A summary of the proceedings of a meeting on the treatment of latent tuberculosis infection in target populations in Brazil

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TO THE EDITOR:

An overview of the diagnosis and treatment of latent tuberculosis infection (LTBI) was provided during a meeting of tuberculosis experts in the city of Rio de Janeiro, Brazil, on July 18, 2018. The experts discussed the tools for LTBI diagnosis and the evolving policies on the preferred method of testing, either interferon-gamma release assay (IGRA) or the tuberculin skin test (TST), the latter being the standard method for LTBI diagnosis in Brazil. Current Brazilian guidelines recommend treatment of all contacts of pulmonary tuberculosis cases in whom LTBI is detected on the basis of a positive TST or IGRA, regardless of age, after active tuberculosis has been ruled out.[1] Although IGRAs are commercially available in Brazil, they have not been incorporated into the *Sistema Nacional de Saúde* (SUS, Brazilian Unified Health Care System).

In 2015 and 2018, the World Health Organization (WHO) issued policies on the management of LTBI that moved from disallowing the use of IGRAs for LTBI diagnosis in low- and medium-income countries to stating that IGRAs are interchangeable with TST for the diagnosis of LTBI.[2]

Tuberculin proteins overlap with proteins present in the BCG vaccine, resulting in TST having poor specificity, estimated at 59% among BCG-vaccinated persons.[3] QuantiFERON-TB Gold Plus (QFT-Plus), a 4th generation IGRA, has an additional CD8+ T cell tube, manufacturing improvements, and flexible blood draw options. Recent data show improved sensitivity of QFT-Plus in active culture-proven tuberculosis when compared with the prior version, known as the QuantiFERON-TB Gold-in-Tube assay.[4] Studies have demonstrated a correlation of CD8 responses with active tuberculosis and recent exposure to the pathogen.[4]

In the meeting of tuberculosis experts, the pros and cons of the use of IGRAs were discussed. The advantages of QFT assays over TST include higher specificity, which reduces the number of people misdiagnosed with LTBI and consequently the number needed to treat. In addition, IGRAs do not require a second patient visit to obtain results. Furthermore, unlike TST, QFT assays do not induce immune boosting if an individual is retested. Moreover, the QFT result is objective and is unaffected by previous BCG vaccination. Finally, quality control of test results is more easily achieved with the QFT assays.[3] However, the drawback of IGRAs is their higher price, lower cost-effectiveness in Brazil compared with TST,[5] and the need for a laboratory network to run tests for the public sector.

Despite the advantages provided by QFT assays, there was consensus among the meeting participants that QFT assays and TST are both fairly good tests for LTBI detection, despite their limitations. Although TST specificity is lower in BCG vaccinated-populations,[6] especially among individuals who are revaccinated after the first year of life, BCG vaccination may have a less pronounced impact in Brazil, because since nearly all children in the country are vaccinated only once, in the first month of life. Therefore, a positive TST (or IGRA) in a contact of a patient with pulmonary tuberculosis or in people living with HIV/AIDS (PLWHA) should be considered LTBI with high confidence and should be treated as such, when applicable. The superior predictive value of IGRAs is controversial, meta-analyses having presented conflicting findings. In children, TST have also been useful for diagnosing active tuberculosis as part of a scoring system. Above all, the benefit derived from treating LTBI in PLWHA, based on a positive TST, has been demonstrated in a number of trials.[7] However, there are few data regarding the use of IGRAs for selecting patients that will benefit from LTBI treatment.

The WHO recommends that treatment for LTBI be offered to individuals in some high-risk groups, such as children under 5 years of age and PLWHA, without testing or regardless of a test result, in order to avoid missing opportunities.[2] The main health care system hurdles, policy barriers, and challenges for the wider use of LTBI treatment include the lack of robust recommendations, the shortage of diagnostic tests/drugs, the need for

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a more robust surveillance/reporting system, and insufficient funding.

