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Tuberculosis diagnostics to reduce HIV-associated mortality

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ABSTRACT

Tuberculosis (TB) was declared a global emergency in 1993 by the World health Organization (WHO), with global and African regional TB incidence rates driven by the HIV epidemic. Much of this burden lay in health facilities in sub-Saharan Africa, with post-mortem studies showing almost half of fatal TB goes undiagnosed, reflecting a failure in the approach to TB diagnostics. HIV-associated TB is often under the clinical radar, and this paper describes strategies to improve TB diagnostics to expedite treatment, reduce the amount of undiagnosed disease and ultimately reduce mortality. Through studies assessing the diagnostic accuracy and yield of new, rapid TB diagnostics, including the Xpert MTB/RIF nucleic acid amplification and urinary lipoarabinomannan (LAM) lateral flow assays, and clinical trials to measure impact on mortality and clinically relevant outcomes, this paper describes how TB diagnostics can reduce HIV-associated morbidity and mortality. With improved TB diagnostics in the pipeline, the future of urine-LAM assays for TB are also discussed.

Introduction

The HIV-associated TB epidemic

Tuberculosis (TB) was declared a global emergency by the World health Organization (WHO) in 1993 as global and African regional TB incidence rates began to increase rapidly (WHO Global Tuberculosis Programme, 1994). This was being driven almost entirely by the HIV epidemic, as at an individual level HIV substantially increases risk of TB disease, accelerates progression and increases mortality due to the importance of CD4 + T-cells in the host immune response to TB (Lawn and Zumla, 2011). However, HIV and TB also interact at a population level, for example through delayed diagnosis, longer infectiousness, overcrowding and transmission in healthcare settings (Mukadi et al., 2001). HIV-associated TB is also more difficult to diagnose owing to atypical presentation, paucibacillary nature of the disease and common extrapulmonary involvement and dissemination.

This increase in TB incidence continued until the early 2000s, but has been slowly declining since due to public health interventions such as scaling up of antiretroviral therapy (ART) in sub-Saharan Africa (SSA), which reduces TB incidence by reducing time spent with low CD4 counts (Fig. 1) (Lawn et al., 2009; Gupta et al., 2012). However, even in 2015 HIV-associated TB was still responsible for one in four TB deaths and one in three HIV deaths globally (TB report 2016) (World Health Organization, 2016). Much of this burden lay in health facilities in sub-Saharan Africa. Observational studies from SSA suggested up to one-third of hospital admissions and deaths in HIV-positive patients were due to TB (Ford et al., 2016). Even more worryingly, post-mortem studies from 1993 to 2013 showed that TB caused between one- and two-thirds of HIV-positive deaths, most was TB disseminated beyond the lungs, and almost half was undiagnosed at the time of death (Rishi et al., 2015).

Failure of TB diagnostic approach and its implications

Diagnosis is becoming increasingly recognised as important gap in the TB care cascade, both patients reaching diagnostic centres and then subsequently being diagnosed with TB (Subbaraman et al., 2016). Data from autopsy studies, supported by observational data from cohorts of patients with HIV admitted to hospital, confirmed the approach to diagnosing TB in advanced HIV is failing. Even when people living with HIV (PLHIV) overcome logistical, social and economic barriers and present to healthcare facilities, they have a very high risk of dying (Gupta et al., 2013; Lawn et al., 2005). It became clear that undiagnosed TB is likely to be contributing to high mortality, and better diagnostics have the potential to reduce mortality by expediting TB treatment and reducing the proportion of patients with undiagnosed TB.

Three new strategies for improving diagnosis were considered as potentially having an impact on patient outcomes. Firstly, there is a need to screen all PLHIV for TB. Diagnostic testing is usually driven by whether clinicians suspect TB (World Health Organization, 2007). Given the non-specific clinical presentations of HIV-associated TB, relying on clinical judgement alone to drive TB testing will lead to missing patients with TB. Whilst TB prevalence is clearly linked to CD4 count, prevalence in those with higher CD4 counts is enough to warrant screening in high-risk groups, for example ART-naïve PLHIV, or hospital inpatients (World Health Organisation, 2008; Lawn et al., 2009). Secondly, new diagnostic assays are needed. Mycobacterial culture is too slow (taking many weeks) and too expense (needing significant laboratory infrastructure), and therefore just not widely available in high-burden, low resourced settings. Sputum smear microscopy, although widely available, is not sensitive enough in PLHIV. New rapid, sensitive and affordable diagnostics that could be easily implemented are needed. Lastly, diagnostics need to use non-sputum based samples. Sputum is a difficult sample to obtain in unwell PLHIV, and extrapulmonary and/or

