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Assessing the impact of prevalent tuberculosis (TB) on mortality among ART initiators: accurate TB diagnosis is essential

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Westreich and colleagues reported on the association between treatment for pulmonary tuberculosis (TB) at baseline in a South African antiretroviral treatment (ART) programme and subsequent mortality risk [1,2]. Although patients receiving TB treatment had higher all-cause mortality risk compared to those not treated, no such association was observed after adjustment for baseline CD4 count, other patient variables and loss to follow-up (hazard ratio,1.06; 95%CI 0.75–1.49) [2]. This finding was robust when additional death registry data were included and follow-up was extended by 18 months [1].

This finding seems counter-intuitive and we are concerned that some might conclude from these studies that strategies to reduce the burden of TB in ART programmes in sub-Saharan Africa are not important with regard to addressing the high mortality in ART programmes in the region. TB is one of the most frequently reported causes of death in this clinical setting [3]. Post-mortem studies conducted in Africa (both before and during the ART era) have reported that approximately 30%–50% of hospital in-patients who died of HIV/AIDS have evidence of active TB, which was often disseminated [4–7]. TB was also identified post-mortem in a high proportion of patients in South Africa who died while receiving ART [8]. It must be noted that much disease identified in these studies was undiagnosed at the time of death.

Despite careful statistical analyses and consideration of various potential biases, Westreich and colleagues have not addressed the fundamental issue as to whether patients in their study were accurately classified as having TB or not. This was defined simply on the basis of whether or not they were receiving treatment for pulmonary TB [2]. No case definition for TB disease was used, no microbiological data were presented and extrapulmonary TB was not accounted for. The disease-free comparator group was simply defined as patients not receiving treatment for pulmonary TB. No systematic microbiological screening of patients was done at baseline to rule-out TB and post-mortems were not done to assess for

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unascertained TB in patients who died in the TB-free group. Moreover, patients developing incident disease during the initial weeks of ART were not excluded from the TB-free group.

Diagnosis of TB in this clinical setting in Africa is challenging due to the non-specific clinical presentation, high rates of sputum smear-negative, extrapulmonary and disseminated disease and co-morbidity that may mimic TB [9,10]. Since widely used diagnostic tools (sputum smear microscopy and chest radiology) are so blunt and culture is very slow and much less used, there is considerable under-diagnosis as well as some over-diagnosis of TB. Much incident disease diagnosed in the first weeks of ART is actually disease that was present at baseline but missed during screening [11,12]. In studies in which patients enrolling in South African ART clinics who have no pre-existing TB diagnosis are intensively screened for TB at baseline regardless of the presence of absence of symptoms, approximately 15%–25% have sputum culture-positive pulmonary TB [13–15].

Potential misclassification of patients into diseased and disease-free groups may substantially undermine the validity of the findings of Westreich and colleagues. We agree with Straetemans and colleagues that currently available data on TB as a risk factor for mortality in ART programmes are insufficient to draw definite conclusions as they have considerable limitations [16]. We suspect that TB (especially undiagnosed disease) is a key factor contributing to high early mortality and that strategies to address this should include rapid microbiological screening of all patients regardless of clinical symptoms [9,15,17]. Further well designed studies are therefore needed and accurate disease ascertainment will be essential for these to be interpretable.

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