Tuberculosis Screening in Patients Starting Antiretroviral Therapy in Sub-Saharan Africa: Stretching Diagnostics to the Limits

To the Editor—We read with interest the article by Bassett et al [1] about intensive screening for pulmonary tuberculosis (TB) among human immunodeficiency virus (HIV)–infected patients initiating antiretroviral treatment (ART) at an outpatient service in Durban, South Africa. All patients without a pre-existing TB diagnosis (median CD4 cell count, 100 cells/μL) were screened using sputum culture, and 19% were confirmed to have pulmonary TB. Only 52% of patients with TB reported cough, and the sensitivity of sputum smear microscopy was only 9%. The authors concluded that, in settings with high TB prevalence, screening using sputum culture should be routine in this patient population. However, infrastructure to do this is currently lacking in many countries.

In similar studies involving patients starting ART in Cape Town, South Africa [2, 3], we also found a very high prevalence of undiagnosed TB of 25% (95% confidence interval, 20%–31%). In view of the low sensitivity of symptom screening and of sputum smear microscopy (14%), compared with liquid culture [2], we similarly concluded that routine sputum culture is required. Intensive screening before ART in our cohort halved the TB incidence rate during the initial months of ART, effectively reducing morbidity and simplifying patient treatment [3].

An important difference between our studies is that Bassett et al [1] collected only a single sputum specimen, compared with our study, in which 2 specimens were obtained at a single clinic visit. Re-examining our data, the first sputum sample yielded 45 TB cases (19% of 235 patients screened), compared with 58 cases (25% of 235) from both samples. Thus, 22% of the TB diagnoses were reliant on a second sample being obtained. This is similar to the 17% incremental yield from a second sample in a study screening for HIV-associated TB in Southeast Asia [4]. Evaluation of intensive TB screening strategies should include analysis of the incremental cost of culturing >1 sample.

The substantially increased yield of TB cases from analysis of a second sample may relate to the fact that the numbers of bacilli present in sputum samples are likely to be very low in these immunocompromised patients. This is consistent with our observations that the sensitivity of smear microscopy was very low [2], chest radiographs were normal in one-third of cases, and pulmonary cavitation was rare [5]. More direct evidence of low bacillary numbers is provided by the prolonged time to sputum culture positivity using automated liquid culture, with a mean duration of >3 weeks [2]. When bacillary concentrations approach the limits of detection in liquid culture (10–100 organisms per mL of sputum), the yield of TB diagnoses will be strongly dependent on the number of samples examined.

Bassett et al [1] did not report on the time to diagnosis. This is a critical issue in this patient group with predominantly sputum smear-negative disease in view of high rates of mortality and nosocomial transmission from undiagnosed TB [6–8]. New rapid diagnostic tests are urgently needed to expedite diagnosis to reduce these risks. The Xpert MTB/RIF assay (GeneXpert; Cepheid) is a novel, fully automated nucleic acid amplification test and represents a major advancement, providing an extremely rapid (<2 h) and specific TB diagnosis with use of near-patient technology [9, 10]. However, when screening for TB among patients starting ART, the assay is likely to be stretched to its limits of detection (95% sensitivity in sputum samples with 131 bacilli per mL [9]). In a recent clinical field evaluation, sensitivities for smear-negative TB were strongly dependent on the number of samples analyzed, detecting 73%, 85%, and 90% of culture-confirmed cases when analyzing 1, 2, or 3 samples, respectively. It will be important to assess the sensitivity of this assay among patients commencing ART in whom bacillary numbers in sputum are likely to be even lower. Thus, multiple samples may be needed to achieve adequate sensitivity. An additional, much cheaper approach to rapid screening and diagnosis in patients with very advanced immunodeficiency may be provided by detection of urinary lipoarabinomannan. Although sensitivity in this patient group is only moderate [2, 11], a simple lateral flow version is being evaluated as a point-of-care test.

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