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Empiric tuberculosis treatment in retreatment patients in high HIV/tuberculosis-burden settings

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Grant Theron and colleagues' Personal View¹ brings necessary attention to empiric tuberculosis treatment in high-burden settings. A bias towards overtreatment rather than undertreatment of tuberculosis is understandable in view of the high pretest probability and mortality attributable to tuberculosis in the setting of HIV co-morbidity (particularly in the preantiretroviral therapy era), coupled with a poorly sensitive test (Ziehl–Neelsen microscopy). Indeed, in individuals who are smear-negative, Xpert MTB/RIF has a negative predictive value of 93%² (vs 87% for all patients with suspected tuberculosis given a smear, with sensitivity of 40% and prevalence of 20%), leaving some doubt as to the true rule-out value for a single test. In this context, prescription of clinician behaviour within diagnostic randomised controlled trials can be ethically problematic.³ However, as countries increasingly achieve widespread antiretroviral coverage leading to true decreases in tuberculosis prevalence, burdens on health systems related to overdiagnosis of tuberculosis could increase .

Patients with history of previous tuberculosis treatment account for about 12% of global tuberculosis cases (nearly 700 000 people in 2012)⁴ and are notified from an even larger pool of patients with suspected drug-resistant tuberculosis, many of whom undergo several courses of tuberculosis treatment. From November, 2011, to November, 2013, we did a prospective observational study in Harare, Zimbabwe, incorporating Xpert MTB/RIF, microscopic observation drug susceptibility (MODS), solid (LJ) and liquid (MGIT) culture into the diagnostic assessment for people with suspected drug-resistant tuberculosis. Among symptomatic individuals registered as retreatment cases, 118 of 328 cases (36%) did not test positive for *Mycobacterium tuberculosis*, despite this extensive testing. Patients were, on average, aged 39 years (SD 11), 86 of 118 (73%) were HIV-infected, and 68 of 86 (79%) were enrolled in antiretroviral programmes. 50 of 118 individuals (42%) had been initiated on anti-tuberculosis medicines at least twice before, and, of those with chest radiographs, 39 of 53 (74%) had abnormalities consistent with previous infection, including bronchiectasis and atelectasis resulting from scarring or fibrosis. In high-HIV burden settings with low

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diagnostic capacity, retreatment of tuberculosis in the modern era represents a common pathway for individuals with chronic lung disease who remain symptomatic after repeated interactions with the public health system. In this group, empiric treatment exposes patients to drug toxicities and increased health-care costs without benefit, imposing unnecessary and potentially substantial costs on national tuberculosis programmes. Continued movement towards universal antiretroviral coverage and widespread access to sensitive diagnostic tests might ultimately regain the confidence of clinicians working in resource-constrained settings that when a test result is negative tuberculosis treatment can safely be withheld.

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