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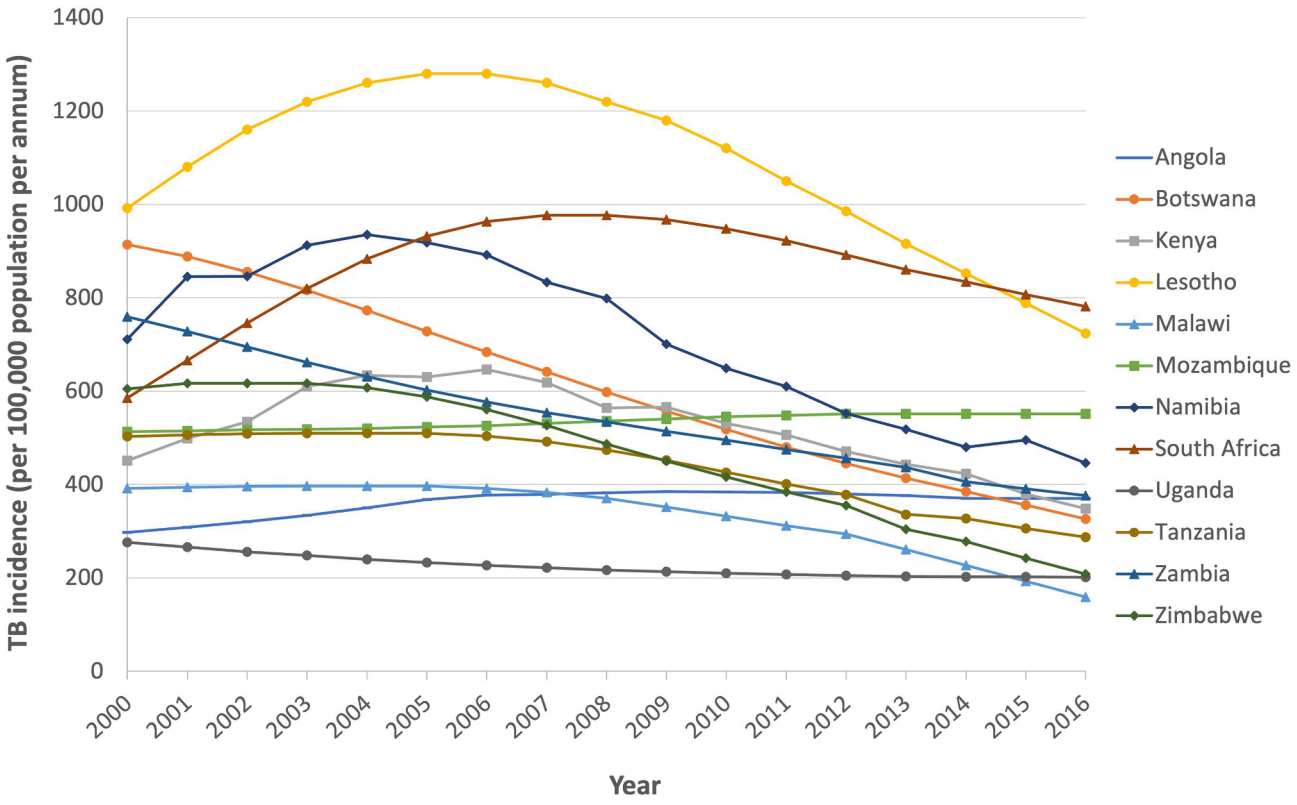

Fig. 1. World Health Organization estimated TB incidence rates in 12 Southern and Eastern African countries from 2000 to 2016, showing only a slow decline in incidence in most countries. Data is from the Global Tuberculosis Report 2017. (World Health Organization. Global tuberculosis report, 2017).

disseminated disease is common making sputum-based tests less useful for diagnosing HIV-associated TB (Lawn et al., 2015).

