversion among HIV-positive patients without active TB on antiretroviral therapy

Study	Design	TB burden	CD4 cell counts cells/μl	Patients *n*	Duration of HAART prior to repeat TST	TST conversion rate, %
Fisk et al., 2003[13]	Cross-sectional	Low, USA	Median: 12	110	2 months	11.8
Girardi et al., 2002[11]	Retrospective cohort	Low, Italy	Median: 295	129	3 years	5.4
Schluger et al., 2002[8]	Prospective	Low, USA	Mean: 115.8	10	2–12 months	0
Moreno et al., 1999[15]	Prospective cohort	Low, Spain	Median: 26.6	211	6–12 months	0.5

TST = tuberculin skin test; HIV = human immunodeficiency virus; TB = tuberculosis; HAART = highly active antiretroviral therapy.

persons with HIV infection, disease caused by NTM does not seem to occur frequently. It is therefore unlikely that several TST conversions were caused by NTM.[33] Additional tests that are *M. tuberculosis*-specific, such as interferon-gamma release assays, could help to address this phenomenon; however, these tests were not performed.[34]

CONCLUSION

The results of this study indicate a high TST conversion incidence rate within a short period of starting ART. These results support the WHO recommendation to provide IPT to all patients with HIV infection in high TB settings who do not have active TB. If TB control programmes choose to provide IPT only to TST-positive patients, repeat TST should be considered following initiation of ART.

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Conflict of interest: none declared.

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RÉSUMÉ

CONTEXTE : Un dispensaire pour le virus de l'immunodéficience humaine (VIH) dans un contexte à prévalence élevée de tuberculose (TB) et de VIH.

OBJECTIF : Etudier l'incidence du virage des tests cutanés tuberculiniques (TST) chez les patients infectés par le VIH sous traitement antirétroviral (ART) et les facteurs qui y sont associés.

SCHÉMA : Etude prospective d'une cohorte de patients VIH sans ART antérieure (décompte de CD4 $<$ 250 cellules/μl) à TST négatif et sans TB active. On a répété le TST après 2 mois et, en cas de négativité, après 6 mois. On a décrit comme positivité du TST une induration de $\geqslant$5 mm. On a réalisé un examen clinique, un cliché thoracique et des décomptes des cellules CD4 au début et lors du suivi. Les proportions et l'incidence du virage du TST ont été calculées. On a réalisé des analyses de régression logistique.

RÉSULTATS : Sur les 142 patients, il y avait 105 femmes (75,5%). L'âge moyen a été de 35,9 années (SD 8,1) et le décompte médian des cellules CD4 a été de 119 cellules/μl (IQR 42–168). L'incidence du virage du TST a été de 30,2/100 années-personne (IC95% 19,5–46,8). Le virage n'est pas en association avec les données cliniques, le décomptes des cellules CD4 ou les anomalies radiologiques.

CONCLUSIONS : On a observé une incidence élevée de virage du TST qui vient en appui à la recommandation de l'Organisation Mondiale de la Santé de donner un traitement préventif à l'isoniazide (IPT) à tous les patients infectés par le VIH dans des contextes à haut prévalence de TB. Si les programmes de lutte contre la maladie choisissent de ne donner l'IPT qu'aux patients dont le TST est positif, il faut envisager la répétition de ce TST après le commencement de l'ART.

RESUMEN

MARCO DE REFERENCIA: Un consultorio de tratamiento de la infección por el virus de la inmunodeficiencia humana (VIH) en un entorno con alta incidencia de tuberculosis (TB) e infección por el VIH.

OBJETIVO: Evaluar la incidencia de conversión de la prueba cutánea de la tuberculina (TST) en los pacientes positivos para el VIH que reciben tratamiento antirretrovírico (ART) y definir los factores que se asocian con esta conversión.

MÉTODO: Fue este un estudio prospectivo de cohortes de pacientes infectados por el VIH en quienes se practicó la reacción TST, que no habían recibido ART (recuento de células CD4 $<$ 250 células/μl) y no presentaban TB activa. Se repitió la TST 2 meses después y cuando seguía siendo negativa, se examinó de nuevo 6 meses después. La positividad de la reacción TST se definió como una induración $\geqslant$5 mm. El examen físico, la radiografía de tórax y el recuento de células CD4 se practicaron al comienzo del estudio y durante el seguimiento. Se calculó la proporción y la incidencia de conversión de la reacción TST y se llevaron a cabo análisis de regresión logística.

RESULTADOS: De los 142 pacientes, 105 fueron mujeres (75,5%). La media de la edad fue 35,9 años (SD 8,1) y la mediana del recuento de células CD4 fue 119 células/μl (IQR 42–168). La incidencia de conversión de la reacción TST fue 30,2 por 100 años-persona (IC95% 19,5–46,8). No se observó ninguna asociación entre la conversión y las características clínicas o radiográficas ni el recuento de células CD4.

CONCLUSIÓN: Se observó una alta incidencia de conversión de la reacción TST, lo cual refuerza la recomendación de la Organización Mundial de la Salud de suministrar el tratamiento preventivo con isoniazida (IPT) a todos los pacientes positivos para el VIH, en los entornos con alta incidencia de TB. Cuando los programas de control de la TB escojan proveer el IPT solo a los pacientes con reacción TST positiva, se debe considerar la repetición de la TST después del comienzo del ART.