Giving a voice to those who die young: the fatal impact of tuberculosis and HIV in South Africa

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Evaluation of: Cohen T, Murray M, Wallengren K, Alvarez GG, Samuel EY, Wilson D: The prevalence and drug sensitivity of tuberculosis among patients dying in hospital in KwaZulu-Natal, South Africa: a postmortem study. *PLoS Med.* 7(6), e1000296 (2010).

The joint epidemic of HIV and TB in southern Africa is having a profound impact on the livelihood of the general population. This study of young people dying in a general hospital, serving a big conurbation in South Africa, points to a number of problems linked to disease control in the community. These include late presentation, low uptake of efforts to treat HIV and TB, a high frequency of people with infectious TB in the community and anti-TB drug resistance. The arguments are convincingly made for an improvement in case detection and earlier institution of adequate treatment. The investigative methodology used by the authors could be more widely applied to advocate for lifesaving measures in other settings sharing similar epidemiological challenges.

The reader of the article by Cohen *et al.* in *PLoS Medicine* [1], investigating the deaths among hospitalized patients in South Africa (KwaZulu-Natal province) should prepare for some disturbing news. Some 4 years ago, workers in the same province reported the deaths of 52 tuberculosis (TB) patients with very advanced drug-resistance patterns [2]. The far-reaching repercussions of that short paper could hardly have been foreseen at the time. The present article eloquently evokes the realities of patients dying in a general hospital. The observations merit serious reflection about the ravages wreaked by TB and HIV in this part of the world, and sound another clarion call to action.

In the 17th Century, TB was poetically termed “the captain of all these men of death” by Bunyan writing in England [3]. This is still an apt description for it today, since, among all infectious conditions prevailing in the world, especially in low resource settings, only HIV/AIDS causes more deaths than TB. TB has been known to afflict humanity from time immemorial, and a long list of eminent personalities have suffered and died from it. While effective treatment for most TB patients has been available and affordable in most of the world and for many years, the disease is nowhere close to being eliminated. Its association with HIV, and the increasing recognition of multidrug-resistant TB strains, have complicated control efforts in recent decades. In 2008, there were

an estimated 9.4 million TB cases worldwide, with 1.8 million deaths among them [4]. Some 440,000 multidrug-resistant (MDR) TB cases are estimated to have emerged that year alone, the majority of them in countries of the former Soviet Union and Asia. However, 69,000 were in Africa. Among MDR TB patients placed on treatment in South Africa in 2007, only 42% had a successful outcome, while at least 20% died [UNPUBLISHED DATA].

One thing that sets southern Africa apart from elsewhere in the world is its extremely high incidence of TB. Whereas the notification rate of TB is generally expressed per 100,000 population, in this part of Africa it is in the region of 1% per year. The high frequency of coinfection with HIV is largely to blame, together with the poverty that ravages the continent in general, and that drives TB, a disease intrinsically linked to poor living conditions.

Cohen *et al.* have analyzed biological specimens collected after death in 240 adults aged 20–45 years who died in a public hospital in 2008–2009. This hospital is not a specialized TB center and, yet, over a quarter of its admitted patients are known to have active TB. Half of the patient specimens examined had viable TB bacilli on culture. These are remarkable findings by themselves, attesting to the high burden of TB, often undetected. Public-health practitioners anywhere would be alarmed to have so many

Keywords

- drug-resistant TB ■ HIV
- Southern Africa
- tuberculosis

individuals with a condition that is lifethreatening, directly transmissible and largely treatable, living in their community on inadequate medication or none at all. Clearly, there is much to be done in terms of active case finding and contact tracing for TB in the catchment area of this hospital.

The observation that 94% of the decedents were vulnerable to TB owing to HIV infection is another reminder of the fatal toll of the coepidemic, particularly among patients who are not on antiretroviral therapy (ART). Only a fifth of those eligible for ART were actually on treatment. This suggests that, in a country where this treatment is widely available, many people living with HIV are actually not receiving it. Some studies from southern Africa have looked at the determinants of access and adherence to ART. Common barriers identified comprise a variety of factors, including patients' beliefs, such as fear of disclosure, feeling better on treatment, inadequate knowledge about the disease and ART, stigma, alcohol use, use of traditional medicine, transport costs, lack of social support (financial and emotional), pill burden and drug side effects [5]. ART is a lifesaving intervention, particularly for TB patients, and needs to be scaled-up urgently. The use of isoniazid preventive therapy (which is not mentioned in this article) is also recommended to avert the reactivation of TB in patients living with HIV [6].

