HIV-Associated Tuberculosis: Diagnostic and Treatment Challenges

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ABSTRACT

Tuberculosis (TB) and the human immunodeficiency virus (HIV) are, individually, two of the world’s greatest ongoing public health threats. In combination, the two diseases can be even more devastating. HIV significantly increases an individual’s chances of reactivation of latent TB infection and progression to active TB disease. HIV’s associated immunosuppression makes it more difficult to diagnose active TB due to a higher likelihood of atypical and extrapulmonary presentation and poorer performance of standard diagnostic tools. TB is the major cause of death in individuals infected with HIV, and the combination of both illnesses creates unique treatment challenges for providers due to interactions between antituberculous and antiretroviral medications, overlapping drug toxicities, and the immune reconstitution inflammatory syndrome. Magnifying these challenges even further is the fact that much of the burden of TB/HIV coinfection exists in some of the world’s most resource-limited settings. Concerted efforts are needed to identify rapid and accurate diagnostic tools for active TB disease and latent TB infection (LTBI) that are practical and inexpensive and that perform well in individuals with HIV infection. Also needed are effective and feasible strategies to optimize management of both conditions in the coinfected patient.

KEYWORDS: Tuberculosis, human immunodeficiency virus, diagnosis, treatment

Mycobacterium tuberculosis (MTB) and the human immunodeficiency virus (HIV) are pathogens that, individually, are responsible for two of humankind’s greatest ongoing health calamities: active tuberculosis (TB) disease, responsible for 1.7 million deaths worldwide in 2006,1 and HIV-related diseases, including the acquired immunodeficiency syndrome (AIDS), responsible for 2.1 million deaths worldwide in 2007.2 In combination, the two diseases are ever more devastating. In 2006, 700,000 of the 9.2 million new cases of active TB and 200,000 of the 1.7 million deaths due to TB were in individuals also infected with HIV.1

HIV dramatically increases an individual’s chances of reactivation of latent TB infection (LTBI) and progression to active TB disease many-fold higher than any other risk factor,3–5 whereas its associated immunosuppression makes it more difficult to diagnose TB due to a higher likelihood of atypical presentation. TB is firmly entrenched as the major cause of death in individuals infected with HIV and creates challenges for providers when both diseases need to be treated simultaneously due to interactions between some antituberculous medications and certain antiretroviral drugs, overlapping drug toxicities, and the common occurrence

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of immune reconstitution inflammatory syndromes. With the rise of multidrug resistant (MDR) TB worldwide and extensively drug resistant (XDR) TB in people infected with HIV, these diagnostic and treatment challenges are steadily multiplying. From a patient’s perspective, having both TB and HIV is particularly difficult. Both conditions are associated with stigma and discrimination, and adherence with treatment for both conditions is particularly challenging.

Complicating matters even further is the fact that much of the burden of TB/HIV coinfection exists in some of the world’s most resource-limited settings, with the brunt of that burden being borne by sub-Saharan Africa where some countries report an HIV prevalence of greater than 50% among new cases of TB. In these resource-limited settings, patients and providers often have little to no access to many of the standard diagnostic and therapeutic options available to overcome some of these challenges, and there is often a paucity of infection control measures, all of which contributes to the ongoing spread of TB.

**ACTIVE TUBERCULOSIS**

**Diagnostic Challenges**

The presence of HIV infection complicates the clinical presentation of active TB through its effect on the immune system resulting in changes in the presentation of active TB disease, which can make diagnosis of active TB more difficult and delay diagnosis. HIV infection can lead to paucibacillary disease in patients with active pulmonary TB, which decreases the sensitivity of the acid-fast sputum smear test, the most widely used and available TB diagnostic method, especially in resource-limited settings. Patients with HIV, especially advanced HIV disease, and active pulmonary TB are less likely to have “typical” chest radiograph findings such as cavity lesions and more likely to have chest radiographs demonstrating lymphadenopathy and/or atypical infiltrates. Patients with HIV and active TB are also more likely to have extrapulmonary TB, especially those with lower CD4 T cell counts.