New, rapid diagnostics for HIV-associated TB

Two assays became available that potentially met these goals. Firstly, the Xpert MTB/RIF assay (Cepheid, CA USA, Xpert), which is a semi-automated, real-time polymerase chain reaction (PCR) was endorsed by WHO in 2010 (World Health Organization, 2013). It is easy relatively easy to perform, and does not require a full molecular laboratory or containment level (CL) 3 facilities. In brief, sputum samples are mixed with sample reagent (which liquifies and inactivates), transferred to the cartridge and loaded into the GeneXpert platform. Results are available in approximately 2 h, and probes targeting the *RpoB* gene also give information about rifampicin resistance. Early data indicated good sensitivity, even in patients with smear-negative, culture-positive TB (Boehme et al., 2010). Clinical studies in PLHIV presenting for ART showed a two-fold increase in diagnostic yield compared to sputum smear microscopy on two samples (Cox et al., 2014; Lawn et al., 2011). However, Xpert is not truly 'point-of-care', and requires a consistent electricity supply, stable room temperature and access to engineers for servicing and maintenance.

Urine-based diagnostics also became of interest as urine is much more easily obtained than sputum. TB can be diagnosed from urine by detection of the mycobacterial cell wall glycolipid, lipoarabinomannan (LAM), which is a major constituent of the *Mycobacterium tuberculosis* (*Mtb*) cell wall. It was first noted that LAM could be detected in urine of patients with TB in early 2000 s with extensive sample processing (Hamasur et al., 2001; Tessema et al., 2002). However, commercial LAM ELISA assays found poor sensitivity (6–21%) using urine samples (Minion et al., 2011). A key observation is that sensitivity was greater in PLHIV, and it was very strongly related to CD4 cell count. Clinical studies found moderate to good sensitivity in advanced HIV (56–85%) (Shah et al., 2014). Importantly, urine LAM testing provided significant incremental diagnostic yield when combined with sputum testing (Lawn et al., 2014). Another important development was the Determine TB-LAM Ag (TB-LAM) assay, a simple lateral flow assay that could be used as a point-of-care test (Lawn et al., 2012). Testing small amounts of urine using the Xpert MTB/RIF assay in PLHIV also showed good diagnostic yield in PLHIV with low CD4 cell counts (Peter et al., 2012; Lawn et al., 2012). Overall, evidence suggested that in advanced HIV, urine diagnostic approached were detecting renal TB secondary to haematogenous dissemination.

Rapid microbiological screening for TB in HIV-positive inpatients

The Xpert MTB/RIF and Determine TB-LAM assays, and sampling urine in addition to sputum showed potential to improve diagnosis of HIV-associated TB. To develop an accurate, high yield TB screening strategy that could give results within 24–48 h of admission, a prospective observational study was undertaken in HIV-positive inpatients in South Africa (Lawn et al., 2015; Lawn et al., 2017). It used the most rigorous reference standard possible (culture and Xpert MTB/RIF of multiple sputum, blood, urine and other appropriate clinical specimens) to describe TB prevalence and assess the yield of different diagnostic tests and samples.

Collecting a mean of four samples per patient, the study found a TB prevalence of 33% among unselected HIV-positive patients admitted to hospital, with 13% of patients without TB symptoms, and 18% of patients in whom TB was not suspected at admission having microbiologically confirmed TB. Most (83%) TB was extrapulmonary, and sputum samples could only be produced by 38% of inpatients. The optimal diagnostic strategy appeared to be Xpert testing of sputum, urine LAM testing and urine Xpert testing, which diagnosed > 80% of prevalent TB within one day of admission, a three-fold increase from the strategy of sputum testing alone. The study concluded that combining

urine testing with sputum testing using Xpert provides major incremental yield in TB diagnosis with very high specificity. This strategy showed promise for reducing mortality, but it remained unclear if rapid early diagnosis could actually impact outcomes.

The rapid urine-based screening for TB to reduce AIDS-related mortality in hospitalised patients (STAMP) trial

A clinical trial was deemed necessary to assess the impact of urine-based diagnostic prior to advocating for implementation, as there are potential disadvantages to new diagnostics above and beyond cost and resources (Gupta-Wright et al., 2016). It was unclear if the impact of higher diagnostic yield in observational studies would be mitigated by 'empirical' TB treatment, or if patients presenting to hospital have such advanced disease that earlier diagnosis and treatment will not improve outcomes. The STAMP trial was designed to assess the impact of TB screening using urine-based rapid diagnostic tests on mortality in HIV-positive patients admitted to hospital. Trial design was key, as previous clinical trials assessing sputum Xpert had failed to show any significant impacts on clinical outcomes (Auld et al., 2016).