What is of added concern is that over half of the patients who were on anti-TB treatment at the time of death were found to be culture positive for TB. This presents two important concerns: was the treatment adequate? And were patients adhering to their prescribed regimens? In total, 17% of the isolates had detectable MDR strains and, thus, had lost susceptibility to isoniazid and rifampicin, the two most potent bactericidal drugs. However, 70% of patients dying while on treatment had strains that were fully sensitive to TB drugs. Thus, this is clearly distinct from the well-known cluster of cases in KwaZulu-Natal in 2006, in which nearly all patients had extensively drug-resistant TB. However, quite clearly, it was no less lethal, and raises the question about the cause of this high frequency of treatment failure.

We do not know precisely from the article for how many months patients had been treated before death, but culture was more likely to be positive in patients dying during the initiation phase of treatment than later. They may, thus, not have had sufficient treatment doses to convert. We know moreover that 42% of

subjects were not suspected of having TB at the time of death. It is very likely that TB contributed significantly to the untimely death of these patients. Health practitioners clearly must maintain a high index of suspicion for TB, particularly in people with HIV developing chest syndromes, or in whom deterioration of the general condition is not explained by a different pathology [7].

While there were slightly more women than men among the patients included in the study, male sex was associated with a twofold higher risk of culture-positive TB. A number of reasons could be at the root of this. TB may be more common in males. Men may be less adherent to their medication and, thus, succumb to TB rather than other opportunistic conditions. However, it may also reflect differences between the sexes in care-seeking behavior. The inference would be that female patients with HIV-associated TB, diagnosed or otherwise, may be staying away from the hospital. Focus on this aspect would be useful in future studies of this type.

Conclusion & future perspective

This study has focused on a subpopulation of patients expected to be very ill. The advent of death within a few days of patients' admission to hospital is revealing of their advanced stage of disease. Coupled with the finding of viable TB bacilli postmortem in many individuals on treatment, these early deaths point to avoidable delays in start of treatment. Patients may be arriving late in the course of their illness, and absence of appropriate care could limit their chances of survival. Late presentation may point to problems with diagnosis, access to treatment and adequate facilities to handle a patient outside the hospital setting. In this study, prior hospitalization only failed to reach a statistically significant association with MDR by a very narrow margin. A plausible explanation of such a relationship in this group would be nosocomial transmission, as has been reported elsewhere [2]. Improvements to infection-control facilities and practices may be expected to reduce such risks in low-resource settings, where such measures are often inadequate.

The authors do not give details on how the calculated sample size was deemed to be representative of the population under investigation. The selection of study subjects, likewise, is not elaborated, although the sample did not differ significantly from other eligible individuals in age, sex, HIV status and proportion

of patients on anti-TB drugs. Thus, any bias if present was likely minimized. Collection of biological specimens on deceased subjects, including biopsy, proved to be effective in identifying the target pathologies. Further work similar to this is required to help understand the patterns of disease in settings where full autopsy may not be possible, either owing to local norms and customs [8] or risk of infection among examiners.

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Executive summary

Objective

- An assessment of the contribution of TB to the death of young adults in a public hospital in the KwaZulu-Natal province of South Africa.

Methods

- In total, 240 inpatients were selected, aged 20–45 years, who died after admission to Edendale Hospital in the 10 months leading up to August 2009.
- Respiratory tract secretions and tissue by needle core biopsies were collected from the lung, liver and spleen.
- Specimens were examined for TB (by fluorescent microscopy and culture) and for HIV infection.
- *Mycobacterium tuberculosis* strains that were isolated were tested for susceptibility to anti-TB medication.

Results

- In total 94% of study subjects were HIV seropositive. Only 17% of them were on antiretrovirals at the time of death.
- In addition, 50% had culture-positive TB. Of the 50% not receiving anti-TB treatment, 42% were culture positive.
- Half of the participants were on treatment for TB at the time of death, and 58% of these treated individuals remained culture positive.
- Of all positive cultures, 17% were multidrug resistant (MDR) and, thus, had lost susceptibility to the two most potent drugs, isoniazid and rifampin.

Conclusion

- A huge burden of HIV in the population of KwaZulu-Natal province is present.
- There is a massive added burden of undetected TB and MDR TB among people living and dying with HIV.
- The majority of patients with bacteriologically positive TB were receiving treatment for it.
- Most patients were infected with drug-susceptible *M. tuberculosis*, suggesting that the diagnosis was made too late to alter the fatal course of their disease.
- Fresh impetus is urgently needed to improve the early diagnosis of TB, and expand the treatment for both HIV and TB in this setting.

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