As a consequence of high rates of sputum smear negativity, atypical chest radiograph findings, and the increased incidence of extra-pulmonary TB, the diagnosis of TB may be missed or delayed in HIV-infected individuals. Smear-negative TB and delayed diagnosis of TB in individuals with HIV have both been associated with increased mortality. Finally, HIV infection has been associated with a high prevalence of subclinical TB in settings of high TB burden, further complicating diagnosis and leading to the need for effective means of screening for active TB in these populations, especially prior to initiation of treatment for LTBI. It is therefore imperative to develop new rapid and accurate means for the diagnosis of active TB in HIV-infected patients with subclinical, smear-negative pulmonary and/or extrapulmonary TB.

In resource-limited areas, the tuberculin skin test (TST) is sometimes used to aid in the diagnosis of active TB. Beyond its lack of specificity for this type of application and its decreased sensitivity in individuals with HIV infection, in settings of high TB prevalence and/or high rates of bacille Calmette-Guérin (BCG) vaccination the TST has been shown to have particularly limited utility as a diagnostic aid for active TB. Researchers have looked at improving the speed and accuracy of active TB diagnosis through the use of other types of immunologic assays aimed at detecting TB-specific antibodies and antigens. Thus far, these strategies, much like the TST, have not yielded results with acceptable sensitivity or specificity.

Breen et al examined improving the rapidity of diagnosing smear-negative tuberculosis by performing rapid immunoassays for MTB purified protein derivative (PPD)-specific CD4 lymphocytes on the induced sputa of traditional sputum-smear-negative or sputum-nonproducing TB suspects. Sixteen of their 42 subjects were HIV infected. Sensitivity and specificity of the immunoassay versus final diagnosis of active TB were 89% and 80%, respectively. In combination with a single sputum smear for acid-fast bacilli (AFB) the sensitivity increased to 93%. Their hopeful results were unaffected by the HIV status of the individual.

Commercially available MTB nucleic acid amplification tests (NAATs) have decreased the time to definitive diagnosis of AFB smear positive pulmonary TB due to their short turnaround time and high sensitivity and specificity. Resource-limited settings, however, generally lack the laboratory infrastructure necessary to reliably perform NAATs for MTB. In addition, the costs associated with NAATs are prohibitive in resource-limited settings. For these tests to become more widely available in resource-limited settings, the technology required to perform them must become simpler and their costs must decrease substantially.

The challenges associated with implementing NAAT technology in resource limited settings have not deterred investigators in those settings from examining possible uses of such technologies. In a study conducted in Tanzania on 120 HIV-infected TB suspects, the investigators in those settings from examining possible uses of such technologies. In a study conducted in Tanzania on 120 HIV-infected TB suspects (28 of whom were subsequently proven to have active TB by culture confirmation), Kibiki et al examined the use of a commercially available whole blood serologic assay for diagnosis of active TB as well as the use of an investigator-developed real-time polymerase chain reaction (PCR) for MTB DNA on bronchoalveolar lavage fluid. The serologic assay fared very poorly in this HIV-infected group of patients, but the PCR assay had a sensitivity of 85.7% and a specificity of 90.9%.
Though performed on small samples of patients and a long way from commercial development and clinical application, especially in settings with limited resources, studies like the two summarized above highlight the inventiveness that will be required to tackle the challenges HIV poses in the diagnosis of TB and lend hope to the possibility of advances in the near future in the rapid and accurate diagnosis of TB in patients with HIV. In this issue of *Seminars in Respiratory and Critical Care Medicine*, Drs. Pai and O’Brien (article 9) review new diagnostics for active TB.

**Treatment Challenges**

The choices, challenges, complications, and future of the treatment of HIV-associated active TB have been recently reviewed. Dr. Nuermberger (article 7) discusses the use of animal models to develop new treatments for TB and Dr. Ginsberg (article 8) reviews emerging drugs for the treatment of active TB. Treatment of TB and HIV disease in patients with both conditions presents multiple challenges, including the correct timing of initiation of antiretroviral (ARV) therapy during TB treatment, the correct choice of drug combinations to limit interactions, and close patient monitoring to watch for drug toxicities (which often overlap) and other consequences, such as immune reconstitution inflammatory syndrome (IRIS).

