Recurrent active tuberculosis in HIV-infected persons: Throwing out the baby with the bathwater!

Of the infectious diseases, tuberculosis (TB) is now the biggest killer worldwide. In 2015, more than 10 million individuals were estimated to have contracted active TB globally.[1] Not surprisingly, Africa bears a substantial TB burden given that HIV co-infection, poverty and overcrowding, malnutrition, indoor air pollution, and smoking are common.[2,3] TB is now the most common cause of death in South Africa (SA), which has the highest incidence of TB among the 22 high-burden countries.[1] In HIV-uninfected persons, it is estimated that the risk of active TB increases twofold following an initial episode of active TB.[4] Furthermore, data from SA have shown that the incidence of recurrent TB (active TB in those previously treated for active TB) was 4 times higher than in those with newly diagnosed active TB (no previous treatment for active TB).[5,6] This risk is extraordinarily higher in HIV-infected individuals, where a recurrence rate of 24 per 100 person-years has been reported, compared with the rate of 4.7 per 100 person-years in their HIV-uninfected counterparts.[4]

In this issue of the journal, Kalema *et al.*[7] highlight the strikingly high prevalence of recurrent active TB in HIV-infected individuals (defined as active TB presenting more than 2 years after the previous episode, thus likely excluding cases of relapse).[5] The prevalence of recurrent TB described in this study is considerably higher than in previous studies from sub-Saharan Africa (35% v. ~20%, respectively).[4-6] Given this high burden of disease in a large at-risk population, and the considerable associated morbidity and mortality, the question arises: what can be done to prevent recurrent TB? The high prevalence of recurrent TB in this study likely reflects high levels of TB transmission. Therefore, interruption of TB transmission is central to addressing the issues highlighted by Kalema *et al.*[7] A good starting point would be to ensure adherence to anti-TB treatment, as rates of TB treatment completion in Africa remain low.[8] Failure to complete treatment is associated with high rates of recurrent disease, which perpetuates transmission, especially when there is HIV co-infection.[9] Furthermore, it is estimated that >40% of TB in Africa remains unreported or undiagnosed in the community – these cases are sentinels for transmission.[8] This 'diagnostic gap' may be due to inaccessibility to healthcare facilities, absence of TB symptoms that are severe enough to require medical attention, paucibacilliary disease, psychosocial factors, and the flawed public health strategy of passive case-finding. This deficiency could be addressed through cost-effective community-based active case-finding strategies. We recently published the first randomised controlled trial (RCT) evaluating the role of new molecular tools (GeneXpert MTB/RIF) for active case finding – the findings indicated that active case-finding was feasible using a mobile van and almost doubled the proportion of patients initiating treatment compared with smear microscopy.[10] There is also an urgent need to develop a low-cost, non-sputum-based, accurate, field-friendly point-of-care diagnostic tool for TB detection. This would facilitate community-based active finding, thereby finding 'open' cases early and interrupting transmission. Another aspect that requires targeting is pre-treatment loss to follow-up. These are microbiologically proven cases that never return to initiate treatment – they make up 20 - 40% of diagnosed cases in some settings.[11,12] These patients are diagnosed with TB but never return to seek treatment, which aids further transmission.

Botha *et al.*[11] and Squire *et al.*[12] also raised an important question about the utility and efficacy of secondary prophylaxis in patients with previous active TB residing in areas with a high force of infection, especially if they are HIV-infected. There are scanty data about the efficacy and risk-benefit ratio of secondary prophylaxis in HIV-uninfected persons, i.e. prophylaxis given to individuals who have completed treatment for active TB. However, in HIV-infected persons, a recent systematic review demonstrated a substantial reduction of ~60% in the incidence of recurrent TB when using isoniazid as preventive therapy.[13] Therefore, for the majority of the patients included in this study (HIV co-infection rate of ~70%), secondary prevention for TB could have been beneficial. Current WHO guidelines recommend TB preventive therapy for all patients infected with HIV irrespective of the CD4 counts, and in whom active TB has been excluded.[13,14] HIV-infected patients who were previously treated for active TB are likely to derive an even greater benefit from TB preventive therapy compared with patients receiving primary prevention for TB.[6,13] Despite the high recurrence risk in HIV-uninfected patients,[4] these patients do not currently receive TB preventive therapy in routine care, as the evidence base for this intervention is weak. Hence, there is a need for additional studies in this area to quantify the benefit-to-harm ratio. The study by Kalema *et al.*[7] highlights this important deficiency.

TB preventive therapy rates (whether for primary or secondary prophylaxis) in HIV-infected individuals in Uganda, and indeed in the rest of the African continent, remain low overall.[15,16] The reasons for the low uptake of TB preventive therapy include the perception of short-term efficacy of isoniazid preventive therapy (IPT), lack of infrastructure to support tuberculin skin testing (TST) required for risk stratification (although not expressly mandated by the guidelines), and the erroneous perception of healthcare workers that patients with advanced HIV, such as those included in the current study (median CD4 count of 20 cells/μL), are less likely to benefit from IPT. Furthermore, the optimal duration for TB preventive therapy in high-transmission settings is currently unclear, and should probably also be individualised.[9,15,18-20] Therefore, provision of secondary IPT in a high-burden setting, such as the setting described by Kalema *et al.*,[7] should be individualised considering CD4 count, risk of hepatotoxicity, likely adherence to treatment, drug-drug interactions, and potential benefit v. harm.

In conclusion, Kalema *et al.*[7] have highlighted the high prevalence of recurrent TB in Kampala, Uganda. Addressing this important but neglected entity will require strengthening of healthcare systems to ensure high TB treatment completion rates. TB preventive therapy in HIV co-infected persons should be implemented as recommended in the WHO guidelines.[14] In general, the utility of pulsed preventive

therapy is currently under study and may have higher efficacy with better compliance. It is currently unclear whether HIV-uninfected patients from high-burden settings would benefit from secondary prophylaxis, what the optimal duration of therapy should be, and what regimens should be used. In the meanwhile, we suggest that treatment of these individuals should be individualised. The search for the elusive holy grail of mycobacterial diagnostics, i.e. a low-cost, non-sputum-based, field-friendly test for TB, continues. Omitting targeted health interventions and follow-up, including secondary prophylaxis, in HIV-infected patients after they have completed TB treatment is counter-intuitive (especially in patients with advanced-stage HIV), erroneously dismissive, and akin to 'throwing out the baby with the bath water'.

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