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Improving Tuberculosis Case Finding in Persons Living with Advanced HIV through New Diagnostic Algorithms

After three decades, the coepidemic of HIV and tuberculosis remains a serious and challenging public health problem. In sub-Saharan Africa, undiagnosed tuberculosis remains an acute and common cause of HIV-related death (1). As a response to this, in 2008 the World Health Organization launched a three-pronged initiative that includes isoniazid preventive therapy, intensified case finding, and tuberculosis infection control partnered with a scale-up of antiretroviral therapy (2). Although improvements have been made in the last 10 years, in 2014, approximately 30 million of the 37 million people living with HIV globally were not screened for tuberculosis (3).

Reliable detection of tuberculosis in persons with HIV is a challenge in resource-constrained settings. In these areas, tuberculosis diagnosis relies heavily on sputum smear microscopy, chest radiography, and symptom screening. However, persons living with HIV often have reduced lung immunopathology and paucibacillary disease (4, 5). Studies of individuals initiating antiretroviral therapy in tuberculosis-endemic settings revealed that up to 15–30% had sputum culture–positive disease (6, 7); however, testing all individuals by sputum culture is resource intensive and may additionally lead to diagnostic delays. To address these challenges, the World Health Organization currently recommends that intensified case finding should include a preliminary symptom screen (i.e., weight loss, current cough, fever, and night sweats) followed by a confirmatory Xpert MTB/RIF test for individuals who screen positive. This algorithm may reliably exclude tuberculosis through the symptom screen (8), but at the programmatic level it is heavily resource intensive and difficult to implement fully (9).

New diagnostic methods for tuberculosis—preferably nonsputum-based, rapid, point-of-care tests—are urgently needed. Toward this end, the World Health Organization issued a target product profile for triage tests that recommends a minimum of 90% sensitivity and 70% specificity. Previous work by Yoon and colleagues demonstrated that point-of-care CRP (C-reactive protein) testing met these benchmarks in a cohort of individuals initiating antiretroviral therapy (10). Although much attention in the tuberculosis diagnostic field has been focused on novel "omics" approaches (11), including transcriptional, proteomic, and metabolic signatures, a simple, rapid test with equivalent or better accuracy is available now for $2. However, questions remain about how optimally to integrate CRP and other diagnostics into systematic screening algorithms for HIV-infected individuals.

In this issue of the *Journal*, Yoon and colleagues (pp. 643–650) report findings from a large, prospectively followed cohort of HIV-infected patients and contribute two important advances (12). First, they were able to evaluate and compare the accuracy of several novel diagnostic algorithms that include CRP, Determine TB-LAM, Xpert MTB/RIF, and culture with the current global guideline for intensified case finding. Second, the authors assessed costs associated with the use of these novel algorithms, which is critical when evaluating novel diagnostics in resource-constrained settings.

In this cohort, all participants were antiretroviral therapy naive and the majority had advanced HIV infection (median CD4 count, 153 cells/μl). All were screened by CRP, urine LAM, sputum Xpert, and sputum liquid culture, and the accuracy, yield, and cost per tuberculosis case detected were compared for various algorithms. This approach generated several important insights into screening in this population. First, although CRP has lower sensitivity than symptom screening (88% vs. 97%), its substantially higher specificity (69% vs. 13%) means that far fewer individuals will require confirmatory testing (40% vs. 88%). Other recent prospective studies of patients with severe HIV and low CD4 counts from Malawi, Ghana, Cameroon, and South Africa have similarly shown that >90% of the patients had a positive symptom screen (13–16). Although symptom screening is simple to implement and low-cost, its low specificity results in a large number of patients needing follow-up diagnostic testing. Findings from this study provide support for considering the replacement of symptom-based screening with CRP as a preliminary "screen-in" test for persons with HIV entering care. Point-of-care CRP testing has the advantages of being inexpensive, nonsputum based, objective, and relatively easy to implement in resource-constrained clinical settings.

A key challenge is that both algorithms—symptom screening and CRP testing, followed by sputum Xpert—have inadequate sensitivity, estimated in this study at 59% and 56%, respectively. Yoon and colleagues (12) demonstrate that the screening resources saved by using CRP tests rather than symptom screening could be used for confirmatory testing by TB-LAM (for those with CD4 < 100) and sputum culture in addition to Xpert. This approach improves the overall diagnostic yield to 78% while containing costs, resulting in a cost per tuberculosis case diagnosed of $92 (compared with $102 for symptom screening followed by Xpert). This algorithm may represent the best balance of yield and costs for clinics in countries with high HIV and tuberculosis burdens, achieving 92% of the yield of the highest-sensitivity algorithm (symptom screening

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followed by TB-LAM, Xpert, and culture) and better specificity at nearly half the cost per case diagnosed ($92 vs. $172).

The past decade has seen major advances in tools for diagnosing tuberculosis in individuals with advanced HIV disease; however, major questions remain about how to effectively integrate these tools into pragmatic screening algorithms in high-burden settings. This study provides evidence that simple algorithms using these new diagnostics can improve case detection while controlling costs. Replication of these findings should be expeditiously conducted in other settings, and, if they are confirmed, global screening guidelines should be revised. Although there is a robust pipeline for new tuberculosis diagnostics, we should not wait to capitalize on the extraordinary progress in diagnostics that has been made over the past 10 years to decrease the 400,000 tuberculosis-related deaths among persons living with HIV every year (17). ■

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Tuberculosis Elimination, Research, and Respect for Persons

Can we eliminate tuberculosis (TB) in the United States? Should we be trying? Can TB be eliminated in this country in a manner that is respectful to persons in terms of the risks and benefits of prevention?

Rates of TB in the United States are at historical lows (1). In 2017, there were barely more than 9,000 cases of TB diagnosed, which corresponds to an incidence rate of 2.9/100,000 persons. Compared with 1953, at the dawn of the antibiotic era for TB, when there were 84,304 cases (52.4/100,000), there has been a 90% reduction in cases.

This is a remarkable public health success story that has taken place despite the fact that TB remains among the 10 leading causes of death in the world each year, and is the leading cause of death caused by a single infectious agent (2). Despite this progress, we are far from eliminating TB entirely in the United States (defined by the Centers for Disease Control and Prevention and the World

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