Expanding the Role of the Microscopic Observation Drug Susceptibility Assay in Tuberculosis and HIV Management

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(See the article by Reddy et al, on pages 988–996.)

Although much progress has been made in improving cure rates for tuberculosis (TB), diagnosis and case detection remain major obstacles to TB control [1]. In the past decade, there has been an unprecedented level of interest, funding support, and activity focused on the development of new tools for TB diagnosis, and the diagnostics pipeline for TB is rapidly expanding [1, 2]. However, the lack of a rapid, point-of-care test for TB and the lack of accurate algorithms for diagnosing smear-negative and childhood TB remain areas of concern. This is especially true in people infected with human immunodeficiency virus (HIV), an area where intensive active case finding is urgently needed [3, 4].

In HIV-infected persons, undiagnosed active TB is common [3, 4]. Before initiation of isoniazid preventive therapy (IPT), an intervention that is highly effective [5] but widely underused [4], it is critical to rule out active TB. However, there is no easy and accurate method to do this in high-burden, resource-limited countries. Clinicians in disease endemic countries often cite their inability to rule out active TB as a major reason for not routinely prescribing IPT to HIV-infected persons [4]. Liquid cultures are more rapid and sensitive than solid cultures [6] and can potentially help in ruling out active TB and thereby facilitate the use of IPT. Although liquid cultures were endorsed by the World Health Organization (WHO) in 2007, high cost and technical complexities limit their uptake and widespread use in developing countries. In this context, is there a role for simple, low-tech, new culture methods that can be effectively deployed in resource-limited countries with high HIV prevalence?

In this issue of *Clinical Infectious Diseases,* Reddy and colleagues report on a study that evaluated the role of the microscopic observation drug susceptibility (MODS) assay as a test to rule out active TB in HIV-infected IPT candidates in Lima, Peru [7]. In this relatively large study in a real-world setting, the MODS assay detected *Mycobacterium tuberculosis* with greater sensitivity and speed and ruled out TB more quickly and with fewer indeterminate culture results than the Lowenstein-Jensen culture [7]. The MODS assay is a noncommercial laboratory technique that uses direct inoculation of decontaminated patient specimens to liquid media, followed by examination with use of an inverted microscope to detect very early mycobacterial growth [8]. It has received increased attention in recent years because of its rapid turnaround time and simultaneous drug-susceptibility testing (DST) capability. Combined with the low-cost supplies and reagents required, the MODS assay appears to have a role in providing expanded access to TB culture and DST services. As shown by Reddy and colleagues, the MODS assay may have a useful role in ruling out active TB in HIV-infected individuals and could potentially overcome 1 of the biggest barriers to the widespread scaling up of IPT, an intervention that is now a key component of the newly launched Three I's initiative (infection control to prevent nosocomial transmission of TB, intensified TB case finding, and IPT) [9].

The need for greater diagnostic capacity in TB control programs has been recognized for several years, and indeed, initiatives are ongoing to strengthen laboratories in low-resource countries [10]. The advent of the HIV epidemic brought into focus the inadequacies of available TB diagnostics, and it became clear that smear microscopy (the standard TB diagnostic tool available for most of the world's population) is not sufficient to deal with this age-old adversary. Although smear mi-

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croscopy will continue to play an important role in detecting the most infectious cases of TB, smear-negative disease, such as that generally seen with HIV coinfection and pediatric TB, requires considerably more sensitive approaches.

In 2007, WHO issued policy recommendations for the use of liquid culture with rapid *M. tuberculosis* speciation for TB detection and DST [11]. Despite concerns regarding biosafety, the speed and improved case detection afforded by liquid media provided motivation for many laboratories to commit the resources required for its implementation. Subsequent WHO recommendations to implement molecular detection of rifampin resistance (ie, using line probe assays [12]) were made based on similar grounds and were followed with a massive UNITAID funded program to roll out rapid molecular tests in 27 high-burden countries [1].

Although commercial liquid culture systems and line probe assays represent the goal of many TB control programs, the reality is that many laboratories currently lack the required infrastructure, expertise, and/or resources required for their implementation. Meanwhile, there were an estimated 1,756,000 incident TB deaths in 2007, and 23% of all HIV deaths are attributed to TB [13]. Rates of multidrug-resistant (MDR) and extensively drug-resistant TB continue to increase, and it is estimated that up to 96% of MDR TB cases are not being diagnosed and treated appropriately [13]. This has led some people to advocate for the expansion of simple and affordable laboratory techniques, such as the MODS assay and other noncommercial assays, to fill an urgent gap in TB diagnostics in settings where more expensive or more complex diagnostics are not currently feasible, even though they might be in the near future. Indeed, a WHO policy on noncommercial rapid culture methods for MDR TB diagnosis is expected in 2010.

