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C-reactive protein and tuberculosis screening: a new trick for an old dog?

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In resource-limited settings, the challenge of screening for active tuberculosis (TB) among people living with human immunodeficiency virus infection (PLHIV) is a barrier to the timely initiation of antiretroviral therapy (ART) and the provision of isoniazid preventive therapy (IPT). To streamline screening for TB, the World Health Organization (WHO) recommends a simplified four-part symptom screen.¹ However, recent prospective studies have suggested that symptom-based screening would deny most PLHIV immediate access to IPT because the vast majority screen positive despite not having active TB.^{2,3}

We therefore read with great interest the recent article by Lawn and colleagues that examined the diagnostic accuracy and prognostic value of serum C-reactive protein (CRP) as a TB screening tool among PLHIV in South Africa.⁴ They found that very low (<1.5 mg/l) or very high (>400 mg/l) CRP levels were useful respectively for ruling out or ruling in TB. However, because only 14% of patients had very low or very high CRP levels, the authors concluded that CRP was not useful as a TB screening test.

We believe that a different conclusion could be reached by comparing CRP with the WHO symptom screen. In their study, using a standard cut-off of 10 mg/l, CRP had similar sensitivity (85% vs. 83%) for active TB to that of the WHO symptom screen, while delivering much higher specificity (58% vs. 33%). Thus, CRP testing would have correctly identified two more TB cases than symptom-based screening, and 101 more patients (239 vs. 138) as immediately eligible for ART and IPT. Lawn and colleagues have previously shown that Xpert[®] MTB/RIF (Cepheid, Inc, Sunnyvale, CA, USA) and Determine[™] TB-LAM (Alere, Inc, Waltham, MA, USA) had lower sensitivity than symptom-based screening in the same study setting,^{2,5} which leads us to ask: could CRP be the best rapid TB screening tool currently available for PLHIV?

While CRP is less sensitive for TB than mycobacterial culture, the most sensitive test available, culture is not feasible in most endemic settings. Clearly, some TB cases will always be missed by any screening strategy that is not 100% sensitive. The cost of missing patients with TB includes possible generation of drug resistance with isoniazid monotherapy, while the benefits to patients without TB include improved outcomes resulting from early ART initiation and possible prevention of future TB with IPT. On a

population level, the cost-benefit ratio will depend not only on the accuracy of the screening test but also on the TB prevalence in the population being screened: the cost of screening will be lower with decreasing prevalence (fewer TB cases missed), while the benefits of screening will increase (more patients without TB initiating early ART and IPT).

Although novel markers are clearly needed, CRP-based TB screening should be evaluated further, particularly in settings where TB prevalence is considerably lower than in Cape Town. In these settings, CRP-based TB screening could enable considerably more patients to begin IPT immediately relative to the WHO symptom screen, while missing a similar number of TB cases. Studies assessing patient outcomes following CRP-based TB screening could help quantify the relative cost of missed TB cases vs. the benefits expected from rapid initiation of ART and IPT.

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