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Survival in XDR TB: Shifting the Curve and Shifting the Paradigm

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The article by Kvasnovsky and colleagues in this issue of JAIDS describing the dismal treatment outcomes of patients with extensively drug resistant tuberculosis (TB) in the Eastern Cape of South Africa[1] - a setting with a high prevalence of HIV and an extremely high TB burden – is a ghastly reminder of the toll exacted by this explosive public health crisis. Multidrug resistant (MDR) and extensively drug resistant (XDR) TB have derailed the relatively few gains made in TB control in areas such as South Africa with high HIV prevalence. It is no surprise that South Africa, with its high incidence of active TB (almost 1% of South Africa's 50 million people were diagnosed with TB in 2009 [2]) and its historically high rates of poor treatment outcomes, should also have a large number of individuals with drug resistant TB. Drug-resistant *Mycobacterium tuberculosis* does not exist in nature – it is the product of human intervention, selected by inappropriate or inadequate treatment and poor adherence. XDR TB - MDR TB that has acquired resistance to second line drugs for TB including the fluoroquinolones and at least one so-called injectable agent - is the product of mismanagement of MDR TB. In South Africa, the mistakes of the past are amplified by the large number of people rendered profoundly susceptible to TB by HIV infection, compounded by ongoing weaknesses in TB control. A significant proportion of individuals with MDR and XDR TB have never had exposure to the selective pressure of TB treatment and appear likely to have been initially infected with a resistant strain [3, 4]. When drug-resistant TB develops, delays in diagnosis and initiation of appropriate treatment exacerbate an already terrible situation by amplification of resistance, ongoing transmission of infection in the community (and health institutions), and rapid progression of disease to death.

The paper by Kvasnovsky and coworkers highlights several important challenges in responding to drug-resistant TB. Firstly, the prognosis of patients with XDR is extremely poor, irrespective of HIV serostatus; one quarter of the XDR TB patients reported in this study died before they received any treatment for XDR, and many of these are likely to have been co-infected with HIV. HIV-seronegative patients comprised a large proportion (45%) of those who survived to receive MDR TB therapy, but over half had died within 2 years of diagnosis. HIV-infected patients treated for XDR TB who did not receive antiretroviral therapy (ART) had extremely poor survival, with only a third surviving to one year. As a comparison, Harries et al reported that 23% of patients with all forms of TB died during TB treatment in Malawi in 1997 [5]. Those fortunate enough to have been started on antiretroviral

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therapy (ART) in the current study had a similar survival to HIV-seronegative XDR patients, but this should be viewed as “equally bad” rather than “equally good.” Two landmark trials comparing optimal timing of ART initiation in relation to TB therapy in HIV-infected adults have clearly shown that early initiation of ART reduces mortality – an effect apparent at both high and low CD4 counts [6, 7]. Differences in prognosis by HIV serostatus and antiretroviral therapy reported here are similar to a larger retrospective report from four treatment centers in South Africa [8] (which appear to include at least some of the patients in the Kvasnovsky article). The survival data reported here – particularly the pre-XDR-treatment mortality rate - are better than those in the report which sounded the initial alarm of the potential threat of XDR to HIV-infected adults. Gandhi et al [3] described short-term outcomes in patients diagnosed at a general hospital in the KwaZulu Natal, Province – neighboring the Eastern Cape Province- about two years prior to those in this paper. The authors reported that 52 of 53 XDR patients in their study died, 70% within a month of the diagnostic specimen being taken and that all who were HIV-tested were HIV-seropositive. In both settings mortality is unacceptably high, underscoring the urgent need for new approaches to managing MDR and XDR TB.

New drugs and new regimens of drug combinations are desperately needed to treat drug-resistant TB. The recent publication of a randomized trial of the novel ATP synthase inhibitor TMC207 in MDR TB patients was an important step forward [9]. Testing of this and other novel TB agents should include both HIV-infected individuals and children if these products are to be used in these populations. Successful regimens for drug-resistant TB require a variety of drugs. They will likely include: new agents, such as TMC 207, OPC-67683[10] and PA-824[11]; re-purposed drugs, such as respiratory fluoroquinolones; and optimized old drugs, including isoniazid and pyrazinamide. Although the world waits in eager anticipation of the novel agents, existing agents are not being optimally used or may be misused. For example, it is abundantly clear that moxifloxacin is a potent fluoroquinolone [12] – more so than ofloxacin [13] - but many programs continue to use ofloxacin because it is less expensive, contributing to treatment failure and the selection of fluoroquinolone-resistant organisms. In addition, there is reason to believe that high-dose isoniazid may be effective in treating organisms with mutations in the *inhA* gene[14] and this could improve and shorten regimens for MDR and XDR TB.

Secondly, the authors highlight delays in diagnosis of XDR TB; patients in this retrospective cohort had a mean of 15.7 months of TB treatment prior to XDR diagnosis and cohort entry. Delays in the clinical triggers to suspect and investigate drug resistant TB, which could be fatal, are compounded by the built-in tardiness of culture-based drug sensitivity testing for first and then second line TB drugs. The line probe assay (Genotype MTBDR*plus*®) which has been made available in several high through-put laboratories in South Africa offers some hope of overcoming lengthy delays in diagnosis of MDR TB and also rapidly confirms infection with *M. tuberculosis*[15]. Unfortunately, its usefulness is restricted to smear positive cases, thereby excluding most HIV-infected individuals with TB, who are likely to be smear negative. The recently described Xpert MTB/RIF® real time polymerase chain reaction (PCR) assay has enormous potential to identify both *M. tuberculosis* infection and genotypic rifampin resistance [16], but expense may limit widespread implementation.

A further issue that complicates management of TB treatment is the possibility of re-infection with another *M. tuberculosis* strain during and after treatment, quite possibly in the clinics or hospitals where patients are receiving their MDR or XDR TB therapy. Although confining patients in sanatoria may prevent spread of resistant TB in the community, the risk of transmission is likely still present, not only between patients but also to health workers who appear to be at higher risk of being admitted to hospital with XDR TB than the populations they serve [17].

Finally, reports such as the one in this issue, of programmatic outcomes, are bedeviled by their retrospective and incomplete nature and describe only a subset of patients who not only survive long delays prior to being diagnosed with MDR or XDR TB, but then have to reach specialist public sector treatment programs which are often long distances from their homes. Highlighting this diagnostic gap is a post mortem biopsy study with mycobacterial culture and drug sensitivity testing conducted at a hospital in KwaZulu Natal that showed 17% of cadavers dying from “natural” causes were infected with MDR TB; only one was on MDR treatment prior to death [18]. There is clearly a pressing need for much improved surveillance of all forms of TB in high-burden countries, including all diagnosed cases, deaths as well as treated patients. Currently, only patients who enroll in DOTS programs are reported in many high-incidence countries, excluding mortality statistics to monitor and assess progress - or the lack thereof.

Important public health and epidemiological lessons have been learnt from the XDR TB epidemic. However, research and control efforts must continue to address all forms of TB, including the approximately 93% of patients who do not have drug-resistant TB. Earlier identification of cases of TB by active case finding [19, 20] together with rapid, routine drug sensitivity testing, coupled with preventive treatment for those without evidence of active TB, efforts to improve treatment adherence, and implementation of infection control measures will reduce incidence of both drug susceptible and drug-resistant TB. Retrospective studies such as this one provide a critical baseline from which progress can be measured, but prospective and complete epidemiologic surveillance, including molecular epidemiology, is crucially important to monitor, respond to and overcome the TB pandemic.

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