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EDITORIAL

Management of tuberculosis in HIV infection: where T-cells matter

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Even 127 years after Robert Koch's identification of *Mycobacterium tuberculosis* as the causative agent of tuberculosis (TB), the diagnosis of active disease still depends in many parts of the world on the same tools that Koch has used: specifically staining of the bacilli and visual observation by microscopy [1]. Thirty years later, von Pirquet developed the tuberculin skin-test (TST), which, instead of observing the pathogenic microbe itself, measures the immunological response to it [2]. We now know that the specific induration in the skin-test is mediated by specifically activated T-lymphocytes that elicit a delayed-type hypersensitivity (DTH) response *via* production of a variety of inflammatory cytokines. While both test systems are still widely used, their sensitivity is highly variable and ranges from 20 to 60% for microscopy [3, 4], and 67 to 80% for skin-testing [5, 6]. In patients with HIV infection and other forms of immunosuppression, the sensitivity is even worse and far beyond being adequate for a modern diagnostic test [7, 8].

In their recent manuscript, LEIDL *et al.* [9] now compare the performance accuracy of the skin-test for diagnosing latent *M. tuberculosis* infection with two commercially available *in vitro* assays that measure interferon (IFN)-γ production of T-cells after stimulation with *M. tuberculosis*-specific antigens. Their patient cohort comprised 128 HIV-infected individuals, of which 19 presented with active TB. The patients showed a varying degree of immunosuppression as evidenced by their absolute number of cluster of differentiation (CD)4-positive helper T-cells. Although all three assays rely on cytokine production predominantly from CD4 T-cells [10], the skin-test, the ELISA-based QuantiFERON TB gold in-tube assay (QFT-G-IT), and the ELISPOT-based T.SPOT.*TB* assay showed variable performance that mainly depended on the CD4 T-cell counts. With T-cells over 250 per μL and in healthy controls, the QFT-G-IT and the TST were superior, although they exhibited decreasing performance upon increasing immunodeficiency. In contrast, the results of the ELISPOT-based T.SPOT.*TB* assay were independent of CD4 T-cell counts and performed markedly better in HIV patients with <100 CD4 T-cells per μL. Based on previous publications [11–14] and the principles of the two *in vitro* assays [10, 15], this result is not entirely unexpected. In the QFT-G-IT assay, IFN-γ is secreted into the supernatant, and the amount of cytokines is a rough correlate of the number of T-cells that were specifically activated by the *M. tuberculosis* antigen. In contrast, in the ELISPOT assay, a defined number of isolated peripheral blood mononuclear cells (PBMC) is used and the percentage of reactive cells is expressed as spot-forming cells per 250,000 PBMC. Thus, by this normalisation to a defined number of PBMC, the cell loss due to progressive disease is at least partially compensated for. However, this clearly has a limit when the amount of *M. tuberculosis*-specific CD4 T-cells comes near to the detection limit of the ELISPOT assay. According to KARAM *et al.* [14], this seems to be the case below approximately 50 CD4 T-cells per μL blood.

Other studies have already assessed the sensitivity of both *in vitro M. tuberculosis* tests with the skin-test in a head-to-head manner in HIV-infected individuals [11–13]. However, those studies were mainly restricted to patients with moderately advanced HIV infection, that had relatively little impact on test sensitivity [11], were performed in a low prevalence country [12], or compared test sensitivities between children and adults [13]. The strength of the present study by LEIDL *et al.* [9] is that it was performed in a high-prevalence country and it includes statistically robust data on HIV-infected patients with low CD4 T-cell counts. It is exactly these places, in which highly sensitive tests are needed most. The high prevalence of both microbes accounts for large numbers of co-infected individuals, in which the progressive immune dysfunction caused by HIV not only affects reliability of immune-based testing but also increases susceptibility to *M. tuberculosis* infection and progression from latent to active TB [16, 17].

What is the actual advantage of an increased sensitivity to detect an *M. tuberculosis* infection in HIV-positive patients? Clearly, patients profit from an earlier diagnosis of a latent infection as they can be provided with a preventive TB therapy before they might develop active disease and further spread the infection. In addition, the morbidity in this vulnerable population is reduced, especially in the absence of anti-retroviral therapy. This is particularly important in countries with a high TB burden, as numerically more patients will be diagnosed and subsequently could benefit. However, as of now, those assays are not yet widely available and respective diagnosis frequently does not translate into the appropriate therapy. To improve this, there is an urgent need for a timely implementation of scientific achievements into clinical practice. This, however, can only be realised with respective political

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commitment and support. In this context, international networks such as the World Health Organization (WHO)– United Nations Programme on HIV/AIDS (UNAIDS) [18, 19], the WHO Stop-TB partnership [20], TB-NET [21], and EUCO-Net [22] are not only emphasising the need for a clear political backing but also advocating the importance of integrative approaches, bringing together a variety of disciplines and countries in order to allow for mutual feedback between basic scientists, clinicians, affected communities, and policy makers. This may then not only lead to an improved management of individual patients but ultimately also to a better global control of the *M. tuberculosis* burden.

STATEMENT OF INTEREST

None declared.

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