

## Perspective

# New and Noteworthy in Tuberculosis Diagnostics and Treatment

*People with HIV infection with latent tuberculosis (TB) infection (LTBI) are at a 10-fold greater risk of developing active disease. Interferon gamma release assays and tuberculin skin testing have approximately 65% to 70% specificity for diagnosing LTBI in HIV-infected patients. LTBI can be successfully treated with isoniazid preventive therapy and early antiretroviral therapy (ART). Rapid molecular diagnostics have approximately 88% sensitivity and 98% specificity for identifying active TB. ART should be started early in patients with TB. A number of ART regimens are recommended in co-treatment that minimize the risk of drug-drug interactions. Although progress has been made, better diagnostics and TB regimens with lower risks of drug-drug interactions and shorter treatment durations are still needed. This article summarizes a presentation by Susan Swindells, MBBS, at the Ryan White HIV/AIDS Program Clinical Care Conference held in San Antonio in August 2017.*

**Keywords:** HIV, TB, diagnosis, treatment, drug-drug interactions

Tuberculosis (TB) remains a major global health problem (Figure 1).<sup>1,2</sup> It is estimated that 23% of the world's population is infected with TB. World Health Organization (WHO) data for 2016 indicate approximately 10 million new cases of active TB disease, with 10% occurring in individuals with HIV infection, and 1.7 million deaths (>1000 deaths per day), with 400,000 occurring in HIV-infected persons.

### Latent Tuberculosis Infection Testing

Consider the case of a 34-year-old man who emigrated from Mexico to the United States 6 years ago and is establishing care. He was diagnosed with HIV infection 6 months ago when he was hospitalized with community acquired pneumonia and was started on tenofovir alafenamide (TAF), emtricitabine, elvitegravir, and cobicistat. His CD4+ cell count has increased to 120/ $\mu$ L and his plasma HIV-1 RNA level is undetectable. It is decided to test the patient for TB using an interferon gamma release assay (IGRA); the result comes back "indeterminate." Given the low CD4+ cell count, the best strategy in this case is to wait until there is additional increase in CD4+ count to above 200 cells/ $\mu$ L before repeating the test.

Risk of progression from latent tuberculosis infection (LTBI) to disease is 10-fold greater in persons with HIV infection than in persons with LTBI and no HIV infection. The Centers

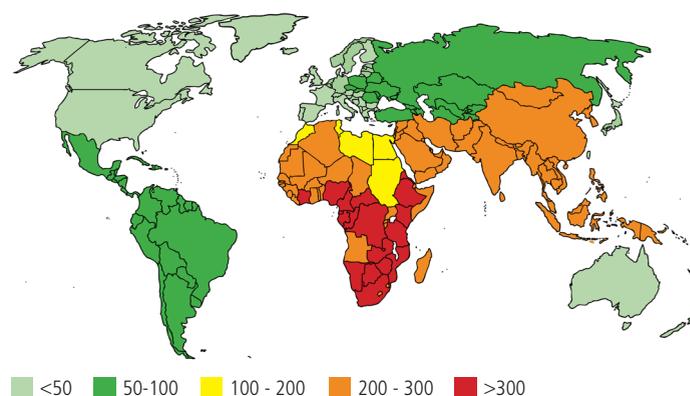
for Disease Control and Prevention (CDC) recommends testing for TB after HIV diagnosis and then annually if testing is negative or if there is exposure risk. If a patient has negative testing for TB infection before the initiation of antiretroviral therapy (ART), testing should be repeated after the initiation of ART. There is no direct diagnostic test for LTBI, but this is presumed from a positive tuberculin skin testing (TST) or IGRA. Neither test predicts risk of progression to active TB. There is no benefit to repeating either test once a positive result is obtained. LTBI testing should not be used to diagnose active TB.

TST and IGRA each have approximately 65% to 70% sensitivity for diagnosing LTBI in patients with HIV infection. The TST requires 2 visits, has the same interpretation regardless of whether the patient has had Bacillus Calmette-Guérin (BCG) vaccine, and the actual test is less expensive than IGRA. It also requires training to administer and interpret. IGRA testing requires a single visit, is also unaffected by prior BCG vaccination, and requires that the blood sample be processed within 8 to 30 hours. Results can be positive, negative, or indeterminate, with an indeterminate result being more common with immunosuppression (eg, CD4+ cell count <200/ $\mu$ L). Restoration of CD4 cell number and function with ART improves performance of the test. There are limited data on its use in young children or those with recent exposure.

