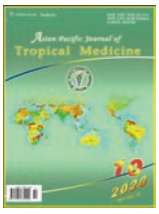

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Performance and correlation of interferon gamma release assays and tuberculin skin test in HIV-infected children and adolescents with immune reconstitution

Keswadee Lapphra[1], Rati Diwitaya[1], Sansnee Senawong[2], Maneeprang Thovarabha[2], Parnwas Pinnobphun[3], Alan Maleesatharn[1], Nantaka Kongstan[1], Benjawan Khumcha[1], Wanatpreeya Phongsamart[1], Orasri Wittawatmongkol[1], Supattra Rungmaitree[1], Kulkanya Chokephaibulkit[1]✉

[1]*Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

[2]*Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

[3]*Biomed Diagnostics (Thailand) Co LTD, Bangkok, Thailand*

ABSTRACT

Objective: To evaluate the performance of interferon gamma release assays and tuberculin skin test in HIV-infected children and adolescents with immune reconstitution.

Methods: A cross-sectional study was conducted in HIV-infected patients aged 5-18 years receiving antiretroviral treatment with CD4 T-lymphocytes >25% or >500 cells/mm^3 for at least 6 months. QuantiFERON-TB Gold, T-SPOT.TB, and tuberculin skin test were performed in each patient.

Results: A total of 50 patients were enrolled with median age of 13.7 years, CD4 counts of 753 (IQR: 587-989) cells/mm^3. Among 27 patients with tuberculosis (16) or tuberculosis exposure (11), 8 (29.6%) were positive to at least one test, 2 (7.4%) were positive QuantiFERON-TB Gold, 3 (11.1%) positive T-SPOT.TB, and 7 (25.9%) had tuberculin skin test ≥5 mm. Among 23 patients without history of tuberculosis or exposure, all had negative interferon gamma release assays, while 2 (8.7%) had positive tuberculin skin test.

Conclusions: All tests had low sensitivity despite immune reconstitution.

KEYWORDS: Children; HIV; TB; Interferon gamma release assays; Tuberculin skin test

1. Introduction

The majority of children and adolescents living with HIV are at risk of tuberculosis (TB). Treatment of latent TB infection (LTBI) in this high-risk populations is a critical strategy towards the mission to end TB. Immunosuppression can alter the reaction of interferon-gamma release assays (IGRA) and tuberculin skin test (TST) utilized for LTBI diagnosis and this may lead to a missed opportunity to provide treatment to prevent TB. It is hypothesized that following immune reconstitution with antiretroviral therapy (ART) that individuals living with HIV will react well to IGRA and TST tests.

2. Materials and methods

This was a cross-sectional study at a pediatric HIV clinic, Siriraj Hospital, in Bangkok, Thailand. The study was approved by the Institute Review Board (Certificate of approval number Si077/2015). We enrolled children with HIV aged 5-18 years on ART for at least 1 year, with evidence of immune reconstitution, defined as a CD4 >25% or >500 cells/mm^3 for at least 6 months. Those having any other condition that may affect immunologic function in the preceding 6 weeks were excluded[1]. Study procedures included two visits: the first visit included a physical examination, checking for BCG scar and vaccination records, chest X-ray, collection of a single blood sample for the two IGRA tests, QFT-GIT (Cellestis Limited, Australia) and T-SPOT.TB (Oxford Immunotec, Oxford, UK), and TST placement using 0.1 mL of PPD RT23 (Staten Serum Institute, Denmark) *via* intradermal injection. At the second visit, 48-72 h later, the TST reaction was read (the same person read the TST reactions throughout the study). Reactions of ≥5 mm induration were considered positive[2]. Subjects were classified into

✉To whom correspondence may be addressed. E-mail: kulkanya.cho@mahidol.ac.th

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three categories based on their medical history: (1) TB (including definite, probable, or possible TB), (2) TB exposure with household members without symptom and normal chest X-ray[3], and (3) no TB or TB exposure.

Data were analyzed using STATA Version 11.2 (Stata Corp LP, TX, USA). Agreement between the QFT-GIT and T-SPOT.TB, and between TST and IGRA were determined by Cohen's kappa coefficient (κ)[4]. Concordance between all tests was defined as the percentage of concordant results (positive or negative) in the same subjects.

