Diagnosing tuberculosis in people with advanced HIV: more is needed

Rachael M Burke (1)(2)

Ankur Gupta Wright (1)(3)

(1) Clinical Research Department, Faculty of Infectious and Tropical Disease, London School of Hygiene and Tropical Medicine, Keppel Street, London.
(2) Malawi Liverpool Wellcome Clinical Research Programme, Queen Elizabeth Central Hospital, Blantyre, Malawi.
(3) Institute for Global Health, University College London, Mortimer Market off Caper Street, London, UK

Correspondence to:

Dr Rachael Burke,

Malawi Liverpool Wellcome Clinical Research Programme,

Queen Elizabeth Central Hospital,

Chipatala Avenue. Blantyre, Malawi.

Rachael.burke@lshtm.ac.uk

Despite tremendous advances in HIV prevention, treatment and care in the past thirty 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 people living with HIV and is especially prevalent and deadly in people with low CD4 cell counts. Suboptimal TB diagnostics contribute substantially to the problem. As three randomised trials (REMEMBER,[1] TB Fast Track,[2] and STATIS [3]) have shown no benefit from empiric TB treatment, there is an urgent need to refocus on how to optimise 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. For example, in South Africa, national laboratory data show one-third 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 antiretroviral therapy (ART) with CD4 cell counts <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 ante-mortem.[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 to 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 report results of a secondary study from the REMEMBER trial, retrospectively testing stored urine for lipoarabinomannan (LAM) among outpatients starting ART with CD4 count <50 cells/mm^3. [reference] 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 two trials of hospitalised PLHIV. Urine LAM is relatively specific for TB disease but is sub-optimally 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, probable 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 randomised trial arm assignment, with twenty-one of the people with positive LAM in the empiric TB treatment group and only seven in the TB preventative therapy (TPT) group.

Given 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 paucisymptomatic TB. Paucisymptomatic and subclinical TB are increasingly recognised as being common and important both epidemiologically for TB transmission and for individual outcomes[8]. It's not surprising that intensifying testing by using urine LAM detected more TB, although it adds a further 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 six months of isoniazid. The small numbers mean it's difficult to interpret the finding that only five of these twenty-eight people with positive LAM developed clinically overt TB disease over six 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's not possible to draw any inference about the likely outcomes in a 'subclinical' LAM-positive population with neither quadruple drug TB therapy or TPT. Regarding 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.[9] Secondly, AlereLAM lateral flow tests can sometimes be difficult to interpret as a negative test with a faint line can be misinterpreted positive, even when using the manufacturer's reference card. Thirdly, the population in this study had a relatively low pre-test probability of TB, decreasing the positive predictive value. Fourthly, urine LAM can be positive in non-tuberculous mycobacterial (NTM) infection.[10] 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.[11]

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 maximise chances of TB detection, including in asymptomatic or paucisymptomatic people with advanced immunosupression. TB 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 existing AlereLAM assay.[12] There is also an important role of increasing access to TB preventative therapy, which has had sluggish uptake by national HIV programmes. 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 [13] showed that a package of prophylaxis reduced deaths, and in 2017 WHO produced the first set of guidelines for managing advanced HIV in a public health approach to help guide National HIV Programmes. Developing interventions to reduce deaths among those with advanced HIV should be a priority, especially through improving TB diagnostic tools and strategies.

Conflict of interest: We declare no conflicts of interest.

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