### Treatment of LTBI

With regard to the patient case, after 6 months of ART, his CD4+ cell count is 300/ $\mu$ L. The repeat IGRA is positive; the patient has no signs or symptoms of active TB and has a normal chest x-ray. How should the patient be treated for LTBI?

The CDC recommendations for treatment of LTBI in HIV consist of isoniazid (INH) daily or twice weekly for 9 months, INH plus rifampine weekly for 12 weeks, or rifampin (or



**Figure 1.** Cases of tuberculosis per 100,000 people.<sup>1,20</sup>

Dr Swindells is Professor of Internal Medicine and the Medical Director of the HIV Clinic at the University of Nebraska Medical Center.

rifabutin) daily for 4 months. A recent study of 1 month of daily INH with rifapentine in 3000 people with HIV infection was noninferior to 9 months of INH, had fewer adverse events, and was more likely to be completed. This ultra-short course TB preventive therapy could be an important new tool to control HIV-related TB.<sup>3</sup> Patients should be monitored monthly for hepatitis and other adverse effects.

Since rifamycins are potent inducers of metabolizing enzymes, the 2 rifamycin-based regimens pose problems with potential drug-drug interactions in patients on ART and other medications. General guidelines are that any ART regimen can be used when INH alone is used for LTBI treatment. However, only efavirenz (EFV) or raltegravir based regimens can be used with once-weekly INH plus rifapentine, and TAF is contraindicated. The potential for drug-drug interactions with rifamycins needs to be carefully assessed. EFV or double-dose dolutegravir can be used with rifampin. A protease inhibitor (PI) can be used with rifabutin at 150 mg daily or 300 mg 3 times a week. Further detailed information can be found at the following sites:

- <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>.
- <http://www.hiv-druginteractions.org>.

Treatment for LTBI in patients with HIV infection is effective. A 2006 meta-analysis of 11 randomized trials including 8130 participants with HIV infection showed that INH preventive therapy (IPT) was associated with a 36% reduction in risk for active disease, with a 62% reduction observed among those with a positive TST.<sup>4</sup> Other data indicate a preventive benefit with early initiation of ART. In the Temprano trial in Côte d'Ivoire, 2056 patients with CD4+ cell counts below 800/ $\mu$ L were randomly assigned to immediate or deferred ART with or without IPT.<sup>5</sup> The 30-month probability of death or severe HIV-related illness was 14.1% in the deferred ART group, 8.8% in the deferred ART plus IPT group, 7.4% in the early ART group, and 5.7% in the early ART plus IPT group. TB accounted for 43% of the end points. Early ART and IPT were independently associated with reduced risk of TB.

## Diagnosis of Active TB

In a second patient case, a 54-year-old woman is admitted to the hospital with cough, fever, and weight loss. She is diagnosed with HIV infection on admission, with a CD4+ count of 70 cells/ $\mu$ L and plasma HIV-1 RNA count of 120,000 copies/mL. Chest x-ray shows pleural thickening and diffuse infiltrate; sputum acid-fast bacillus testing is negative, as is bronchoscopy for *Pneumocystis jirovecii*.

Light microscopy was the staple of TB diagnostics for 2 centuries, and still is in many parts of the world. We now have rapid molecular diagnostics that perform better and are much simpler. The first to become available was the Xpert MTB/RIF assay. With this assay, patient sputum is put into a small cartridge, inserted into the machine, and 'yes/no' results are available in 2 hours for TB, and if positive, for rifampin resistance. The assay is more sensitive than smear

testing, works in children and extrapulmonary TB, and permits screening for drug-resistant TB.<sup>6</sup>

A recent study by the AIDS Clinical Trials Group on 992 participants from numerous US sites and sites in South Africa and Brazil, including 45% with HIV infection (median CD4+ cell count, 151/ $\mu$ L), assessed the Xpert MTB/RIF assay for identifying pulmonary TB.<sup>7</sup> The overall sensitivity of the assay in US participants was 85.2%, including sensitivity of 96.7% in smear-positive/culture-positive cases and 59.3% in smear-negative/culture-positive cases. Overall specificity for 2 tests was 98.9%, including 100% in smear-positive/culture-positive cases and 98.9% in smear-negative/culture-positive cases. It is noteworthy that the very high specificity of the assay provides enough confidence in negative results that hospitalized patients with negative results can be removed from respiratory isolation.