The STAMP trial recruited 2,600 patients across two sites in Malawi and South Africa (Gupta-Wright et al., 2018). Importantly, consecutive

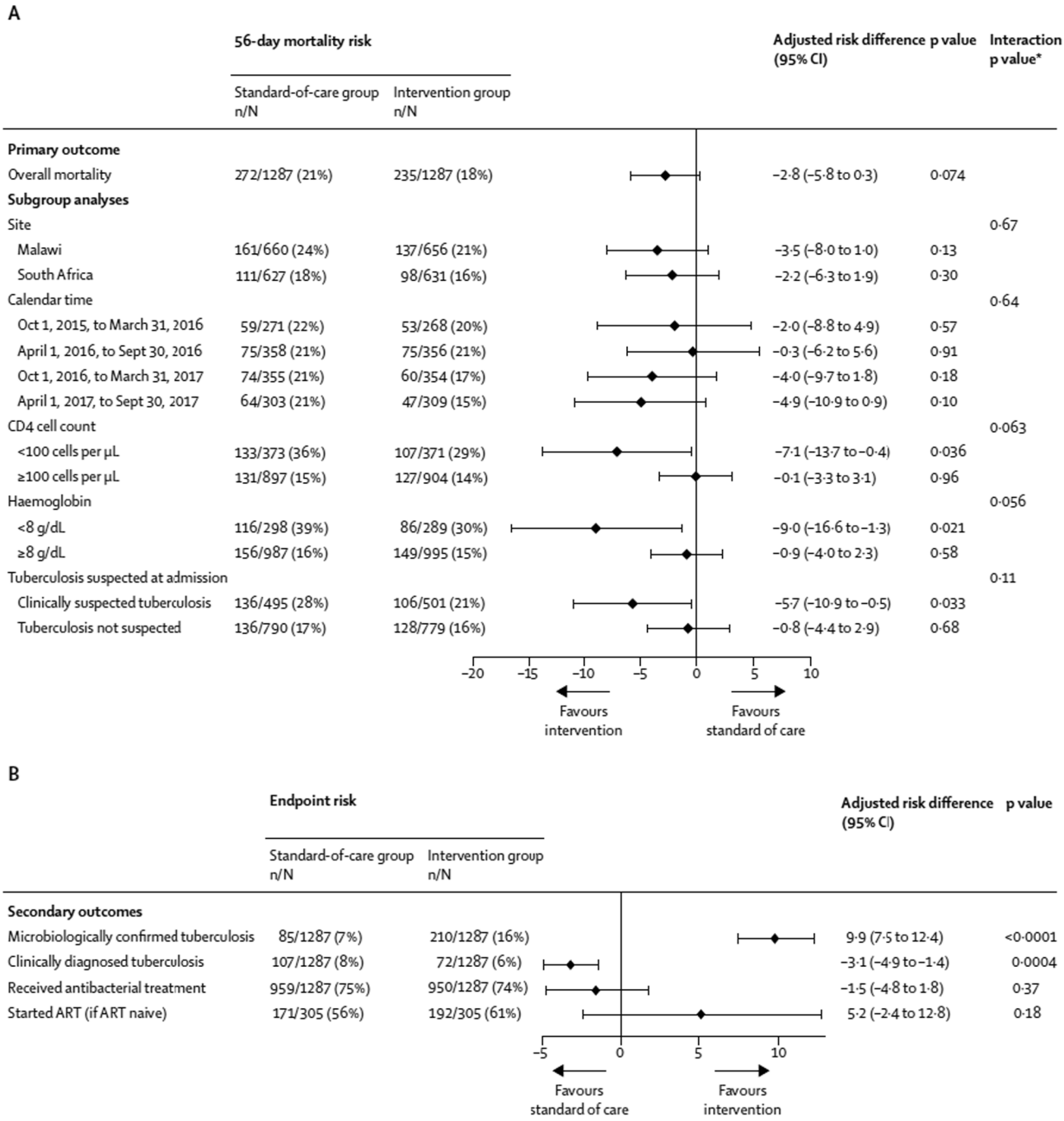

Fig. 2. Primary outcome and predefined subgroup analyses (A), and secondary outcomes (B) from the STAMP trial. All analyses are adjusted for study site. (A) The primary outcome is mortality at 56 days after randomisation. Risk differences are the risk in the intervention group minus the risk in the standard-of-care group. (B) Secondary outcomes are measured at the end of hospital admission except for those who started ART, which is measured at 56 days. Antibacterial treatment excludes anti-TB medications. ART = antiretroviral therapy. *Interaction between study group and subgroup. Reproduced from Gupta-Wright et al. (Gupta-Wright et al., 2018).

patients, irrespective of TB symptoms or reason for presentation to hospital, were recruited. Patients already taking, or recently taking TB treatment or TB preventative treatment were excluded, as were those unable to consent. Eligible, consenting patients were individually randomised to TB screening with sputum Xpert alone (standard of care arm, SOC) or sputum Xpert and urine testing with TB-LAM and Xpert (intervention arm). The screening tests were performed by the study team, and the results reported back to clinicians in real-time, with clinicians making decisions about TB treatment and other management (without involvement of the study team). Clinicians and the study team (except the lab technician performing the tests) were blinded to study arm to reduce bias and changes to empirical TB treatment by clinicians. Results were reported as 'TB screening test' positive or negative.

