EDITORIAL

Tuberculosis in HIV: Making Good with What We Have

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From recent estimates by the World Health Organization (WHO), there were nine million cases of pulmonary tuberculosis (TB) worldwide in 2011 alone and nearly one in five also had Human Immunodeficiency Virus (HIV) infection. During that same year, 1.5 million persons died from tuberculosis, a curable respiratory illness (1). Significant strides have been achieved through Millennium Development Goal 6 (MDG6) and the Stop TB Partnership, with half of the patients living with TB and HIV co-infection being started on antiretroviral therapy (ART), and HIV testing among persons diagnosed with TB increasing from three per cent in 2004 to 69 per cent in 2011 (2, 3). In this regard, Jamaica surpasses the current global average for patients with TB with known HIV status, standing at 81 per cent in 2011 (1). However, the true burden of TB remains underestimated based on current diagnostic algorithms, the mainstay of which has been microscopic examination for acid-fast bacilli (AFB), which has poor sensitivity, detects patients with high bacillary burden (misses patients with paucibacillary disease), misses the majority of patients with actual TB, and does not assess drug resistance (4–6). Patients with TB who are not detected by microscopic examination (smear-negative TB) are an important source of transmission of TB (7–9).

In developing countries, the risk of pulmonary TB in patients with HIV is two to six times that of persons without HIV infection (10, 11). The mortality among persons with HIV and TB is high. Even with the availability of ART, the risk of TB is reduced by ART in persons with HIV but is still not restored to a level comparable to persons without HIV infection. The cure rate for pulmonary TB among persons who are HIV negative exceeds 80 per cent in most series, compared to just about a 50 per cent cure rate among persons who are HIV positive; and mortality rates exceed 20 per cent among persons with HIV and TB in several series, compared to under five per cent in patients without HIV (12). In a two-year prospective study in Uganda, among patients with HIV initiating ART, cumulative mortality was five-fold higher among patients with TB compared to those without (13). Immune exhaustion consequent on direct cytopathic effects of HIV as well as the host immune response to attempt to clear the virus, compounded by chronic antigen exposure due to TB infection, results in general immune dysfunction, and impaired or aberrant immune responses to TB. The typical signs, symptoms and response to diagnostic modalities are therefore impaired. Patients with HIV have impaired responses to tuberculin skin testing (TST), and the chest radiograph appears normal in a third of patients with HIV who have culture-positive pulmonary TB (14–16). Even interferon gamma release assays (IGRA) perform poorly in screening for TB among patients with HIV, having a sensitivity of just over 60 per cent among patients with smear-positive TB (17). The TST and IGRA perform similarly (similarly poorly) at about 60 per cent sensitivity, but the tests correlate poorly when matched up against each other (18). These factors make early detection of TB difficult, with negative implications for management outcomes and controlling the spread of TB.

With respect to the clinical management of TB in persons living with HIV, there have been several seminal studies on which current good clinical practice is based. We have learnt from SAPit (Starting Antiretroviral Therapy at Three Points in Tuberculosis), ACTG 5221 (AIDS Clinical Trials Group 5221), and CAMELIA (Cambodia Early *versus* Late Introduction of Antiretroviral Drugs) about the optimal timing of antiretroviral therapy and anti-TB medications in patients with TB and HIV (19–22). Although the effect of isoniazid prophylaxis for latent TB has been shown to significantly reduce mortality among patients with HIV, there is a need for improved education of healthcare workers to allay fears about isoniazid resistance, and additional appropriately designed clinical trials would also be useful (23, 24).

The most pressing challenge is the early identification of cases of TB, having implications for limiting transmission and mitigating mortality. In high prevalence settings, such as South Africa and the Zambia, introduction of the Gene Xpert, an automated polymerase chain reaction (PCR) based method that rapidly identifies TB and drug resistant TB, has reduced work-up time, but concerns regarding cost for acquiring and maintaining this machine are real. The sensitivity of the Gene Xpert in detecting smear-positive culture-positive TB is 98 per cent, but sensitivity is just over 60 per cent for smear-negative cases that are later confirmed culture-positive (25–27). Operationally, this is troublesome, as national TB screening and treatment algorithms focus on smear positivity, and are likely to miss a significant proportion of patients with TB due to lack of culturing facilities. Smear negative TB cases contribute to transmission. Indeed,

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improved diagnostic modalities, such as IGRA, urinary lipoarabinomannan (LAM) and the nitrate reductase assay (NRA) may be useful, and must meet high standards for their expanded clinical use (28–32). In resource-poor settings, the MODS (microscopic observation drug susceptibility) assay has proven cost-effective and reliable in detecting TB and drug-resistant TB (33–35). In addition to these tools, simple techniques can be utilized to improve sensitivity of screening algorithms, including nebulization that increases detection by 17 per cent, use of auramine/fluorescence microscopy that increases detection of acid fast bacilli by 10 per cent and the practice of 'front loading' where two microscopic slides prepared from a single sputum sample can be done without loss of sensitivity and obviating the three early morning sputum samples rule (5, 6, 36–39).

The most significant impact on case finding and treatment of TB will be improved public health leadership and simplification of operational algorithms. Useful diagnostic tools already exist; newly developed tools are hardly as sensitive as conventional methods in detecting TB. And these tools should be expected to complement clinical acumen, not replace them.

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