Tuberculosis screening in adults with HIV: beyond symptoms

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Accurate and scalable tuberculosis screening tests in people with HIV would facilitate early diagnosis of tuberculosis, which reduces onward transmission, morbidity, and mortality.[1–3] Screening is also important to exclude tuberculosis before initiating tuberculosis preventive therapy. Until 2020, WHO recommended a symptom screen (any one of cough, fever, loss of weight, or night sweats) followed by a rapid molecular diagnostic test for those with a positive symptom screen in people with HIV,[4] but this algorithm had a sensitivity of only 58% in an individual participant meta-analysis.[5] In *The Lancet Global Health*, Reeve and colleagues[6] report on various tuberculosis screening tests and algorithms in ambulatory people with HIV presenting for initiation of antiretroviral therapy (ART) in a high tuberculosis burden setting. Strengths of the study include the use of sputum induction for participants who were sputum scarce, two sputum samples for culture as reference standard, and the evaluation of C-reactive protein (CRP) and rapid urine diagnostic tests.

Reeve and colleagues reported a sensitivity of 77% and specificity of 48% for the WHO symptom screen. The algorithm of a positive symptom screen or CRP of 10 mg/L or more had a sensitivity of 85% and specificity of 36%; using a CRP cutoff of 5 mg/L or more increased sensitivity to 90% and decreased specificity to 28%. A sequential algorithm of symptom screening followed by CRP, in those with a positive symptom screen, increased specificity but decreased sensitivity. Sputum Xpert MTB/RIF Ultra (Xpert Ultra; Cepheid, Sunnyvale, CA, USA), a WHO-recommended rapid molecular test for tuberculosis, had a sensitivity of 71% and specificity of 98%, irrespective of symptoms or CRP. Finally, the authors assessed urine-based tests and haemoglobin, and concluded that these performed poorly in their study population. WHO currently recommends the point-of-care Determine TB LAM Ag (Abbott, Chicago, IL, USA) urine lateral flow assay only in selected outpatients at high risk of tuberculosis.[7]

Although Reeve and colleagues present data on various screening strategies, it is important to highlight that their findings are only generalisable to ambulatory patients not yet on ART in a high tuberculosis prevalence setting. An important evidence gap has been identified regarding the role of CRP screening in people with HIV established on ART and in pregnancy.[5] Furthermore, among inpatients with HIV, both the WHO symptom screen and CRP have poor specificity.[8]

WHO's targets for tuberculosis screening tests are a sensitivity of 90% and a specificity of 70%.[9] None of the various tests and algorithms assessed in the study,[6] or in the individual participant data meta-analysis,[5] met both targets. The meta-analysis, which included data from Reeve and colleagues, reported sensitivity and specificity of 82% and 42% for symptom screen, 87% and 60% for CRP of 5 mg/L or more, and 73% and 98% for sputum Xpert Ultra.[5] CRP screening would decrease unnecessary confirmatory testing while missing a minimal number of tuberculosis cases, compared with symptom screen. The move by WHO in 2021 towards ambulatory screening with CRP of 5 mg/L or more, or rapid molecular tests, in addition to symptom screen, is informed by these findings.[1] Unselected tuberculosis screening with sputum Xpert Ultra within high-risk groups, the majority of whom were people with HIV, was assessed in a cluster-randomised trial in South Africa: a non-significant 14% increase in tuberculosis diagnoses was seen in the group with unselected rather than symptom-based tuberculosis testing, but a significant 17% increase in year-on-year tuberculosis diagnoses with the intervention was reported,[10] suggesting a potential role for this strategy in all people with HIV.

The shift from symptom screen to expanded or alternative algorithms within large programmes serving high-burden settings has major resource implications. CRP is available as an affordable point-of-care test, but algorithms based on CRP still have sub-optimal diagnostic performance. Further research is needed on tuberculosis screening in other groups of people with HIV, and on alternative, affordable strategies that meet all WHO screening test requirements.

We declare no competing interests.

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