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Editorial



# It's Time for Latent Tuberculosis Infection Screening in HIV-infected Individuals

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▸ See the article "Good Agreement between an Interferon Gamma Release Assay and Tuberculin Skin Tests in Testing for Latent Tuberculosis Infection among HIV-Infected Patients in Indonesia" in volume 34, number 40, e259.



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*Mycobacterium tuberculosis* (*M.TB*) infection in human immunodeficiency virus (HIV)-infected patients is one of the major opportunistic diseases, leading to severe morbidity and mortality. According to World Health Organization (WHO) tuberculosis (TB) reports,[1] the number of patients with TB-HIV coinfection was 900,000 and the number of deaths was 300,000 in 2017. Comparing to the mortality rate of 16% due to TB in the general population, the percentage of deaths in TB-HIV patients was double at 33%. However, it is not easy to manage TB in immunocompromised hosts due to variable reasons: 1) vague symptoms related with TB, 2) low yields for microbiologic tests, 3) nontypical radiologic findings, 4) drug-drug interaction between anti-TB and anti-retroviral therapy (ART), 5) immune reconstitution inflammatory syndrome during the treatment, most of which are hurdles related with diagnosis. Therefore, the best strategy is to confirm and treat latent TB infection (LTBI), an early stage of TB infection that is characterized by a status of persistent immunity to *M.TB* antigen without manifestations of active disease, in HIV patients. Recently, WHO guidelines for LTBI[2] also recommend that for adults living with HIV, LTBI should be treated in cases with unknown or a positive tuberculin skin test (TST) and without the evidence of active TB, irrespective of regional TB prevalence, the degree of immunosuppression, and use of ART.

There is no gold standard to diagnose LTBI. Immune response-based tests such as TST and interferon-gamma release assay (IGRA) are widely used. However, both of them have a limited diagnostic performance and a low predictive value to active TB, especially in immunocompromised hosts such as individuals living with HIV. Data comparing TST and IGRA in detecting LTBI in the immunocompromised have shown inconclusive results.[3,4] In this issue, Dr. Reviono et al.[5] conducted the comparison of TST and T-SPOT.TB, one of the IGRAs, to diagnose LTBI among HIV-infected patients. They reported that detection rates for LTBI by TST and T-SPOT.TB were 19% and 18% of the 112 participants, respectively, in a high-TB incidence country, showing good agreement between the tests. This finding provides the evidence that TST is preferable to IGRA in diagnosing LTBI in adults living with HIV. It could be good news to policy managers, clinicians, and HIV infected patients, especially living in resources-limited settings. In fact, whereas IGRA is more specific due to no cross-reactivity to other species than *M.TB* and more convenient due to requiring only one-visit, unlike TST, the former has more technical difficulty and economic burden than the latter. However,

considering that there have been a few studies reporting results that conflict with the above findings and this research was a cross-sectional study, which could not follow-up the patients for developing active TB, a surrogate marker of LTBI, further accumulating evidence is needed to make a concrete conclusion about this topic. In this context, WHO recommends the two tests as equivalent options and furthermore that LTBI testing by TST or IGRA is not a requirement for initiating preventative treatment in people living with HIV, based on the fact of imperfect performance of the two tests, leading to false negative results in those immunocompromised hosts.[2]

In this article,[5] they also provided other clinically valuable messages. First, while 98% of enrolled subjects had Bacillus of Calmette and Guérin (BCG) scar, high agreement to diagnose LTBI between TST and T-SPOT.TB proved that BCG vaccination did not affect the TST results. This is contrary to existing belief that BCG immunization could have an influence on the TST result, however, a recent meta-analysis[6] also reported that BCG vaccination in early infancy, commonly underwent in high-TB incidence countries, did not have an effect on TST result later in life. This finding can make clinicians more confident with TST results even in BCG immunized subjects and consequently mean that BCG vaccination is not a decisive factor in choosing a test for LTBI. Second, in the subjects with severe immunocompromised state, with a CD4+ level < 200 cells/mm$^3$, T-SPOT.TB showed a higher detection rate of LTBI than TST, consistent with the results in most of previous studies.[7] Therefore, under severe immunodeficiency in HIV infected individuals, a more thoughtful approach with cautious interpretation of the tests is needed to diagnose LTBI.

HIV infected patients with LTBI have a 5%–10% annual risk of developing active TB, whereas immunocompetent persons have 10% risk of it during their whole life. Early detection and treatment of LTBI in the immunocompromised can reduce the development of active TB by 62% and the related mortality by 26%.[8] However, in real practice, the rate of LTBI screening in HIV infected individuals is relatively low. Prevention is more effective than treatment. Now is the time to do a screening of LTBI in HIV-infected persons.

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