3. Results

A total of 50 children and adolescents with HIV were enrolled (64.0% male) with a median age of 13.7 years (Figure 1). All subjects reported receiving BCG vaccination at birth. Forty (80.0%) of subjects had moderate to severe nadir CD4 suppression[5]. The median CD4 count at enrollment was 753 (IQR: 587-989) cells/mm^3. The median duration of CD4 count >500 cells/mm^3 or >25% was 93.3 (IQR: 67.2-139.1) months. All subjects were receiving ART [median duration 104.6 (IQR: 83.3-142.8) months] and the median age of ART initiation was 3.4 (IQR: 1.1-7.4) years. All subjects were virologically suppressed [median duration 78 (IQR: 46.9-93.8) months]. Sixteen (32.0%) subjects had a history of TB, 10 probable and 6 definite; all were diagnosed more than one year prior to enrollment. Eleven (22.0%) subjects were household TB-exposed; 9 were exposed more than one year prior to enrollment. All children with TB and TB exposure complete the appropriate TB treatment.

Among the 27 subjects who had TB or TB exposure, 8 (29.6%) children had a positive results to at least one of the IGRA tests or TST. Of these, 2 (7.4%) had positive QFT-GIT, 3 (11.1%) had positive T-SPOT.TB, and 7 (25.9%) had positive TST results. Among those with no history of TB or TB exposure, none had a positive IGRA test, while 2 (8.7%) had a positive TST.

More subjects with TB/TB exposure had positive test results of either IGRA or TST compared to those without TB/TB exposure (29.6% *vs.* 8.7%, P=0.08). Overall agreement between QFT-GIT, T-SPOT.TB, and TST were slight to fair: κ=0.12 for QFT-GIT *vs.* TST (P=0.11), κ=0.23 for T-SPOT.TB *vs.* TST (P=0.02). The agreement between QFT-GIT *vs.* T-SPOT.TB was good (κ=0.65, P<0.01 for all patients, and κ=0.78, P<0.01 in TB/TB-exposed patients). No independent factor associated with negative test results for both IGRA and TST was identified.

In subjects without TB/TB exposure, although the concordance between tests were high (87.0%), the agreement between any of the tests was difficult to interpret due to the few positive results (Table 1).

4. Discussion

We found in children and adolescents living with HIV on ART with immune reconstitution that IGRA and TST had low sensitivity and the concordance between two IGRA and TST was 80.0%, most

