Reply to Schepisi et al

To the Editor—On behalf of my coauthors, I thank Schepisi et al for their interest in our article. The design of the study, exclusion criteria, and main outcome measures in our study were similar to those in their study [1, 2]. Moreover, overall percentages of interferon γ (IFN-γ) release assay (IGRA) concordance were 86% and 89%, with reversion rates of 33% and 27%, respectively. Thus, our results are in accordance with those of Schepisi et al. Furthermore, this is supported by published data involving human immunodeficiency virus (HIV)–uninfected subjects [3]. Additionally, in a cohort of 769 Malaysian healthcare workers who were retested with the IGRA after 1 year, the reversion rate was even higher, at 46.7% [4]. Furthermore, the value of IGRA for serial testing of German health-care workers was limited by a substantial IGRA for serial testing of German health-care workers with QuantiFERON-TB Gold In-Tube screening for latent Mycobacterium tuberculosis infection among HIV-infection persons in a country with a low tuberculosis incidence. J Infect Dis 2015; 211:1852–3.


In terms of conversion rates, Schepisi et al reported lower rates than those in our study. Interestingly, Schepisi et al provide further insights on the influence of CD4 T-cell count variation on IGRA results. At follow-up, the average CD4 T-cell count increased by 206 cells/μL in the conversion group and by 200 cells/μL in the concordant group (from 337 to 537 cells/μL). In patients with a reverted IGRA result, in contrast, an average decrease of 17 cells/μL was found [1]. Schepisi et al conclude that reversions and conversions of IGRA results over time might be linked to the variation in patients’ immunological condition. Other potential sources for variability in immune responses include medications, stress, and infection. Alternatively, conversions may reflect immune reconstitution in individuals with unrevealed latent M. tuberculosis infection who had false-negative test results at enrollment.

Although Schepisi et al address variation in CD4+ T-cell counts, quantitative IGRA response changes over time should also be taken into account, especially when interpreting conversions and reversions. Recently, investigators at the Centers for Disease Control and Prevention noted the importance of evaluating the quantitative response in IGRA assays, considering the potential risk of overtreatment if non-specific increases in IFN-γ levels are misinterpreted as conversions [6]. Our current understanding is that there is nothing latent about latent M. tuberculosis infection. Tuberculosis is a dynamic condition; the IGRA response reflects this fact, and some variation in response is to be expected. Previous studies have suggested implementing a so-called gray zone of test results, to account for biological variability [7]. However, optimal thresholds to distinguish new infections from nonspecific variation are yet to be defined.

Thus, we agree with Schepisi et al that a large prospective, multicenter study is necessary to evaluate serial IGRA testing. Importantly, this needs to incorporate both immunological variations, as well as quantitative IGRA changes, over time.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References


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