Subclinical Tuberculosis in HIV-Infected Patients: Another Challenge for the Diagnosis of Tuberculosis in High-Burden Countries?

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(See the article by Mtei et al. on pages 1500–7)

For the more than 2 decades that tuberculosis has been recognized as a major opportunistic infection in patients with HIV infection/AIDS, the extraordinary spectrum of clinical presentations has made the diagnosis of tuberculosis very challenging. This spectrum includes both pulmonary and extrapulmonary disease, which often has atypical clinical and radiographic manifestations in HIV-infected patients, compared with those in HIV-negative patients [1]. The problem is compounded even more in developing countries where rates of *Mycobacterium tuberculosis* and HIV coinfection are high [2] and the resources and facilities for both radiographic and microbiologic diagnoses are often limited or nonexistent. For example, in many parts of the world, sputum smears for detection of acid-fast bacilli (AFB)—but not cultures—are used for the diagnosis of pulmonary tuberculosis.

In resource-poor settings, diagnosis and treatment of active tuberculosis are the most important—and, sometimes, the only—components of tuberculosis-control programs (i.e., parts of the “DOTS” strategy). However, given the high incidence of tuberculosis among HIV-infected patients, where resources permit, the World Health Organization (WHO) has recommended the use of preventive therapy for HIV-infected persons who are tuberculosis positive with latent tuberculosis infection (LTBI) or are at high risk for LTBI (e.g., household contacts of patients with tuberculosis) [3]. This control strategy necessitates a distinction between the diagnosis of active tuberculosis, for which patients require multidrug therapy, and the diagnosis of LTBI, for which isoniazid alone is effective. As the use of antiretroviral therapy increases in developing countries, and because opportunistic infection prophylaxis (including treatment of LTBI) will be offered as part of a package of care, the need for this distinction is becoming even more important [4].

The study by Mtei et al. [5] in this issue of *Clinical Infectious Diseases* presents a potential new challenge for the diagnosis of subclinical tuberculosis in asymptomatic patients, and it may have implications with regard to treatment decisions (i.e., therapy for active disease vs. therapy for LTBI). As part of a study of an investigational mycobacterial vaccine for HIV-infected patients with CD4 cell counts of >200 cells/mm³ and no evidence of active tuberculosis, subjects in Tanzania underwent screening for tuberculosis, with an assessment for symptoms (weight loss and cough or fever), performance of tuberculin skin tests (TSTs), chest radiography, obtention of sputum and blood specimens for cultures for AFB, and in vitro immunologic studies. Patients with active tuberculosis were referred elsewhere for treatment with a multidrug regimen, and those thought to have LTBI (as determined by TST reaction sizes of ≥5 mm, absence of symptoms, and normal chest radiograph findings) received isoniazid for 6 months. After positive sputum culture results were detected in some patients who were asymptomatic, the algorithm was changed to await the results of screening tests before patients were enrolled in the study.

In the first phase of the study, 14 (15%) of 93 patients screened were found to have tuberculosis; 10 of these patients had clinical tuberculosis (defined as symptoms of tuberculosis, chest radiography findings indicative of tuberculosis, and/or positive culture results), and 4 had subclinical tuberculosis (defined as absence of symptoms of tuberculosis, normal chest radiography findings, and positive culture results). In the second phase of the study, screening of an 407 additional patients re-
vealed 6 more patients with a diagnosis of subclinical tuberculosis. DNA fingerprinting of *M. tuberculosis* isolates recovered from patients with subclinical tuberculosis revealed unique IS6110 patterns, suggesting that laboratory cross-contamination that resulted in false-positive cultures was not a factor [6]. In 7 patients with subclinical tuberculosis who were tested for immunologic parameters, lymphocyte proliferation indices to *M. tuberculosis* antigens were elevated, compared with indices for patients who did not have tuberculosis, suggesting that these patients were truly infected and not colonized with *M. tuberculosis*. Of note, of the 10 patients with subclinical tuberculosis, 6 had lymphadenopathy, which was significantly greater than the number of patients with clinical tuberculosis who had lymphadenopathy (2 patients). Absence of lymphadenopathy and TST reaction sizes of <10 mm had a negative predictive value of 99% for both types of tuberculosis in this patient population with CD4 cell counts of ≥200 cells/mm³.

Of 10 patients with subclinical tuberculosis, 8 were initially treated with isoniazid; 7 of these patients received isoniazid monotherapy for ≥28 days before therapy was switched to a 4-drug regimen after positive culture results occurred. These patients responded well to therapy (9 patients survived for a median of 22 months), compared with patients with clinical tuberculosis (3 survived for a median of 22 months).

What are the implications of this study for screening to exclude the diagnosis of tuberculosis in HIV-infected patients who are being considered for preventive therapy in resource-poor settings? Should the current recommendations by the WHO [3] be reconsidered or modified? Patients with symptoms and selected signs of tuberculosis should be evaluated with sputum smears and, where available and feasible, cultures and chest radiographs. If any component of this evaluation suggests active tuberculosis (and not some other opportunistic illness), then therapy with a multidrug antituberculosis regimen should be initiated. In asymptomatic patients, lymphadenopathy may be considered to be a potential indicator of tuberculosis, as suggested in the study by Mtei et al. [5]. Chest radiography has been recommended for all potential recipients of preventive therapy, but this has been of limited utility, because radiographic abnormalities consistent with tuberculosis occurred in 0.2%–3% of largely asymptomatic patients in 2 studies in sub-Saharan Africa [7, 8].

What about asymptomatic patients with positive culture results and normal chest radiograph findings, the novel finding of this study? Prior studies have indicated that patients with normal chest radiograph findings and AFB-positive smear or culture results tend to be more immunocompromised than the participants in this study, but there is some variability in these findings [1, 9]. As noted by Mtei et al. [5], the “incipient” form of tuberculosis described in the study may represent recent primary infection or early respiratory tract disease [10], and it is not completely surprising that this occurred in an area where tuberculosis is endemic. Importantly, although the number of participants with subclinical tuberculosis was small, these patients had good prognoses, with good responses to multidrug therapy, despite prior receipt of isoniazid monotherapy. Given the low inoculum of organisms, this form of subclinical tuberculosis may have responded well to isoniazid therapy alone, without a switch to multidrug therapy. Furthermore, the ability to perform serial AFB cultures for evaluation of active tuberculosis was unique to their research project and would not be a practical approach in many settings.

Is there a significant danger that following the current WHO recommendations to exclude active tuberculosis (i.e., primarily based on symptom evaluation prior to offering preventive therapy) would result in widespread use of isoniazid monotherapy, then causing treatment failures and the emergence of resistance to isoniazid? I think not, for the reasons stated above. This series of events may certainly occur in select patients, especially in circumstances in which patients are not always forthcoming about their symptoms. However, patients with isoniazid-resistant tuberculosis respond well to 4-drug regimens that contain rifampin [11], which will still be the mainstay of therapy for patients who present with active tuberculosis and who have previously received isoniazid preventive therapy.

The study by Mtei et al. [5] is provocative and serves as a reminder of the complexity of tuberculosis in HIV-infected patients, especially in high-burden countries. The solution to the enormous problem of 2 interrelated and overlapping epidemics will rely on increased collaboration and coordination between tuberculosis-control and AIDS-control programs, enhanced detection of both tuberculosis and HIV infection, and availability of both antituberculosis therapy and antiretroviral therapy to coinfected patients, with use of standardized regimens and ongoing monitoring [4]. This remains a daunting task, but I hope that greater advances to that end will occur as increased funding and resources are directed toward high-burden countries [12].

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