Comment
THELANCET-D-16-01621
S0140-6736(16)00699-1
Embargo: [add date when known]

Why are HIV-positive individuals still dying of tuberculosis?

Tuberculosis and HIV have been seen as intertwined since the earliest report of AIDS more than 30 years ago.[1] Despite the remarkable success of the expansion of access to antiretroviral therapy, deaths due to HIV-related tuberculosis remain common. WHO estimated the number of such deaths to be 0·4 million in 2014.[2] This number is not straightforward to estimate. The more clinicians test for tuberculosis in patients with advanced HIV, the more patients with tuberculosis they find.[3] Yet the introduction of more sensitive diagnostic tools has not reduced mortality.[4] For years pathologists have highlighted that many patients dying with HIV infection do so either from or with tuberculosis, and that the diagnosis of tuberculosis had often not been made ante-mortem.[5,6] Epidemiologists show that in adults found in random population samples from Africa and Asia with respiratory samples from which *Mycobacterium tuberculosis* can be cultured, a substantial proportion deny having any symptoms that would make a clinician consider a diagnosis of tuberculosis.[7,8] Pragmatists have therefore proposed that to reduce mortality, we should consider giving patients with advanced HIV infection empirical treatment for tuberculosis regardless of whether or not such a diagnosis can be confirmed.[9]

The REMEMBER study team report the first of three large randomised trials[10] to address the question of whether such empirical treatment can reduce mortality in those with advanced HIV infection. 850 individuals with advanced HIV (CD4 cell counts of <50 cells/μL) were randomly assigned (1:1) to either the empirical group (antiretroviral therapy and empirical tuberculosis therapy; n=424) or the isoniazid preventive therapy group (antiretroviral therapy and isoniazid preventive therapy; n=426). Although the study did not suggest a difference in the primary endpoint (mortality or unknown vital status after 6 months) with 22 events in each group (absolute risk difference –0·06% [95% CI –3·05 to 2·94]) of which only two were of unknown vital status, both in the empirical group, the low event rate limits the power of the study. The exclusion of participants with suspected but not confirmed tuberculosis excludes one group of patients who would be expected to benefit from the empirical treatment strategy.

A somewhat surprising observation was that, even during the 6 month treatment period, incident tuberculosis was diagnosed more commonly in the empirical treatment group than in those given isoniazid alone. However, this study is an open-label trial without strong diagnostic criteria, and therefore this observation must not be overinterpreted. A possible explanation for this finding is that adherence to the empirical treatment was likely to be lower than to the isoniazid treatment because of the higher pill burden and greater toxicity of pyrazinamide. Any lack of adherence would have reduced the power to show a benefit of empirical treatment.

Nonetheless, as the authors point out, the study could not suggest any additional benefit of empirical treatment for tuberculosis in patients in whom thorough screening had been done. By contrast, the study suggests that isoniazid preventive therapy is safe and well tolerated, even in the context of advanced HIV infection. Other studies[12] have also confirmed the clear benefit of isoniazid preventive therapy for HIV-positive individuals in Africa regardless of their CD4 cell count[11] and in addition to the benefits of antiretroviral therapy.[12]

A different and more pragmatic approach to empirical treatment was used in the TB Fast Track trial[13] presented at the 2016 Conference on Retroviruses and Opportunistic Infections. In this cluster-randomised trial, 24 primary care clinics in South Africa were randomly assigned to either a continued standard of care or to a nurse-led strategy that used a positive urine lateral flow assay for lipoaribinomannan, a haemoglobin concentration of less than 10 g/dL, or a body-mass index of less than 18·5 to categorise patients with HIV infection and less than 150 CD4 cells per mL into a high probability of tuberculosis group, in whom empirical treatment was started immediately, followed by antiretroviral therapy. Despite many more patients receiving empirical treatment in the fast track group of the study, no difference was reported in the primary endpoint of mortality (which was around twice as high as that found in the REMEMBER study). The authors of the TB Fast Track study noted that although patients in the intervention group started antituberculosis treatment quickly, a smaller proportion had started antiretroviral thearpy within 1 month of recruitment

than in the control group, possibly because of ongoing reluctance in primary care staff to initiate antiretroviral therapy in patients who had recently started antituberculosis treatment.

