Characteristics of Xpert MTB/RIF-Negative Patients With Pulmonary Tuberculosis

To the Editor—Lawn and colleagues [1] recently described the clinical characteristics of patients with pulmonary tuberculosis who tested negative by Xpert MTB/RIF but had radiographically less advanced tuberculosis and fewer adverse outcomes compared with those who tested positive, prior to commencing antiretroviral therapy in Cape Town, South Africa. In a primary care clinic based in the same city, and using archived samples from a prospectively recruited cohort, we demonstrated MTB/RIF-negative tuberculosis patients to have a significantly diminished sputum bacillary load compared with those who tested positive [2]. We also described the use of different tests, including chest radiography, when further investigating individuals who are MTB/RIF-negative [3].

Given the diminished performance of this test in patients who are infected with human immunodeficiency virus (HIV) (approximately 1 in 10 with a negative MTB/RIF result will have active tuberculosis [2, 4]), and the different patient population in our study, there are several issues that warrant further highlighting. These gain importance as MTB/RIF is rolled out.

Lawn and colleagues report MTB/RIF to possess superior sensitivity in HIV-infected patients with a low CD4 count, suggesting that these patients have a greater sputum bacillary load than those who are less immunosuppressed. This finding is contrary to the observed low frequency of pulmonary abnormalities in the former group; however, as suggested by the authors, such radiographic data do not always correlate well in patients with an attenuated immune response. A correlation of bacillary load (eg, measured using liquid culture time-to-positivity [TTP] or MTB/RIF-generated C_T values) with CD4 count would have been useful for supporting this conclusion; however, these data are absent and are required to clarify the findings presented. Furthermore, wide overlap exists in the comparison of MTB/RIF sensitivity stratified by CD4 count, and several of the groups appear to not differ significantly (or possess only borderline statistically significant differences).

Indeed, in our cohort of symptomatic tuberculosis patients who were HIV-infected, a trend in the opposite direction (MTB/RIF sensitivity diminishing with CD4 count) was observed, but this did not reach significance because of our small sample size [2]. However, sputum bacillary load was elevated in tuberculosis patients who were less immunosuppressed (median culture TTP [95% confidence interval] of 12 [6–18] in CD4 count ≥200 cells/µL vs 15 [14–21] in CD4 <200 cells/µL; P = .03).

Thus, our data imply that, contrary to what is suggested by Lawn and colleagues, MTB/RIF is more likely to miss HIV-infected individuals with advanced immunosuppression. As low CD4 count is strongly associated with higher mortality [5], one would expect MTB/RIF-negative patients to have a higher likelihood of adverse outcomes relative to those who test positive; however, given the small sample sizes of both studies, the conflicting findings, the impact of declining CD4 count on sputum-based MTB/RIF still remains unclear. Importantly, findings from both studies need to be considered preliminary and context-specific, and further work, especially focusing on the outcome-related impact of extrapulmonary or disseminated tuberculosis in patients who have paucibacillary sputum, is required to clarify them.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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