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Dear editor,

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Dear Editor,

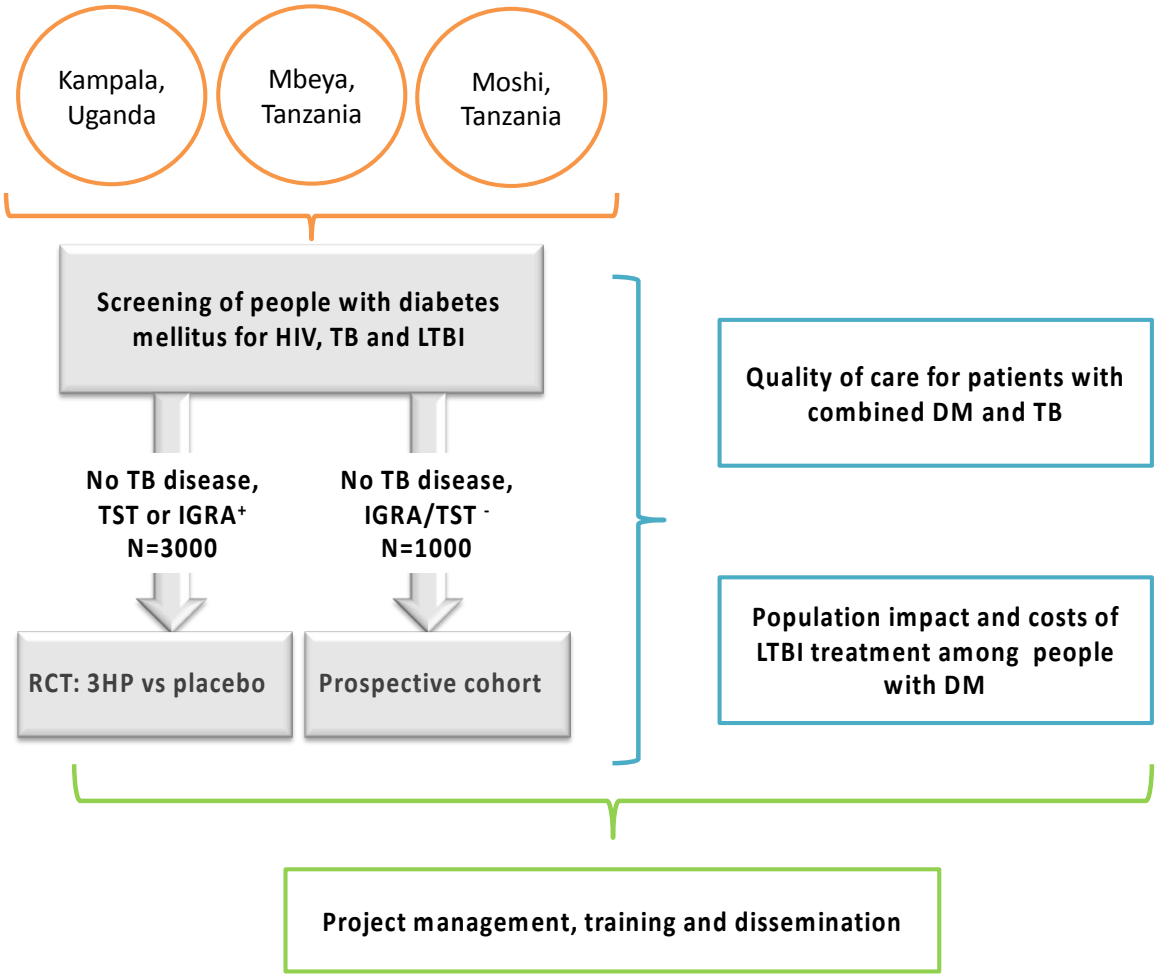
In a recent editorial Professor Anthony Harries made a plea for studies to assess the value of targeted TB preventive therapy among people with diabetes (DM).[1] We are happy to report that we will soon start the first randomised controlled trial globally to address this issue.

People with DM are an estimated 3.7 times more likely to develop TB than those without DM, this risk is higher with poorly controlled DM, and is likely to largely be due to high rates of reactivation of latent TB infection (LTBI).[2] It is estimated that DM now accounts for >10% of TB globally, and this will increase significantly in the coming decades due to the disproportionate rise in type 2 DM in TB endemic settings. DM not only increases someone's risk of developing TB disease, but is also associated with more severe TB disease, TB treatment failure, recurrent TB disease and death.[3] Recently issued guidelines for TB and DM focus on screening patients with active TB for DM and on properly managing people with combined disease.[4,5] This focus on screening and treatment of active disease may be clinically relevant but will have very little impact on the population burden of TB.

Treatment of latent tuberculosis infection (LTBI) among people with DM on the other hand, if proven safe and effective, would help improve TB control by reducing TB incidence in this large risk group. Preventive treatment among people with DM would also have significant indirect benefits: since DM is associated with higher TB bacillary loads (thus with more infectious forms of pulmonary TB), and higher treatment failure and recurrence rates,[3] people with DM may be disproportionately responsible for onward community TB transmission. Indeed, a recent mathematical model of TB-DM in India estimated that LTBI preventive treatment targeted at people living with DM (assuming 50% uptake), could potentially prevent up to 11% of all population incident TB cases and 13% of TB-related mortality in the entire population, with even larger effects expected over the coming decades.[6]

To establish the first empiric evidence for LTBI management among people with DM, our PROTID study will randomize 3300 people with DM and LTBI in Tanzania and Uganda to a 12-week course of rifapentine and isoniazid preventive therapy or placebo, with cumulative incidence of TB disease over 24-months follow-up as the primary endpoint. While DM is with a relatively increased risk of developing LTBI,[7] evidence suggests that the increased risk of TB in people with DM is largely from reactivation disease and a recent study from Indonesia found that among people with DM those with LTBI had a 3.5-fold higher TB incidence compared to those without LTBI.[8] In parallel to the RCT we will follow a 1000 people with DM but without evidence of LTBI to confirm whether their incidence of TB in this group is indeed too low to warrant preventive treatment. In addition, PROTID will evaluate optimal ways to screen people with DM for LTBI and TB; address gaps in prevention and therapeutic management of combined TB and DM; and estimate the population impact and cost-effectiveness of treatment of LTBI in people living with DM on TB incidence and transmission (**figure**). This first study will take place in sub-Saharan Africa, which witnesses the fastest growth of type 2 DM including a large proportion with undiagnosed and poorly controlled DM.[9] We have submitted a similar project for funding to be conducted in Asia, which currently carries the highest burden of combined TB and DM.[10] If proven successful, these studies will provide crucial information to guide policy and practice regarding prevention and management of combined TB and DM.

Figure: conceptual overview of PROTID



PROTID ("Randomised Controlled Trial of Preventive Treatment of Latent Tuberculosis Infection in people with Diabetes Mellitus "), is is part of the EDCTP2 programme, supported by the European Union (grant number RIA2018CO-2514-PROTID).

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