

culture or Xpert test, both of which represent insufficiently robust reference standards. In a similar inpatient study population in Cape Town, South Africa,¹⁴ our results showed that the specificity of the same urine-LAM lateral-flow assay exceeded 99% when compared with a rigorous microbiological reference standard that incorporated sampling of sputum, blood, and urine, for which we did a mean of 5.6 reference standard tests per patient.

In summary, Peters and colleagues report findings from their landmark trial that provide key evidence showing that urine-LAM testing is an effective means of rapid, low-cost, ante-mortem diagnosis for the large burden of HIV-associated tuberculosis. This burden for the past 25 years has only been brought to light by a long series of post-mortem studies.⁴ With the recent backing of WHO recommendations, we strongly advocate that the Determine TB-LAM point-of-care assay should be implemented by national tuberculosis programmes in sub-Saharan Africa to reduce AIDS-related inpatient deaths.

*Andrew D Kerkhoff, Stephen D Lawn

Department of Medicine, University of California San Francisco School of Medicine, San Francisco, CA 94143, USA (ADK); Department of Global Health, Academic Medical Center, Amsterdam Institute for Global Health and Development, University of Amsterdam, Amsterdam, Netherlands (ADK); Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK (SDL); and The Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa (ADK, SDL) andrew.kerkhoff@ucsf.edu

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Why are people living with HIV 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

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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 trials¹⁰ 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 per 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 have also confirmed the clear benefit of isoniazid preventive therapy for HIV-positive individuals in Africa regardless of their CD4 cell count¹¹ 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 trial¹³ 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 lipoarabinomannan, a haemoglobin concentration of less than 10 g/dL, or a body-mass index of less than 18.5 kg/m² 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 study¹³ noted that although patients in the intervention group started antituberculosis treatment quickly, a smaller proportion had started antiretroviral therapy within 1 month of recruitment than in the control group, possibly because of ongoing reluctance among 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 WC1E 7HT, UK (PG-F, HA) faussettp@unaids.org

PG-F 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.

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Sustainable development and global mental health—a *Lancet* Commission



In 2007, *The Lancet* published a groundbreaking Series on global mental health that ended with a call to action to scale up services for people with mental health problems guided by the twin principles of the right to evidence-based care and the right to dignity.¹ This Series helped catalyse a movement that has raised the profile of mental health in public policies and promoted research, capacity building, and delivery of mental health care worldwide. The Series also influenced the launch of the Grand Challenges in Global Mental Health,² which, in turn, inspired substantial funding commitments. These investments led to a flourishing

of innovative approaches to implementation of mental health interventions,³ some of which were included in a second *Lancet* Series in 2011.

The knowledge generated by these initiatives has shown that many mental health problems can be prevented and treated effectively, that a range of best practice interventions can be implemented across a range of population, community, and health-care delivery platforms in low-resource settings, and that public financing of scaling up is affordable and increases financial protection for individuals and families affected by mental disorders.⁴

For the 2007 *Lancet* Series on global mental health see <http://www.thelancet.com/series/global-mental-health>

For the 2011 *Lancet* Series on global mental health see <http://www.thelancet.com/series/global-mental-health-2011>