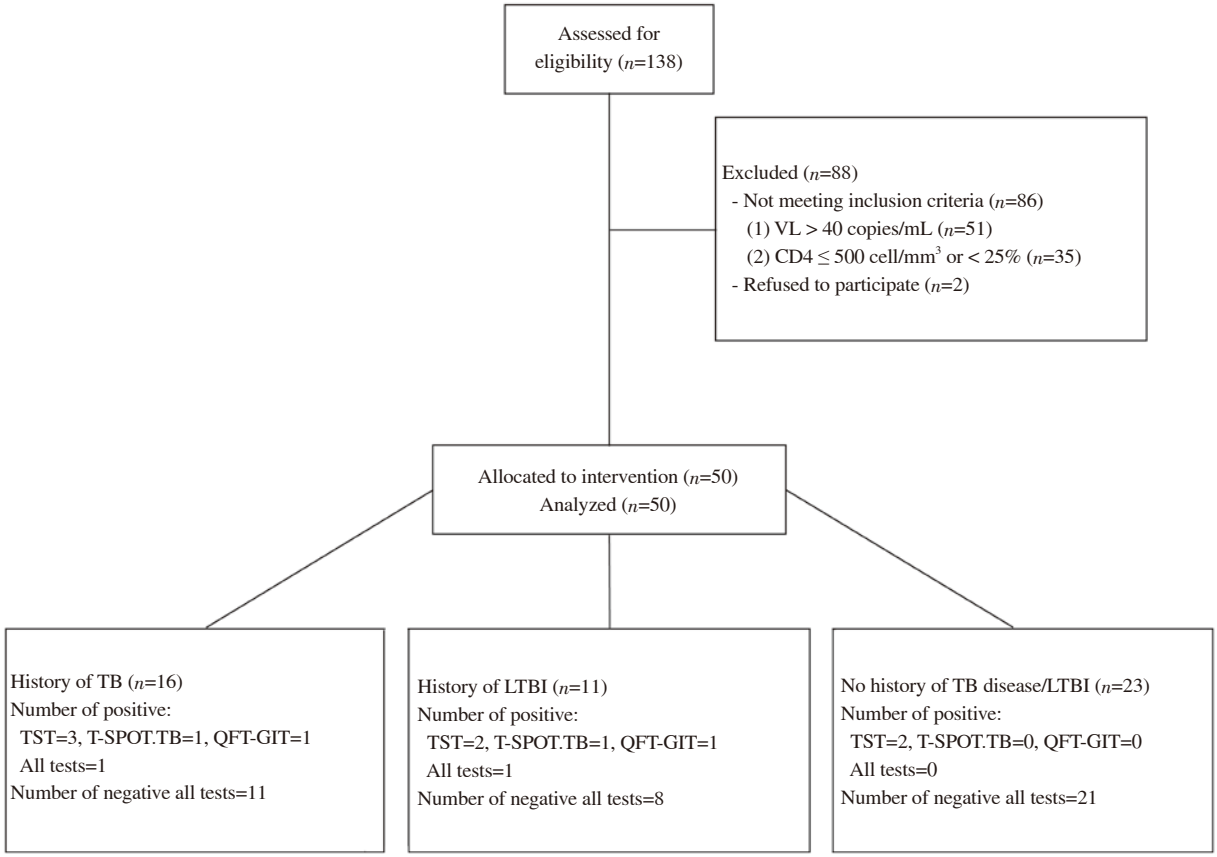

Figure 1. The study flowchart. TB: tuberculosis.

Table 1. Agreement and overall concordance of QFT-GIT, T-SPOT.TB and TST ≥5 mm.

Patient characteristics	Agreement between tests						Overall concordance among the tests [*n* (%)]	
	QFT-GIT *vs*. T-SPOT.TB		QFT-GIT *vs*. TST		T-SPOT.TB *vs*. TST		All matched	At least one positive
	n (%)	κ (*P*-value)	*n* (%)	κ (*P*-value)	*n* (%)	κ (*P*-value)		
No history of TB or TB exposure (*n*=23)	22 (95.7)	0.00 (-)	21 (91.3)	0.00 (0.50)	20 (87.0)	-0.02 (0.62)	20 (87.0)	2 (8.70)
With history of TB or TB exposure (*n*=27)	26 (96.3)	0.78 (<0.01)	20 (74.1)	0.12 (0.20)	21 (77.8)	0.28 (0.04)	20 (74.1)	8 (29.60)
All (*n*=50)	48 (96.0)	0.65 (<0.01)	41 (82.0)	0.12 (0.11)	41 (82.0)	0.23 (0.02)	40 (80.0)	10 (20.0)

Note: "-" stands for unable to calculate.

of which was driven by negative results. Agreement between each IGRA test and TST were slight to fair, and agreement between the two IGRA tests was good.

Early diagnosis and treatment of LTBI is an essential component of the WHO strategy to control TB[6,7], but the diagnostic test is still challenging. We found only a third of children with a history of TB or TB exposure were positive to at least of the two IGRA tests or TST; and IGRA tests were less likely to be positive than TST. There are a few published studies exploring the performance of IGRA in children with HIV[8] and our results add to this limited knowledge. While QFT-GIT and T-SPOT.TB results had 96% concordance, the two IGRA tests had only 80% concordance with TST at 5 mm.

A study of QFT-GIT in children with HIV in Botswana reported similar results to our study with IGRA positive rates around 10%, and TST positive rates around 25%, in children with prior TB/LTBI, despite suppressed viral load and normalized CD4 counts in an area with a high prevalence of TB[8]. Altogether it is suggested that T-cell dysfunction remain despite 'normalized' CD4 counts[9]. Reversion (the change to a negative TST following a previous positive result) is uncommon in healthy individuals, occurring in less than 10%[10]. The reversion rate is unknown in people with HIV.

In conclusion, both IGRA tests and TST had low sensitivity; positive rate at best using combination of the tests was only one third of those who had prior TB/TB exposure. IGRA and TST may not be reliable to detect LTBI or TB in children and adolescents with HIV even after immune reconstitution.

Conflict of interest statement

The authors declare they have no personal or professional conflicts of interest regarding any aspect of this study.

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Authors' contributions

KL, KC, and RD designed, performed study procedures and analyzed data. KL, RD, NK, and BK established the cohort including subject finding, invitation, and inform consent process. SS, MT, and PP performed IGRA tests. AM assisted with data analysis. All authors provided clinical care and contributed to manuscript writing.

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