The trial analysed 2,574 patients in the intention-to-treat analysis, recruited between October 2015 and October September 2017 (Gupta-Wright et al., 2018). Overall, 18% (n = 474) of patients were diagnosed with TB. Urine-based screening substantially increased TB diagnosis and microbiologically confirmed TB by 7.3% and 9.9% respectively. Mortality at 2-months was 21% in the SOC arm, and 18% in the intervention arm, with an absolute risk reduction of 2.8% (p = 0.07). In pre-planned subgroup analyses, urine-based screening significantly reduced mortality in sicker patient groups; baseline CD4 counts < 100 cells/μL, severe anaemia and clinically suspected TB (absolute risk reduction 7.1%, 9.0% and 5.7% respectively, Fig. 2). Urine-based screening led to a survival benefit in sicker patients, and a broader benefit in terms of reducing discharge with undiagnosed and untreated TB. Another multi-centre clinical trial undertaken at a similar time across four countries in sub-Saharan Africa found a similar reduction in mortality from testing patients using the TB-LAM assay, although that trial only recruited patients clinically suspected to have TB (Peter et al., 2016). Cost-effectiveness analyses of the STAMP study intervention suggested adding urine LAM screening to sputum Xpert would be cost-effective within a 2-year horizon, affordable and improve patient outcomes (Reddy et al., 2018).

Urine-LAM testing – What is the future?

Both clinical trials assessing urine LAM testing in hospital inpatients, along with observational studies in outpatients and cost-effectiveness analyses led to definitive guidance from WHO in 2019 (World Health Organization, 2019; World Health Organization, 2015). It recommended urine LAM testing in HIV-positive inpatients with signs and symptoms of TB, those who are seriously unwell (based on WHO danger signs), and those with advanced HIV or CD4 cell counts < 200 cells/μL. It was also recommended in ambulatory PLHIV outpatients with signs and symptoms of TB or CD4 cell counts < 100 cells/μL. Despite these guidelines, the strong evidence base, and adoption by several high HIV/TB burden countries into national policy, urine LAM testing remains poorly implemented (Singhroy et al., 2020). Barriers include costs, and incorporating tests within budgets and workflows, administrative and logistical hurdles and clinicians and test-users being unfamiliar with the test. Further implementation science and operational research to optimise impact is needed (Gupta-Wright and Manabe, 2019).

Urine LAM testing also seems to provide prognostic as well as diagnostic benefit (Kerkhoff et al., 2014) Several studies have demonstrated higher mortality in PLHIV diagnosed with TB who have positive urine LAM tests, and this increased mortality risk appears to be independent of CD4 cell count and other risk factors for dying (Gupta-Wright et al., 2016). A 2016 *meta*-analysis suggested a two-fold increased risk of death if those with positive urine LAM tests overall, and an even higher risk in outpatients (Gupta-Wright et al., 2016). As urine LAM is implemented for diagnosis in hospitals, patients with detectable urine LAM (and/or other high-risk factors) could be targeted for additional care in view of their increased risk of mortality (Gupta-Wright et al., 20200).

Multivariable predictive modelling using data from the STAMP trial identified six variables, including urine LAM results (Fig. 3), included in a pragmatic mortality risk score (Gupta-Wright et al., 2019). The score was able to identify a group with a very high mortality risk (46% by 2-months, 6-fold increased odds of death compared to patients with a low score). The score was also validated in a completely independent dataset, with similar performance. Such scores show potential to identify patients who could benefit from enhanced clinical care and follow-up, and as a research tool for assessing new interventional strategies. For example, it could be delivered at admission for patients diagnosed with TB, or used alongside urine LAM to recruit high risk patients into clinical trials of adjunctive therapies.