## ART and TB Treatment

The patient in the current case is diagnosed with TB on the Xpert MTB/RIF assay, with culture results pending. She is started on treatment with the standard 4-drug regimen of INH, rifampin, ethambutol, and pyrazinamide. When should ART be started?

ART should be started early. The rationale is based on findings of the large-scale CAMELIA (Cambodia),<sup>8</sup> SAPIT (South Africa),<sup>9</sup> and STRIDE (international) trials,<sup>10</sup> which examined immediate TB therapy with ART started at 2 weeks or started at 8 weeks. The CAMELIA trial showed a 34% reduction in all-cause mortality ( $P = .004$ ) for immediate vs delayed ART; the STRIDE study showed a 19% reduction in risk for AIDS or death with immediate vs delayed ART ( $P = .45$ ); and the SAPIT trial showed an 11% reduction in risk for AIDS or death with immediate vs delayed ART ( $P = .73$ ). The benefit of earlier ART was most pronounced in patients with lower CD4+ cell counts. Earlier ART was also associated with some increase in risk for immune reconstitution inflammatory syndrome (IRIS).

Currently, WHO,<sup>11</sup> American Thoracic Society,<sup>12</sup> IAS-USA,<sup>13</sup> and US Department of Health and Human Services<sup>14</sup> guidelines all recommend initiation of ART within 2 weeks for those with CD4+ cell counts less than 50/ $\mu$ L and within 8 weeks for those with CD4+ cell counts greater than 50/ $\mu$ L. An exception is when TB meningitis is present, given the findings in a randomized trial showing increased adverse events and deaths with early ART.<sup>15</sup>

HIV/TB co-treatment options for adults are shown in Table 1. The most clinical experience is with EFV plus 2 nucleoside reverse transcriptase inhibitors (RTIs) if rifampin is being used and a ritonavir-boosted PI plus 2 RTIs if rifabutin is being used. Alternative regimens consist of raltegravir or dolutegravir plus 2 RTIs with rifampin.

Currently, TAF use is contraindicated with rifamycins. Tenofovir disoproxil fumarate (TDF) has been studied with rifampin without substantial drug-drug interactions being observed. However, based on modeling data, carbamazepine reduced TAF exposure by 55% and TAF is known to be more

**Table 1.** Recommendations for drug dose adjustments for HIV/tuberculosis cotreatment

ARV <sup>a</sup>	Rifamycin	Dose Adjustment	Comments
Efavirenz	Rifampin	None	
Lopinavir/ritonavir or Darunavir/ritonavir	Rifabutin	Rifabutin 150 mg once daily	Monitor for uveitis
Raltegravir	Rifampin	Raltegravir 800 mg twice daily	Limited clinical experience Do not administer raltegravir 1200 mg once daily with rifampin
Dolutegravir	Rifampin	Dolutegravir 50 mg twice daily	Limited clinical experience

<sup>a</sup>All ARV to be given with 2 reverse transcriptase inhibitors but not with tenofovir alafenamide.

highly affected by P-glycoprotein induction than TDF. Interaction studies of TAF with rifamycins in humans are ongoing.

Rifabutin is often used for TB treatment in the US, because the drug has fewer interactions and can be used with boosted PIs in individuals with HIV infection. However, a Cochrane review found that there are “insufficient data to be assured of the effectiveness of rifabutin in TB treatment”.<sup>16</sup> Furthermore, clinical trials comparing rifabutin with rifampin largely have been conducted among patients not on ART. In addition, the correct dose is uncertain; most pharmacokinetics studies have been done in uninfected volunteers, and there are data to suggest that 300 mg 3 times a week is insufficient in patients with HIV infection. The agent poses risk of uveitis, is expensive, and has no pediatric formulation.

With regard to ART, the prescribing information for single-agent EFV, but not co-formulated products including EFV, states that if the drug is co-administered with rifampin to patients weighing 50 kg or more, an increase in the dose of EFV to 800 mg once daily is recommended. In the author’s opinion, this recommendation is wrong, having been based on studies in non-infected volunteers. Co-administration in patients who have HIV and TB paradoxically results in increased rather than decreased EFV exposure.<sup>17</sup> Thus, in co-treatment, the EFV dose does not need to be increased.

