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HIV infection and tuberculosis mortality among adults in Cape Town

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Although a curable disease, tuberculosis (TB) remains a significant cause of mortality worldwide. In 2015, an estimated 1.8 million TB deaths occurred globally, including 0.4 million TB deaths among people living with human immunodeficiency virus (HIV) infection (1). TB currently ranks 9th in the leading causes of death among people worldwide and 1st among people living with HIV. Reducing TB mortality is one of the key targets of the new global TB control strategy, called the End TB Strategy (2). The ambitious strategy seeks to reduce the number of people who die from TB by 95% in the year 2035, relative to the 2015 baseline level (2).

Better knowledge about underlying risk factors that lead to death among people with TB can guide policy making towards effective control measures for reducing the loss of lives from the disease. In a systematic review of studies on TB-associated mortality (3), risk factors for TB death among patients treated between 1966 and 2010 were described. While non-infective comorbidities, sputum smear-positive disease, alcohol and substance abuse were all risk factors for TB mortality in low TB incidence and HIV prevalence settings, HIV positivity, advancing immunosuppression, smear-negative disease and malnutrition were identified as the most important factors in high TB/HIV settings. The authors noted that more prospective research into deaths during TB treatment, particularly in the first month of treatment, is needed.

Mortality during TB treatment in Cape Town

Cape Town is a city with high TB morbidity and high mortality. In 2009, 29 478 TB cases were notified (856/100 000 population), about half of whom were documented to be co-infected with HIV (4). To create a basis for further research into TB and HIV-associated mortality in this metropolitan setting, we conducted a retrospective analysis of deaths occurring during TB treatment in Cape Town (5). We analyzed data for 93 133 adults treated for non-multidrug-resistant TB in Cape Town between January 2009 and June 2012. Data on demographics (age and gender); disease (site of disease, sputum smear results, treatment regimen, HIV status and CD4 count); and TB treatment outcomes (treatment completed, cured, lost to follow-up, died, failed) were extracted from an electronic TB register database (ETR.net) which is a completed at sub-district level from paper-based facility treatment registers. We used a binomial log-linear regression model to investigate risk factors associated with death during TB treatment. Knowing that HIV infection is a major risk factor for TB mortality, we looked at interactions between HIV infection and various other risk factors towards the risk of death from TB during treatment.

A total of 4,619 TB cases were documented to have died during TB treatment, 5.0% of all patients treated in the study period. We found that people with HIV infection (adjusted risk ratio [RR]: 2.19; 95% confidence interval [CI]: 2.03, 2.37) and those with undocumented HIV status (RR: 1.86; 95 % CI 1.57, 2.21) were at increased risk of death during treatment. Other risk factors for death included male sex (RR: 1.06; 95% CI: 1.01, 1.12), age greater than 65 years (RR: 9.16; 95% CI 7.79, 10.80), extra-pulmonary TB (RR: 1.14; 95% CI: 1.04, 1.26), smear-negative TB (RR: 1.13; 95% CI: 1.06, 1.22) and previous TB treatment (RR: 1.33; 95% CI: 1.23, 1.45).

Compared to HIV-negative TB patients, those HIV-positive with a CD4 count < 50 cells/mm^3 had an elevated risk of death (RR: 3.83; 95 % CI: 3.48, 4.21) whereas those with a CD4 count above 350 cells/mm^3 had a similar risk of death (RR: 1.07; 95 % CI: 0.93, 1.23) most likely reflective of more severe immunosuppression due to HIV.

We found a significant interaction between HIV infection and other risk factors for death during TB treatment. The association between HIV infection and death was greatest in young people aged 15-24 years (RR of HIV-infection: 4.82; 95% CI: 3.88, 5.99) compared to older people, in women (RR: 2.74; 95% CI: 2.43, 3.08) compared to men, and TB cases with smear-positive disease (RR: 2.82; 95%CI: 2.58, 3.07) compared to those with smear-negative disease.

In summary, our published study shows that HIV-positive patients with TB in Cape Town are at elevated risk of death during TB treatment, especially those with advanced stages of immunosuppression (i.e. low CD4 count). The relative risk of HIV infection appears to be highest in groups that are otherwise at relatively lower risk of dying during TB treatment, such as young people aged between 15 and 24 years, and women. We show that especially elderly people are at substantially increased risk of death, independent of HIV status. Where we have shown an increased

risk of death among those with smear negative TB, consistent with previous findings (6), additional evaluation is required to ascertain if this additional risk truly relates to TB or rather misdiagnosis of other pathology as TB among both HIV positive and negative patients.

Our study had limitations as a retrospective analysis of routinely collected data. The electronic register data was not validated against facility records to ensure correctness. In addition, our data may be limited by residual confounding, as we were not able to evaluate additional factors that may be associated with both TB and mortality such as smoking, alcohol and substance abuse, and co-morbidities. Very importantly, we are unable to define causal relationships as the routine data set includes all deaths occurring during TB treatment and this includes those who may have died from causes unrelated to TB.

Way forward

Following this study, we have identified priority areas for future research. Prospective studies are needed to better understand the risk of death especially in the early phase of treatment as well as the risk of death prior to TB treatment. These studies are needed to understand how treatment delay and initial lost to follow-up (lost before treatment initiation) contribute to death from TB. The effect of early initiation of HIV treatment towards reducing the risk of death from TB also requires prospective evaluation. Finally, an important priority for future research will be to understand the long-term mortality associated with an episode of (treated) active TB. Preliminary data from a TB low-burden setting suggest that individuals who recover from TB are at higher long-term risk of death compared to the general population, and their causes of death are different (7). In TB and HIV high-burden populations previously treated people may represent a large subgroup in the general adult population (8). Studies to understand the risk of death from TB and residual lung disease in this group will therefore be important.

While the limitations of the published study have been noted, the study has contextualized TB mortality as reported from routine TB treatment registers in Cape Town. Risk factors for TB in this setting have been described and some of the interactions with HIV have been evaluated. Future studies will explore the additional complexities addressed above and we anticipate that some of the results from this ongoing work will be able to contribute to plans to reduce all mortality related to TB in South Africa and similar settings.

This article is based on the following published article. The data referred to in the text can be found in full detail in the tables of the original article: Osman M, Seddon JA, Dunbar R, Draper HR, Lombard C, Beyers N. The complex relationship between human immunodeficiency virus infection and death in adults being treated for tuberculosis in Cape Town, South Africa. BMC Public Health. 2015;15:556

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