

A PEER-REVIEWED ARTICLE

## **HIV and TB: Dual immunosuppressive diseases**

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March 24<sup>th</sup> marked World TB day in commemoration of the discovery of *Mycobacterium tuberculosis* (MTB), causative agent of tuberculosis, in 1882 by Dr. Robert Koch.<sup>1</sup> Centuries later, identification of MTB remains a challenge with the need for a clinician to frequently start empiric anti-TB therapy while awaiting laboratory confirmation. With the ongoing HIV epidemic, TB diagnosis and management continue to be a clinical challenge in patients who are co-infected. This is in part due to the immunosuppression caused by both MTB and HIV and the varied presentation. This article will focus on key issues an HIV clinician needs to consider when evaluating and treating for TB, in conjunction with the local health department.

### **Why evaluate for TB?**

TB is a communicable, airborne disease that infects the unsuspecting individual. If untreated, it leads to cachexia and death. Society as a whole is affected due to the decrease in an individual's functional capacity and quality of life given the chronicity of this disease. TB is a major public health concern and is one of the nationally notifiable (reportable) diseases.<sup>2</sup>

The World Health Organization reported an estimated 9.27 million cases of TB worldwide in 2007, with 1.37 million incident cases (15%) in HIV-positive individuals.<sup>3</sup> In the US, there has been a steady decline in TB cases for the past 16 years,<sup>4</sup> after a period of resurgence in the mid-1980s and early 1990s that correlated with the onset of the HIV epidemic. In 2008, the TB case rate was 4.2 cases per 100,000 with an estimated 6% HIV coinfection (with known HIV test results).<sup>5</sup>

HIV-positive individuals are at a higher risk of progression from latent TB infection (LTBI) to active TB disease, with an estimated 7%-10% annual risk, compared to a total lifetime risk of 5%-10% in HIV-negative individuals.<sup>6</sup> In HIV-positive individuals, low CD4 cells/advanced immunosuppression causes increased risk of TB. Active TB disease may accelerate HIV progression and is associated with increased risk of mortality in HIV patients.<sup>7</sup> HIV-infected individuals with a positive TB skin test, untreated or partially treated with isoniazid, have a higher risk of developing active TB disease.<sup>8</sup> Thus, it is essential to screen for latent TB infection and provide preventive treatment to decrease the risk of active disease and progression of HIV.

### **Screening and diagnosis of TB (infection and disease) in the HIV infected**

Until recently, one of the widely used TB screening tests was the Mantoux test or the Tuberculin Skin Test (TST). This test is based on delayed type hypersensitivity reaction to the Purified Protein Derivative (PPD) injected intradermally into the forearm, with the induration response assessed at 48-72 hours after placement. An induration  $\geq 5$  mm is considered positive TST in HIV-infected individuals.<sup>9</sup> Recent meta-analysis of studies that also included non-HIV populations revealed sensitivity of 77% for this test and specificity of 59% in BCG vaccinated with higher specificity 97% in non-BCG vaccinated.<sup>10</sup> Limitations of TST include the need for a return/second visit for reading, inter-reader variability, as well as response affected by overall immune status. Therefore, a negative TST does not exclude TB infection or active TB disease in the HIV-infected, especially in people with symptoms of active TB.

Since 2005, a blood test, the Interferon Gamma Release Assay (IGRA), QuantiFERON®-TB Gold,<sup>11</sup> and the newer generation QuantiFERON®-TB Gold In-Tube has been approved in the US for TB screening. Recent meta-analysis of studies that also

included non-HIV populations, revealed sensitivity of 70% of QuantiFERON®-TB Gold In-Tube and a pooled specificity of 99% in non-BCG vaccinated and 96% in BCG vaccinated.<sup>12</sup> One caveat of this test in HIV-infected individuals is that Interferon Gamma Release is influenced by the CD4 count, with higher CD4 count corresponding with higher values of Interferon gamma released and lower CD4 associated with indeterminate results.<sup>13</sup> Therefore, the HIV clinician has to consider the patient's CD4 count when evaluating results of this new blood test for TB screening.