Studies of MODS assay performance have shown it to have high sensitivity in detecting *M. tuberculosis* [8, 14–22], comparable to that of commercial liquid culture systems, likely because of its similar use of liquid media. It is this high sensitivity that allows the use of the MODS assay to effectively rule out active TB in HIV-infected individuals, especially if >1 culture is performed [7]. Concerns about contamination rates and cross-contamination have not been borne out in published evaluations. Turnaround times remain the most cited reason for enthusiasm, with mean time to results being ~9 days. By nature of the MODS protocol, DST results are available on the same day positive cultures are detected, leading to time savings even compared with automated liquid culture systems used with molecular resistance detection.

As is highlighted by Reddy et al [7], not only do turnaround times have implications for patient care and the initiation of appropriate therapy but also the chance of patient loss to follow-up. Access to diagnostics for MDR (and now extensively drug-resistant) TB and TB and HIV management are limited in most areas of the world, creating a significant barrier for TB control programs that seek to minimize the spread of these difficult-to-treat infections. Often a lack of diagnostic capacity leads to diagnostic delays and unacceptable rates of patient dropouts. In vulnerable populations, such as those with HIV coinfection, these delays not only feed the cycle of selecting for increasingly resistant strains but are associated with significant morbidity and mortality.

Because of its highly infectious nature, biosafety will always be a significant issue when dealing with cultured isolates of *M. tuberculosis*. Liquid media cultures have traditionally posed increased risk, compared with solid media, because of the higher risk of aerosolization during manipulation. In addition, although it is feasible to visualize colony growth on solid media, allowing for presumptive speciation, positive liquid cultures typically require aspiration of culture material for staining and visualization under microscopy. The MODS procedure attempts to minimize these biosafety concerns by sealing the microtiter plates and placing them inside plastic bags after inoculation of patient specimens. These plates are visualized through the bags, without cultured material ever being manipulated directly by the technologists. The visualization of microcolony growth is reportedly specific to differentiate *M. tuberculosis* from nontuberculous mycobacteria [8], thus also allowing presumptive identification without exposing technologists to highly infectious material.

Although noncommercial assays such as the MODS assay hold promise, it is important to pay careful attention to published standard operating procedures and accepted quality assurance systems, especially because these are not standardized kits. Careful development of systems for training and ongoing supervision will be required for assays such as the MODS assay to be widely implemented. The MODS assay is likely to be subject to operator-dependent skill and motivation similar to smear microscopy, where operational performance and maintenance of proficiency continue to create challenges for rigorous quality assurance beyond the implementation stage. Given the expected learning curve, it is important for MODS assay implementation to be planned carefully with use of a phased approach, and its performance should be monitored and evaluated at each stage. New users should review available training materials, including videos [23], training manuals, and standard operating procedures (available at http://www.modsperu.org).

Although there are many exciting potential diagnostics being investigated in TB diagnosis and DST, the TB epidemic requires us to take action now. As has been demonstrated in modeling studies, the expansion of currently available culture and DST services is likely to have a substantial impact on TB and MDR TB control [24, 25]. To delay implementation of these needed services while waiting for something better is a gamble that sacrifices real lives now while saving hypothetical dollars

in the future. Although not unsympathetic to the stresses demanded of TB programs when implementing even the smallest changes, it cannot be denied that the pace of evolution in TB control is not likely to abate any time soon. Laboratories and TB control programs will need to learn to be flexible and reactive to implementing new procedures and new diagnostics as lessons are learned, technologies are developed, and strategies evolve. The concept of a perfect TB control strategy is not likely to appear in the near future and is certainly more than a few steps away.

In conclusion, the study by Reddy and colleagues [7] is a timely and useful demonstration of the potential for noncommercial rapid cultures to improve the management of IPT in HIV-infected persons in resource-limited settings. The next step would be to show that use of noncommercial rapid cultures can actually improve patient-important outcomes and can positively affect the trajectory of the TB and HIV epidemic.

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