With regard to the patient case, she starts ART at 2 weeks, and 10 days later has recurrent fever, followed by worsening dyspnea and cough. A chest x-ray shows progression of pulmonary infiltrates. IRIS is suspected.

IRIS is more common with early ART in those with low CD4+ cell counts. It is rarely severe or fatal, and the possibility of its occurrence should not delay start of ART. Management includes making certain of the diagnosis, ruling out drug-resistant TB or a new opportunistic infection, and then surgical drainage, use of nonsteroidal antiinflammatory drugs (although the quality of evidence of benefit is low), and use of prednisone. A prednisone regimen of 1.5 mg/kg per day for 2 weeks and then 0.75 mg/kg per day for 2 weeks reduced the risk of adverse events in a randomized trial in hospitalized patients.<sup>18</sup> However, more data to support this approach are

lacking. A study evaluating prophylactic prednisone (40 mg/day for 2 weeks followed by 20 mg/day for 2 weeks) has shown some promise in high risk patients.<sup>19</sup>

## Conclusion

TB disease can be prevented by treating HIV and by treating LTBI. There have been major improvements in TB diagnostics, however, there are not enough new drugs in the pipeline. New options include bedaquiline, which is approved for use in the US, and delamanid, which will soon be approved; each is active against drug-resistant TB. Although drug-drug interactions complicate HIV and TB co-treatment, TB and HIV should be treated concurrently, and safe and effective regimens are available. More research investment and advocacy are needed to help us reach the goals of better TB regimens with lower risk of drug-drug interactions and shorter treatment durations, and better treatments for infected children. 

*Presented by Dr Swindells in August 2017. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Swindells in May 2018.*

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## References

- Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med.* 2016;13(10):e1002152.
- World Health Organization. Global Tuberculosis Report 2017. [http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/). Accessed on February 13, 2018.
- Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine/isoniazid to prevent TB in people with HIV: BRIEF-TB/A5279 [CROI Abstract 37LB] In Special Issue: Abstracts From the 2018 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med.* 2018;26(suppl 1):1-483.
- Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev.* 2004;(1): CD000171.
- Badje A, Moh R, Gabillard D, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *Lancet Glob Health.* 2017;5(11):e1080-e1089.
- Lawn SD, Mwaba P, Bates M, et al. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. *Lancet Infect Dis.* 2013;13(4):349-361.
- Luetkemeyer AF, Firnhaber C, Kendall MA, et al. Evaluation of Xpert MTB/RIF Versus AFB Smear and Culture to Identify Pulmonary Tuberculosis in Patients With Suspected Tuberculosis From Low and Higher Prevalence Settings. *Clin Infect Dis.* 2016;62(9):1081-1088.
- Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med.* 2011;365(16):1471-1481.
- Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med.* 2011;365(16):1492-1501.

10. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365(16):1482-1491.
11. World Health Organization. Universal antiretroviral therapy (ART) for all HIV-infected TB patients. [http://www.who.int/hiv/topics/tb/art\\_hivpatients/en/](http://www.who.int/hiv/topics/tb/art_hivpatients/en/). Accessed on February 13, 2018.
12. Nahid P, Dorman SE, Alipanah N, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis*. 2016;63(7):853-867.
13. Günthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA panel. *JAMA*. 2016;316(2):191-210.
14. US Department of Health and Human Services. AIDS info Website. Updated website for AIDS treatment guidelines, including guidelines for adults, women, pregnant women, and children. <http://www.aidsinfo.nih.gov>. Accessed on January 31, 2018.
15. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin Infect Dis*. 2011;52(11):1374-1383.
16. Davies G, Cerri S, Richeldi L. Rifabutin for treating pulmonary tuberculosis. *Cochrane Database Syst Rev*. 2007;(4):CD005159.
17. Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis*. 2013; 57(4):586-593.
18. Meintjes G, Wilkinson R, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. 2010; 24:2381-2390.
19. Mientjes G, Stek C, Blumenthal LTF, et al. Randomized Controlled Trial of Prednisone for Prevention of Paradoxical TB-IRIS. CROI. 2-16-2018; Seattle, Washington, USA.
20. World Health Organization (WHO). Global tuberculosis report. [http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf). Accessed on May 18, 2017.

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