Empirical tuberculosis treatment or improved diagnostics?

We read the article by Lawn and colleagues[1] with great interest. Atypical presentation and limited diagnostic capability in resource-limited settings lead to delays in treatment that could contribute to high rates of antiretroviral therapy (ART) associated TB.[2] To address the potential role of empiric TB treatment in immunosuppressed patients first presenting for care, we proposed the 'Prevention of early mortality by presumptive TB treatment in HIV-infected patients initiating antiretroviral therapy' (PROMPT) study, which was funded by the European Developing Country Clinical Trials Programme (EDCTP) in October 2010. We have started enrolling 334 patients from four geographically diverse countries (Gabon, Mozambique, South Africa and Uganda) in a randomised open label clinical trial targeting a population of people with high mortality risk: patients with CD4 T-cell count $<$ 50 cells/μl and body mass index (BMI) $<$ 18 kg/m^2.

Severely immunocompromised patients with low BMI in the intervention arm will receive presumptive four-drug anti-tuberculosis chemotherapy and subsequently initiate ART within 2 weeks, compared to ART alone in the control arm. Patients with previously treated TB will be excluded, and all enrolled patients will receive a screening TB smear and culture. Patients whose baseline culture becomes positive and who are not randomised to receive anti-tuberculosis treatment will then be treated.

The main objective is to measure early mortality in the group presumptively treated for TB in addition to ART compared to those receiving ART only. Other sub-objectives are to determine the predictors of early mortality and the causes of death by autopsy, to determine if presumptive anti-tuberculosis treatment affects viral suppression with ART, and to assess drug toxicity in dually treated patients. The trial is anticipated to be completed by June 2013. Because of the high rates of TB co-infection in sub-Saharan Africa in the HIV-infected, we hypothesise that patients presumptively treated for TB in addition to ART will have a lower mortality rate than patients receiving ART only. The trial has been registered at www.clinicaltrials.gov.

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In reply

Between 8% and 26% of patients enrolling in antiretroviral treatment (ART) services in sub-Saharan Africa die within the first year of therapy, and the majority of these deaths occur within the first few months.[1] Tuberculosis (TB) is the leading cause and yet much disease remains undiagnosed.[2] In this regard, we thank Manabe and colleagues for their letter regarding the randomised controlled trial (PROMPT), which aims to determine whether empirical TB treatment reduces mortality risk in HIV-infected patients in sub-Saharan Africa with extremely advanced immunodeficiency but in whom there is no overt evidence of TB. Such a strategy has long been discussed, and it is good that this hypothesis will finally be addressed.

Absolutely central to the rationale for this strategy is the poor performance of the current diagnostic tests for HIV-associated TB that are most widely used in sub-Saharan Africa.[2,3] The need for an empirical TB treatment strategy trial is therefore an overt admission of the woeful inadequacy of these tools, typically sputum smear microscopy and chest radiology. Times are changing, however, and recent progress in the field of TB diagnostics is encouraging. In Cape Town, South Africa, two new diagnostic assays have recently been evaluated for systematic screening of all HIV-infected patients (regardless of symptoms) for TB prior to starting ART.[4,5]

The first of these, the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), has been endorsed by the World Health Organization as a replacement for sputum smear microscopy, especially for use in high HIV prevalence settings. This assay has a sensitivity for smear-positive TB of 99–100%, 57–83% for sputum smear-negative TB and 53–95% for extrapulmonary TB.[6] When used for pre-ART screening in the Cape Town study, the overall sensitivity of Xpert MTB/RIF for culture-confirmed pulmonary TB among those with a CD4 cell count $<$ 50 cells/μl was 72% using a single assay cartridge compared to 33% with sputum microscopy.[4,5] While this rapid molecular assay is a major step forward, it is nevertheless currently regarded as unaffordable and not yet ready to be included in routine diagnostic operations in district level health facilities in most countries in sub-Saharan Africa.

A more recent development is the first true point-of-care assay for HIV-associated TB. The Determine TB-LAM Ag test (Alere, Waltham, MA, USA) is a simple, lateral flow assay (dip-stick type test) that detects the mycobacterial antigen lipoarabinomannan (LAM) in urine samples from patients with advanced

immunodeficiency. This provides a highly specific diagnosis of TB within 30 minutes at the point of care in the clinic or bedside.[5] A key observation is that the lower the blood CD4 cell count, the greater the sensitivity of the assay, probably reflecting the increasing risk of disseminated TB with progressive immunodeficiency. Among those with blood CD4 cell counts of <50 cells/μl and culture-confirmed TB, the sensitivity of the LAM point-of-care test was 67%.[5] When the results of the LAM test and smear microscopy were combined (either test positive), sensitivity increased marginally to 72% (identical to that of a single Xpert MTB/RIF assay). Thus, the LAM assay is a low-cost alternative that has potential utility among the very sickest patients who have highest mortality risk and in whom a rapid point-of-care diagnosis is most urgently needed.

Does the development of these new diagnostic assays render the strategy of empirical TB treatment redundant? The answer is that we don't know. What is clear, though, is that even when such patients are screened for TB by testing two sputum samples using automated liquid culture (the highest sensitivity diagnostic assay), there is still a substantial, albeit reduced, rate of new TB presentations thereafter.[7] These cases represent either prevalent disease that was missed by culture or new incident TB arising from reactivation of latent disease or recent exogenous exposure. Each of these possibilities would potentially be addressed by a course of empirical therapy started at baseline. Moreover, additional benefits may arise from the activity of rifampicin against gram-positive organisms such as *Streptococcus pneumoniae*, which is a very common pathogen in patients with advanced HIV even in the context of antibiotic prophylaxis.[3] We therefore conclude that a range of different trials is needed to determine how new diagnostic tools and various treatment strategies (empirical or targeted) can best be used to reduce the huge mortality toll that is caused by HIV-associated TB.

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Interferon-gamma release assay T-SPOT®.*TB* and HIV-related tuberculosis

Interferon-gamma release assays (IGRAs) are in vitro diagnostic tests for the detection of *Mycobacterium tuberculosis* infection.[1] There are limited data, however, on the efficacy of IGRAs in the patient population with HIV/AIDS (human immunodeficiency virus/acquired immune-deficiency syndrome). Furthermore, few studies have evaluated the T-SPOT®.*TB* assay (T-Spot) in HIV-positive individuals with culture-confirmed tuberculosis (TB). We therefore aimed to evaluate the performance of T-Spot among TB patients, post-TB subjects and TB-free subjects with HIV/AIDS.

From September 2007 to May 2008, 34 subjects with HIV/AIDS were evaluated with T-Spot: 9 with active TB (Group 1), 11 with previously treated TB (Group 2), and 14 without positive cultures for TB, including 2 with latent tuberculosis infection (LTBI) and 12 TB suspects (9 with cultures positive for non-tuberculous mycobacteria [NTM]). Patients' CD4 T-cell counts ranged from 23 to 792 (7.6–39%). The study population had a mean age of 43 years (range 24–62). Males represented 86% and females 14% of the patients. The ethnic composition was 64% Hispanic, 17% African American, 14% Asian Pacific Islander, and 5% white (born in the United States).

Whole venous blood was drawn into two 8 ml CPT tubes. The T-Spot assay was performed on peripheral blood mononuclear cells according to the manufacturer's instructions (http://www.oxfordimmunotec.com).

T-Spot was positive in all patients (9/9) with active