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EDITORIAL COMMENTARY

Diagnosing Tuberculosis in People With Advanced Human Immunodeficiency Virus: More Is Needed

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(See the Major Article by Matoga et al on pages e870–7.)

Despite tremendous advances in human immunodeficiency virus (HIV) prevention, treatment, and care in the past 30 years, people living with HIV (PLHIV) who have advanced immunosuppression remain at an unacceptably high risk of death. Tuberculosis (TB) is the leading cause of death in PHIV and is especially prevalent and deadly in people with low CD4 cell counts. Suboptimal TB diagnostics contribute substantially to the problem. As three randomized trials (Reducing Early Mortality and Morbidity by Empiric TB Treatment [REMEMBER] [1], TB Fast Track [2], and Systematic or Test Guided Treatment for Tuberculosis in HIV-infected Adults [STATIS] [3]) have shown no benefit from empiric TB treatment, there is an urgent need to refocus on how to optimize and intensify TB screening in order to reduce deaths.

Advanced HIV (defined by World Health Organization [WHO] as a CD4 cell count <200 cells/mm^3) [4] is a persistent problem despite substantial improvements in coverage of antiretroviral therapy (ART). For example, in South Africa, national laboratory data show that one-third of PLHIV entered HIV care with advanced HIV [5]. Advanced HIV carries an extremely high mortality; for instance, 25% of people in the STATIS trial, which recruited people starting ART with CD4 cell counts of less than 100 cells/mm^3, had died by 24 weeks. A minimally invasive autopsy study from the TB Fast Track trial, which recruited people with advanced HIV starting ART, showed that TB was the leading cause of death and that TB diagnosis was often missed antemortem [6]. This finding—that TB is a common cause of death in PLHIV and often undiagnosed—is in keeping with other autopsy studies and has not substantially changed over the last decade [7]. Empiric TB treatment seemed like an attractive solution to high TB-related mortality and difficulty in discriminating between who has TB disease and who does not. But, since REMEMBER, TB Fast Track and STATIS have conclusively shown that empiric TB treatment does not reduce mortality when compared with intensive TB screening and TB preventative therapy (TPT), it is imperative to find better ways to diagnose TB, or at least to risk-stratify those at highest risk of TB and most likely to benefit from treatment.

In this issue of *Clinical Infectious Diseases*, Matoga and colleagues [8] report results of a secondary study from the REMEMBER trial, retrospectively testing stored urine for lipoarabinomannan (LAM) among outpatients starting ART with CD4 counts less than 50 cells/mm^3. LAM is a mycobacterial cell-wall component and can be detected in urine of some people with TB. Simple to use lateral flow tests can detect LAM, and urine LAM testing has been shown to reduce deaths in 2 trials of hospitalized PLHIV. Urine LAM is relatively specific for TB disease but is suboptimally sensitive, and therefore needs to be combined with other TB diagnostics. The population in Matoga and colleagues' study was not representative of the general population of immunosuppressed PLHIV starting ART; participants with confirmed TB, probable TB, or who were suspected to have TB after screening with sputum testing and chest X-ray were excluded. Their main finding is that, despite low clinical suspicion of TB, there was a 5% incremental yield in people with TB diagnosed from urine LAM testing, where TB would otherwise have been missed. In the study, there was a marked imbalance in LAM positivity by randomized trial arm assignment, with 21 of the people with positive LAM in the empiric TB treatment group and only 7 in the TPT group.

Given that those with clinical evidence of TB disease were excluded in Matoga and colleagues' study, those people with positive urine LAM tests would have had subclinical, or at least pauci-symptomatic, TB. Pauci-symptomatic and subclinical TB are increasingly recognized as being common and important both epidemiologically for TB transmission and for individual outcomes [9]. It is not surprising that intensifying testing by using urine LAM detected more TB, although it adds a further

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strand of evidence to the autopsy data demonstrating how current symptom- and sputum-based TB screening approaches may be inadequate.

One of the key questions from this study is the clinical significance of the positive urine LAM tests, including the possibility of "false positives." Answering this question is not straightforward, as most people with a positive LAM test from Matoga and colleagues' study were randomly assigned to receive empiric TB treatment and the others received TPT with 6 months of isoniazid. The small numbers mean that it is difficult to interpret the finding that only 5 of these 28 people with positive LAM developed clinically overt TB disease over 6 months, and all were on empiric TB treatment. Details of the timing of TB symptoms in relation to TB treatment or ART initiation or the results of other TB diagnostic tests are not presented. There was no ART-only arm in REMEMBER, so it is not possible to draw any inference about the likely outcomes in a "subclinical" LAM-positive population with either quadruple-drug TB therapy or TPT. With regard to whether some urine LAM results were false positive, we know it is notoriously difficult to define a reference standard against which to evaluate TB diagnostics, including AlereLAM Alere/Abbott (Chicago USA) [10]. Second, AlereLAM lateral flow tests can sometimes be difficult to interpret as a negative test with a faint line can be misinterpreted as positive, even when using the manufacturer's reference card. Third, the population in this study had a relatively low pre-test probability of TB, decreasing the positive-predictive value. Fourth, urine LAM can be positive in nontuberculous mycobacterial (NTM) infection [11]. However, even with those caveats, false positives from urine LAM are relatively rare and unlikely to account for many of the LAM-positive patients not developing symptomatic TB in this study [12].

Current evidence, supported by WHO guidance and by this study, is that PLHIV should be screened for TB, particularly when they first present (or re-present) to health services. Existing diagnostic tools, including lateral flow urine LAM testing, should be used to maximize chances of TB detection, including in asymptomatic or pauci-symptomatic people with advanced immunosuppression. Tuberculosis screening in people starting ART is not a "one-off" activity and should be repeated at every clinic visit, particularly being aware of risks of unmasking TB immune reconstitution inflammatory syndrome (IRIS) around the time of ART start. However, there remains a pressing need to improve TB diagnostic strategies for PLHIV with advanced immunosuppression. There are new TB diagnostics tests on the horizon that might hold promise, particularly Fujifilm SILVAMP LAM, which appears more sensitive than the existing AlereLAM assay [13]. There is also an important role of increasing access to TB-preventive therapy, which has had sluggish uptake by national HIV programs. Advanced HIV remains too common and too deadly, although in recent years there is a welcome concerted effort being applied to find evidence-based ways to reduce deaths. The REALITY trial [14] showed that a package of prophylaxis reduced deaths, and in 2017, the WHO produced the first set of guidelines for managing advanced HIV in a public health approach to help guide national HIV programs. Developing interventions to reduce deaths among those with advanced HIV should be a priority, especially through improving TB diagnostic tools and strategies.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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