These large rigorous studies of empirical tuberculosis treatment did not support an effect on mortality in those with advanced HIV infection. Both studies highlight the ongoing tragedy of deaths associated with late presentation with advanced HIV disease. The solution is conceptually easy, has widespread political support, and has been advocated for many years, but clearly remains a challenge in many communities. We should remove the social, financial, and health and laboratory system barriers that prevent earlier diagnosis of HIV; we should offer antiretroviral therapy to all people with HIV long before their CD4 cell counts fall to the levels seen in the participants in these studies; and, as REMEMBER reminds us, we should screen all HIV-positive individuals for tuberculosis, with the best tools that we have available and, where there is no strong suspicion of tuberculosis, we should offer individuals isoniazid preventive therapy.

Peter Godfrey-Faussett, Helen Ayles
Office of the Deputy Executive Director, UNAIDS, Geneva, Switzerland (PG-F); ZAMBART, Lusaka, Zambia (HA); and Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK (PG-F, HA)
faussettp@unaids.org

PGF is Chair of the Data Safety Monitoring Board for the ANRS STATIS trial, also testing the effect of empirical tuberculosis treatment on mortality. The Data Safety Monitoring Board is independent of the investigators.

1 Pitchenik AE, Cole C, Russell BW, Fischl MA, Spira TJ, Snider DE Jr. Tuberculosis, atypical mycobacteriosis, and the acquired immunodeficiency syndrome among Haitian and non-Haitian patients in south Florida. *Ann Intern Med* 1984; **101:** 641–45.
2 WHO. Global Tuberculosis Report 2015. Geneva: WHO, 2015.
3 Lawn SD, Kranzer K, Edwards DJ, McNally M, Bekker LG, Wood R. Tuberculosis during the first year of antiretroviral therapy in a South African cohort using an intensive pretreatment screening strategy. *AIDS* 2010; **24:** 1323–28.
4 Churchyard GJ, Stevens WS, Mametja LD, et al. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. *Lancet Glob Health* 2015; **3:** e450–57.
5 Lucas SB, Hounnou A, Peacock C, et al. The mortality and pathology of HIV infection in a west African city. *AIDS* 1993; **7:** 1569–79.
6 Omar T, Variava E, Moroe E, Billioux A, et al. Undiagnosed TB in adults dying at home from natural causes in a high TB burden setting: a post-mortem study. *Int J Tuberc Lung Dis* 2015; **19:** 1320–25.
7 Ayles H, Muyoyeta M, Du Toit E, Schaap A, Floyd S, Simwinga M, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. *Lancet* 2013; **382:** 1183–94.
8 Jia Z, Cheng S, Ma Y, Zhang T, et al. Tuberculosis burden in China: a high prevalence of pulmonary tuberculosis in household contacts with and without symptoms. *BMC Infect Dis* 2014; **14:** 64.
9 Lawn SD, Ayles H, Egwaga S, et al. Potential utility of empirical tuberculosis treatment for HIV-infected patients with advanced immunodeficiency in high TB-HIV burden settings. *Int J Tuberc Lung Dis* 2011; **15:** 287–95.
10 Hosseinipour MC BG, Miyahara S, Sun X, et al. Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial. *Lancet* 2016; **387:** 1174–85.
11 Temprano ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med 2015; **373:** 808–22.
12 Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet* 2014; **384:** 682–90.
13 Grant A, Charalambous S, Tlali M, et al. Empirical TB treatment in advanced HIV disease: results of the TB Fast Track trial. Conference on Retroviruses and Opportunistic Infections; Boston, MA; Feb 22–25, 2016. 155.