At the meeting, data on tuberculosis/HIV coinfection were presented by a representative from the Brazilian National Ministry of Health, who pointed out that tuberculosis continues to be the leading cause of death from an infectious agent among PLWHA in Brazil. Of the approximately 70,000 new tuberculosis cases reported annually, approximately 9.5% occur in PLWHA. Despite the increase in the proportion of new tuberculosis cases tested for HIV infection in recent years (76.3% in 2016), comprehensive HIV testing is still a challenge. Brazilian guidelines, published in June of 2018,[1] recommend that all HIV patients with a CD4+ cell count < 350 cells/mm^3 be treated for LTBI, assuming that active tuberculosis has been excluded, without the need for a TST or IGRA.

Prison inmates are plausible candidates for tuberculosis screening because they are "institutional amplifiers" of tuberculosis. Genotypic evidence supports transmission linkage between tuberculosis cases in prisons and the general population.[8]

The following is a summary of the main points discussed at the meeting of tuberculosis experts in Rio de Janeiro:

1. A network of the close contacts of each pulmonary tuberculosis case should be registered so that the contacts can be screened and treated for LTBI.

2. Each health care facility should use local data to identify risk groups to target and to create a cascade of LTBI diagnosis and treatment.

3. All new policy initiatives and variables for each step of the LTBI diagnosis and treatment cascade should be monitored in order to evaluate program performance and progress.

4. The results of tests, including TST, and chest X-ray findings should not be allowed to create a barrier to access to preventive therapy for the most vulnerable populations, such as PLWHA and children under 5 years of age.

5. The CD4+ cell count should not be allowed to create a barrier to access to LTBI treatment for PLWHA.

6. The QFT assays could play an important role in the event of continued shortages of TST, as an alternative to TST in some settings, and for target populations, such as PLWHA. There is a need for a laboratory network to promote future incorporation of QFT assays into the routine at public health care facilities and an update of the cost-effectiveness analyses, as well as for economic analyses in other target populations.

7. Children will benefit from shorter course rifampin regimens for LTBI. A 4-month course of rifampin is safer than is treatment with isoniazid alone or with any other regimen[9,10] and has been included as an option in Brazilian national guidelines.

8. Providing inmates with treatment for LTBI at the time of their release from prison could be a priority innovation approach to reduce the impact of tuberculosis transmission in the community.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Programa Nacional de Controle da Tuberculose. Manual de Recomendações para o Controle da Tuberculose no Brasil. 2nd ed. Brasília: Ministério da Saúde; 2018.

2. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018. PMID: 30277688

3. Trajman A, Steffen RE, Menzies D. Interferon-Gamma Release Assays versus Tuberculin Skin Testing for the Diagnosis of Latent Tuberculosis Infection: An Overview of the Evidence. Pulm Med. 2013;2013:601737. https://doi.org/10.1155/2013/601737

4. Sotgiu G, Saderi L, Petruccioli E, Aliberti S, Piana A, Petrone L, et al. QuantiFERON TB Gold Plus for the diagnosis of tuberculosis: a systematic review and meta-analysis. J Infect. 2019;79(5):444-453. https://doi.org/10.1016/j.jinf.2019.08.018

5. Steffen RE, Caetano R, Pinto M, Chaves D, Ferrari R, Bastos M, et al. Cost-effectiveness of Quantiferon®-TB Gold-in-Tube versus tuberculin skin testing for contact screening and treatment of latent tuberculosis infection in Brazil. PLoS One. 2013;8(4):e59546.https://doi.org/10.1371/journal.pone.0059546

6. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. PLoS Med. 2011;8(3):e1001012. https://doi.org/10.1371/journal.pmed.1001012

7. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010;2010(1):CD000171. https://doi.org/10.1002/14651858.CD000171.pub3

8. Mabud TS, de Lourdes Delgado Alves M, Ko AI, Basu S, Walter KS, Cohen T, et al. Evaluating strategies for control of tuberculosis in prisons and prevention of spillover into communities: An observational and modeling study from Brazil [published correction appears in PLoS Med. 2019 Mar 1;16(3):e1002764]. PLoS Med. 2019;16(1):e1002737. https://doi.org/10.1371/journal.pmed.1002737

9. Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, Obeng Baah J, et al. Safety and Side Effects of Rifampin versus Isoniazid in Children. N Engl J Med. 2018;379(5):454-463. https://doi.org/10.1056/NEJMoa1714284

10. Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. Ann Intern Med. 2014;161(6):419-428. https://doi.org/10.7326/M14-1019