One limitation of urine LAM testing is the sensitivity, which is moderate at best (Shah et al., 2016). Since clinical trial of the TB-LAM assay, several groups have worked on newer LAM assays with a lower limit of detection. This could be done by sample preparation steps which concentrate LAM antigen, or steps to remove inhibitors in urine (Paris et al., 2017; Wood et al., 2019; Hamasur et al., 2001; Connelly et al., 2021). However, these assays have general mycobacterial LAM targets which are not specific to *Mtb*, which may limit the specificity of clinical tests. The most promising diagnostic involves improved monoclonal antibodies targeting methyl-thio-xylose (MTX) on the LAM molecule, which is specific to Mtb, and combining it with a silver based

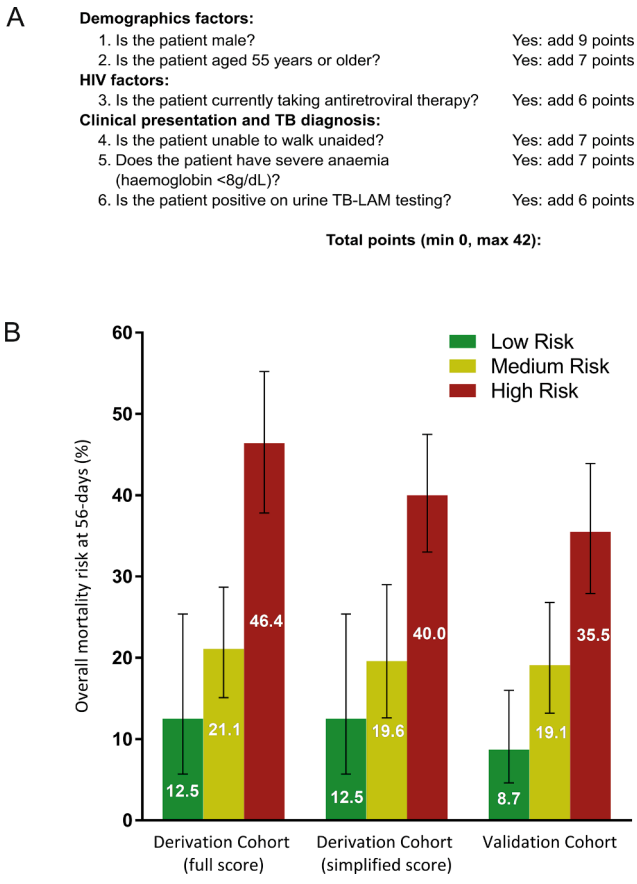

Fig. 3. (A) Risk score calculation to predict mortality in hospitalised patients with HIV and TB co-infection. (B) Observed mortality risk at 56 days in the derivation and validation cohorts, stratified by risk score category (derivation and validation cohorts) and simplified risk score category (derivation cohort). Numbers on bars represent absolute mortality risk; error bars represent 95% confidence intervals. For the full risk score, low risk was defined as 10 points or fewer, medium risk as 11 to 20 points, and high risk as more than 20 points. For the simplified risk score, the low-risk group had a predictor score of 0 or 1 point, the medium-risk group had a predictor score of 2 points, and the high-risk group had predictor score of ≥ 3 points. p-Values based on chi-squared tests between groups for derivation and validation cohorts are p < 0.001. TB, tuberculosis; TB-LAM, Determine TB LAM Ag. Reproduced from Gupta-Wright et al. (Gupta-Wright et al., 2019).

amplification step (Fujifilm SILVAMP TB LAM assay, Fujifilm, Japan) (Sigal et al., 2018; Tobias et al., 2020). Early clinical data from stored urine samples suggests a significant increase in sensitivity compared to Abbott TB-LAM, similar sensitivity, a similar prognostic value and potential utility in HIV-negative patients with TB (Broger et al., 2020; Broger et al., 2020). Prospective clinical data to confirm these findings are still pending, and clinical studies to demonstrate impact on clinically relevant outcomes.

Conclusion

Globally, HIV-associated TB still causes a huge burden of morbidity and mortality, contributed to by inadequate diagnostic tests and strategies causing many missed diagnoses. This is especially true in more advanced HIV disease. Studies clearly show improved diagnostic strategies such as universal screening in high risk groups, and using non-respiratory sampling can improve patients outcomes. Improved diagnostics can improve patient outcomes if implemented in the correct patient population, although challenges scaling-up still exist. Current urine LAM assays are cost-effective and should be implemented in appropriate high burden settings. The prognostic uses of LAM testing have yet to be fully utilised, and new more sensitive assays show promise to improve diagnosis even further. TB diagnostics are key to Ending TB, new technologies and diagnostics in the pipeline offer some hope.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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