It is recommended that antituberculous treatment be promptly initiated upon diagnosis of TB in an effort to decrease mortality and infectiousness. Additionally, emphasis has been placed on starting ARV therapy, when indicated, during TB treatment due to the high morbidity and mortality in patients with HIV coinfection even when receiving appropriate antituberculous treatment. The World Health Organization recommends that the timing of initiation of ARV therapy in these patients be based on the degree of immunosuppression as defined by CD4 cell count. Although not an unreasonable approach, further research is necessary to better define the optimal time for initiation of ARV therapy during TB treatment.

Several factors may complicate concurrent ARV therapy, including additive toxicities of medications, drug interactions, risk of immune reconstitution events, and difficulty in medication adherence. Despite these challenges, use of ARV therapy for those who qualify during TB treatment is important because it improves outcomes and decreases mortality. The choices of ARVs that can be used safely during TB treatment are severely limited by the necessary use of rifampin (or other rifamycins) in most regimens for the treatment of rifampin-susceptible TB due to rifampin’s effect on the metabolism of antiretroviral drugs resulting in severely reduced levels of protease inhibitors (PIs), significantly reduced levels of the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and mild to moderate reductions in the level of efavirenz, another NNRTI.

The Centers for Disease Control and Prevention (CDC) has recently released guidelines on the management of drug interaction in the treatment of HIV-associated TB. In resource-limited settings, nevirapine-based regimens are used in most national ARV treatment programs but coadministration with rifampin is not recommended. Efavirenz-based ARV regimens are recommended in this scenario. However, it is unclear if standard dosing of efavirenz is adequate to compensate for any increases in efavirenz metabolism due to the concomitant use of rifampin. Matters become more complicated in the treatment of HIV-associated TB in pregnant women, a setting in which efavirenz is not recommended, and children, whose first-line ARV regimens often include PIs.

A few projects have assessed coadministration of these antituberculous and ARV agents with excellent preliminary results. A recent retrospective study in Thailand comparing HIV/TB coinfected individuals receiving rifampin-based TB therapy who started ARV therapy with either efavirenz or nevirapine at standard doses encouragingly showed no difference in virologic and CD4 outcomes between the two ARV treatment groups, though this study may have been underpowered. More pharmacokinetic and larger prospective and randomized clinical studies using various interventions and monitoring tools are urgently needed in patients receiving concomitant antituberculous and antiretroviral drugs to determine the exact risks and benefits of the various guidelines currently in use. The feasibility and effectiveness of rifabutin, which is less prone to drug interaction, in resource limited settings should also be urgently evaluated.

Paradoxical worsening of TB in HIV-negative patients after initiation of effective treatment for active TB is a long recognized clinical entity; in HIV-associated TB the rates of paradoxical worsening in patients on TB treatment who then start ARV therapy are much higher, likely due to ARV therapy’s beneficial effect on the immune system, and have been categorized as one of the many types of immune reconstitution inflammatory syndromes (IRIS) that patients with HIV are prone to developing after initiation of ARVs. The incidence of TB-IRIS in HIV/TB coinfected individuals receiving therapy for both diseases varies from study to study but is likely in the range of 20 to 30% of patients. TB-IRIS poses significant challenges to providers because there is no single diagnostic test that can distinguish TB-IRIS from treatment failure (an especially difficult problem in resource-limited settings where culture and drug susceptibility testing is often unavailable to help distinguish the two), no agreed upon case definition of IRIS, and no...
prospective or randomized trial data on how to best treat and manage TB-IRIS. More research in these areas is urgently needed.

Infection control measures for inpatient and outpatient settings need to be put in place whenever and wherever HIV-associated tuberculosis is being managed but perhaps most importantly in resource-limited settings, where the association between HIV and MDR- and XDR-TB secondary to hospital-based transmission and spread has highlighted the need for better preventive practices. Improved infection control measures and increased program capacity in such settings are necessary to avoid further overwhelming the public health system. To be successful, however, not only will increased resources be necessary, but, in addition, TB and HIV treatment programs will need to collaborate in this effort.44

**LATENT TUBERCULOSIS INFECTION**

**Diagnostic Challenges**

Despite its shortcomings, which include lower sensitivity in HIV-infected patients45,46 and cross-reactivity with components of the BCG vaccine, the TST is the accepted standard for diagnosis of LTBI. HIV-infected individuals with LTBI, as defined by lack of symptoms or signs consistent with active TB and with a positive TST, have a higher risk for reactivation than HIV-uninfected individuals with LTBI.47 In many resource-limited settings, however, tuberculin skin testing is rarely available for a variety of reasons, including lack of access to clean needles and syringes for planting PPD and unavailability of properly refrigerated storage facilities for tuberculin.

