Think tuberculosis—but is thinking enough?

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In *The Lancet Infectious Diseases*, David Barr and colleagues[1] report on *Mycobacterium tuberculosis* bloodstream infection (BSI) in seriously ill HIV-infected adults. In a systematic review and meta-analysis of individual patient data from 20 published and three unpublished studies and datasets, Barr and colleagues found a higher prevalence of *M tuberculosis*-positive blood cultures in critically ill HIV-infected patients with tuberculosis than previously reported in a review in a less selected population[2] (45% *vs* 15·5%) and a higher risk of mortality within 30 days in those with *M tuberculosis* BSI than in those without (adjusted hazard ratio 2·48, 95% CI 2·05–3·08). Furthermore, they found that delaying tuberculosis treatment for more than 4 days in critically ill patients with *M tuberculosis* BSI was associated with increased early mortality compared with no delay (odds ratio 3·2, 95% CI 1·2–8·8).

The conclusions of the study seem straightforward: as with any bacterial BSI we should not delay antimicrobial treatment for HIV-infected patients with *M tuberculosis* BSI. However, how do we identify these patients? Even in settings where blood cultures for tuberculosis can be done, the results will only be available after more than 10 days, too late to define early treatment strategies based on microbiology results. A tuberculosis-positive blood culture is a marker of disseminated tuberculosis but by no means a perfect one. As with bacterial blood cultures, the likelihood of finding positive results depends on the amount of blood that is cultured, and with one or even two negative cultures we cannot exclude disseminated tuberculosis.[3] Disseminated tuberculosis is associated with HIV-induced immunosuppression, especially in patients on antiretroviral therapy and with low CD4 cell counts.[4] Although tuberculosis usually progresses slowly because of the long generation time of the bacterium, disseminated tuberculosis might also present rapidly, akin to sepsis (so-called Landouzy sepsis, named after the French physician Louis Théophile Josef Landouzy, 1845–1917). This manifestation is more often encountered in regions with high HIV and tuberculosis prevalence. Since HIV-infected patients with disseminated tuberculosis rarely have cavitary lung disease with high mycobacterial load in sputum, rapid sputum-based diagnostic tests, such as microscopy or PCR-based Xpert MTB/RIF, might be negative, as was the case for 28% of the patients with *M tuberculosis* BSI in the analysis (appendix p 14). By contrast, tests for urinary lipoarabinomannan (LAM) are more likely to be positive in disseminated tuberculosis than in pulmonary tuberculosis, and the diagnostic yield of urine LAM for patients with *M tuberculosis* BSI in the study was 52% (95% CI 35–69). The authors estimate that the combined diagnostic yield of rapid sputum diagnostics and urinary LAM for prediction of *M tuberculosis* BSI is 82% (71–90%; appendix p 14). Therefore, in about one in six (100/18) patients with tuberculosis BSI we would have no positive rapid laboratory test pointing towards tuberculosis.

Coming back to the clinical situation, we are confronted with a seriously ill HIV-infected patient with danger signs, such as increased respiration rate, high temperature, elevated heart rate, or inability to walk. According to WHO guidance,[5] we would start with empirical antibacterial therapy and look for tuberculosis by Xpert MTB/RIF. If Xpert is negative and the patient shows no clinical improvement after 3–5 days of parenteral antibiotics, WHO recommends starting tuberculosis therapy. However, taking the data from Barr and colleagues' study[1] into account, is delaying tuberculosis treatment the right thing to do?

In patients at risk of disseminated tuberculosis with danger signs, we would, on the basis of Barr and colleagues' findings, add a urinary LAM test to Xpert and start tuberculosis treatment if one of these tests is positive. However, even with these two rapid tests we would probably miss about 18% of patients with disseminated tuberculosis and put them at higher mortality risk if we defer tuberculosis treatment for 4 days or more. Does that mean we should treat every patient with anti-tuberculosis therapy, in addition to empirical antibiotics, irrespective of tuberculosis test results, from the beginning?

This decision depends on the prevalence of tuberculosis in the population we care for. If the risk of tuberculosis is near to zero (eg, in regions with low tuberculosis prevalence), the negative aspects of treating all patients for tuberculosis, including costs, side-effects, and drug interactions, outweigh

the potential benefits. However, in settings where tuberculosis prevalence is high (eg, in sub-Saharan Africa and south and southeast Asia), not delaying tuberculosis treatment might be recommended even in patients with negative rapid tuberculosis test results.

Although such an approach is feasible in regions with low prevalence of multidrug-resistant (MDR) tuberculosis, how would we start tuberculosis treatment in settings where prevalence of MDR tuberculosis is high. In case of a positive Xpert MTB/RIF, we have decision guidelines[6] to start tuberculosis treatment according to the result of the rifampicin test. But what would we do in the case of positive urinary LAM or negative rapid tests but a high pre-test likelihood of tuberculosis? Would we start an MDR tuberculosis treatment regimen with even more side-effects and costs, or would we start conventional tuberculosis treatment? Finally, should we give a full course of tuberculosis treatment to all critically ill patients in settings of high tuberculosis prevalence with negative rapid tuberculosis tests, thus confirming a diagnosis of tuberculosis if the patient's health improves in a few days?

These questions must be answered before we can design algorithms for diagnosis and treatment of suspected *M tuberculosis* BSI for integration into public health strategies. Therefore, let us think, discuss, and design implementation trials for the sake of our patients' survival.

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3 Barr DA, Kerkhoff AD, Schutz C, et al. HIV-associated *Mycobacterium tuberculosis* bloodstream infection is underdiagnosed by single blood culture. *J Clin Microbiol* 2018; **56:** e01914–17.

4 Havlir DV, Barnes PF. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med* 1999; **340:** 367–73.

5 WHO. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents. Recommendations for HIV-prevalent and resource-constrained settings. Geneva: World Health Organization, 2006.

6 WHO. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization, 2019.