CD4 counts are also associated with varied clinical presentation of active TB in HIV patients. Low CD4 counts are associated with extrapulmonary TB (CD4  $\leq$ 100), mycobacteremia (CD4  $\leq$ 100) and mediastinal adenopathy ( $\leq$ 200).<sup>14</sup> Therefore, the HIV clinician needs to send other body fluid specimens (blood, urine, stool, CSF) for Acid Fast Bacilli smear and culture, along with regular sputum sample testing in HIV patients as part of a TB work-up. Radiographic manifestations of pulmonary TB are also influenced by the CD4 count. CD4 count  $<$ 200 are associated with normal chest radiograph<sup>15</sup> and with hilar/mediastinal adenopathy; CD4 counts  $\geq$ 200 are associated with cavitations.<sup>16</sup>

TB needs to be considered in the differential diagnosis in the management of HIV patients, especially in those who present with: chronic cough (in smokers and nonsmokers), unexplained weight loss despite good virologic control on antiretroviral therapy, night sweats, fevers, headaches, change in mental status (especially with CSF findings of low glucose) or mediastinal lymphadenopathy. If there is a high index of clinical suspicion for TB, it is prudent to start patients on empiric anti-TB therapy, pending microbiologic/culture confirmation.

#### **Treatment of TB (with or without antiretroviral therapy)**

TB treatment<sup>17</sup> is divided into two phases: the intensive phase with four different medications (isoniazid, rifampin, pyrazinamide, ethambutol) for two months, followed by the continuation phase of two medications (isoniazid and rifampin) for 4-7 month to complete a total of 6-9 months by directly observed therapy (DOT), under supervision of local health departments. Routine monitoring of TB medication side effects and drug toxicity are required with evaluation of complete blood cell count, renal, and liver panel testing. Visual acuity needs to be assessed at baseline and at least in one month intervals while patient is on ethambutol. Patients should also be advised to read daily fine print for early detection of vision changes.

If an HIV patient is on antiretroviral therapy (ART) prior to anti-TB medications and is tolerating the regimen well with virologic suppression, it is imperative to notify the local health department of all ART medications the patient is taking. This will avoid any potential drug-drug interactions or failure of ART regimen by initiating rifampin-based TB treatment. An efavirenz-based regimen can be used with rifampin without further dose adjustments.<sup>18</sup> However, protease inhibitors (PIs) and rifampin interactions can cause significant toxicities.<sup>19</sup> Therefore, if a patient is on a boosted PI-based regimen, rifabutin (150 mg every other day) should be prescribed instead of rifampin. Irregular PI intake can lead to lower rifabutin levels with this intermittent dosing. Thus, the Health Department DOT worker can have a discussion with the patient about regular intake of PIs along with TB medications in order to avoid underdosing of rifabutin in the absence of PIs.

If TB treatment precedes the initiation of ART, the above mentioned drug-drug interactions need to be considered when choosing an ART regimen. A recently published study revealed higher mortality in patients who were started on ART after completion of TB therapy as compared to those with ART initiation during TB treatment.<sup>20</sup> A lower CD4 count requires early initiation of ART. However, most TB-HIV clinicians consider starting ART after a two-week period to assess TB medication side effects or avoid possible early development of immune reconstitution inflammatory syndrome.

#### **One patient, dual disease, multidisciplinary team**

In summary, a multidisciplinary approach and close interactions with health departments can achieve TB cure in HIV patients. Patients need to be advised of the

significant pill burden associated with management of these dual diseases and the common side effects (rash associated with rifampin or efavirenz or TMP/SMX). Therefore, the DOT worker is a key team member in co-management of these diseases, providing expeditious communication of medication or social issues that are potential barriers for both TB and ART medication intake. The HIV clinician can play a critical role by consulting with the local health department to facilitate effective TB-HIV care and TB cure. ❖

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