In recent years, advances in LTBI diagnostics have been spurred by the elucidation of the *Mycobacterium tuberculosis* genome and the characterization of TB-specific antigens.48,49 These TB-specific antigens have led to the development of diagnostic tests for LTBI based on interferon-gamma production by T cells stimulated by these antigens, and have been dubbed interferon-gamma release assays (IGRAs). Three IGRAs are now commercially available: the QuantiFERON-TB Gold and the QuantiFERON-TB Gold In-Tube (Cellestis Inc., Valencia, CA), and the T-SPOT.TB (Oxford Immunotec Limited, Abingdon, Oxfordshire, UK). The QuantiFERON is approved for use in the United States, with approval for the T-SPOT.TB expected to be imminent at the time of this writing. In this issue of Seminars, Drs. Pai and O’Brien (article 9) review these new diagnostics for LTBI. In brief, IGRAs have been shown, in immunocompetent adult subjects, to have excellent specificity for TB infection and good to excellent sensitivity for LTBI. The CDC has issued guidelines on the use of the QuantiFERON but cautions that it has not been extensively studied in children and immunocompromised individuals and that it may have a different sensitivity in these populations.51

Studies examining the performance of these new T cell–based IGRAs in immunocompromised and HIV-infected individuals have had mixed results. Some studies have shown the enzyme-linked immunosorbent assay (ELISA)-based tests to have an increased incidence of indeterminate results in these populations. Other studies have shown the evaluability and performance of the enzyme-linked immunosorbent assay (ELISPOT) assay–based tests to be less effective in detecting LTBI in HIV-infected patients.55,57,58

**Treatment Challenges**

Adherence to and completion of treatment for LTBI are key to maximizing its effectiveness. Low perceived benefits of treatment increases the risk of noncompletion,59 but shorter regimens have been shown to improve completion rates.60 In this issue of Seminars, Dr. Sterling (article 6) reviews new strategies for the treatment of LTBI.

Randomized trials in resource-limited settings have shown that the use of isoniazid (INH) for treatment of LTBI in HIV-infected patients can reduce the incidence of TB and is cost-effective,61 but that benefit may wane over time,62 probably because of the high likelihood of reinfection in high TB burden settings. Another challenge to the successful treatment of LTBI in people infected with HIV in these settings includes a hesitancy on the part of many National TB Control Programs in implementing LTBI treatment programs using INH for fear that patients started on this regimen may, in fact, have undiagnosed active TB, especially subclinical, smear-negative, or extrapulmonary TB, and thus would inadvertently receive monotherapy for active TB disease resulting in emergence of drug-resistant TB. Systematic and standardized screening for active TB in high TB burden and resource-limited settings leads to increased case detection but it is unclear how sensitive these strategies are and whether they can confidently be used to rule out all active TB disease prior to treatment for LTBI. Developing diagnostic tools and screening algorithms that can accurately diagnose LTBI in individuals with HIV while excluding active TB are areas needing further investigation.

**CONCLUSION**

HIV-related TB is a major global health threat. All currently available diagnostic methodologies in use are suboptimal in individuals with concomitant HIV...
infection. Concerted efforts are needed for the development of new rapid and accurate diagnostic tools for active TB disease and LTBI that perform well in patients with HIV disease.

In resource-limited settings where the greatest burden of HIV-associated TB exists, many of the tests described here, with the exceptions of the TST and sputum smear, are prohibitively expensive and/or require sophisticated laboratory infrastructure. Thus new diagnostic tools for TB and LTBI are needed that are practical, inexpensive, and feasible to implement in resource-limited settings.

Many unanswered questions and challenges also remain in the management and treatment of HIV-related TB, including the optimal timing of initiation of ARV therapy, the safest and least interaction-prone combinations of antituberculous and ARV drugs, and accurate and effective methods for diagnosis and management of TB-IRIS. Further clinical research, particularly prospective and randomized trials, is needed to answer the open questions in this area.

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