

## Novel and Adjunct Treatment for Drug Resistant Tuberculosis: A Public Health Imperative

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### Abstract

The emergence and continued spread of drug resistant forms of tuberculosis (TB) presents an enormous challenge to both TB control programmes and global public health. This is of particular concern in high burden HIV settings where the two epidemics seem to have converged.

**Keywords:** Drug-resistant tuberculosis; HIV infection; Novel adjunct treatment; Public health

### Introduction

Conventional multi- and extensively-drug resistant TB (MDR/XDR-TB) treatment regimens lack efficacy, are protracted, toxic, resource intensive and are plagued by poor patient adherence. It is therefore no surprise that treatment success rates are dismal. Despite considerable economic investment, South African data show that standardized treatment for MDR-TB resulted in an overall treatment success rate of just 46% [1]. Treatment success rates are even lower in XDR-TB, with two independent studies reporting successful treatment outcomes in just 22% [2] and 16% [3] of patients.

The limitations of current MDR/XDR-TB regimens account for the large proportion of unfavourable treatment outcomes. Clinical outcomes for XDR-TB remain poor irrespective of HIV status. Our quantitative and qualitative studies suggest that the adverse effects associated with the XDR-TB drugs and cumulatively high pill burden compared to anti-retroviral therapy (ART) may lead to preferential ART adherence and consequently improved survival, however this did not translate into more favourable XDR-TB treatment outcomes [2,4,5]. In addition, treatment failure and mortality rates are high with 19-23% of patients with XDR-TB remaining unresponsive to therapy and 42-46% dying within two years of treatment initiation. Furthermore, Pietersen and colleagues found that after 5 years of follow-up 73% of XDR-TB patients had died [3]. Alarming, 42% of patients with XDR-TB that were discharged had failed treatment. The median survival time of these patients was 19.84 months from the time of discharge. Genotypic methods later showed evidence of disease transmission, from a discharged patient who failed treatment, to another family member. Similarly, a 19 year old HIV negative female was treated for MDR-TB in 2011. She was appropriately treated at an MDR-TB facility, culture converted, remained cultured negative for 18 months and deemed cured. Nine months later she presented to the same facility with recurrent MDR-TB infection. It later emerged that she resides with her aunt and best friend, both of whom have MDR-TB infection and are poorly adherent to treatment. These circumstances highlight inadequacies in current MDR/XDR-TB treatment and

management strategies and their greater public health significance, especially in vulnerable populations.

The development of novel anti-TB agents, the use of re-purposed drugs and major improvements in point-of-care diagnostics such as Xpert MTB/RIF offer some hope to a TB control programme in crisis. Clinical trials have shown that bedaquilin, delamanid and linezolid improve sputum culture-conversion rates in MDR/XDR-TB patients with attendant adverse events of a predominantly mild to moderate nature [6-8]. Expert MTB/RIF has the potential to significantly reduce the time to treatment initiation compared to conventional drug susceptibility testing, potentially reducing the risk of disease transmission. While these scientific advances are encouraging, their long-term epidemiological effect may be limited; these recently available drugs are expensive, are yet to be freely available to all patients and their efficacy in pragmatic, overburdened and resource limited settings is still to be evaluated. In addition, such drugs fail to address key barriers to adherence; they do not reduce the pill burden nor do they shorten current treatment regimens. While Xpert MTB/RIF has important public health benefits, Churchyard *et al.* found that Xpert MTB/RIF did not reduce the mortality, compared to smear microscopy, in patients with drug-susceptible TB [9]. The impact on Xpert MTB/RIF on clinical outcomes in patients with MDR-TB is yet to be evaluated.

There is an urgent need for new treatment regimens to manage the increasing numbers of drug-resistant TB cases diagnosed post Xpert MTB/RIF. While there are numerous potential drugs in various phases of clinical development, it may be several years before they are incorporated into new treatment regimens. Gradually however, genomic mutations in *Mycobacterium tuberculosis* bacilli may render these drugs vulnerable to acquired resistance. Adjunct TB therapies in combination with standard drug regimens offer some promise in the fight against drug resistant forms of TB. A recent open-label phase 1 safety trial found that autologous mesenchymal stromal cell infusion, in combination with standard chemotherapy, in patients with MDR/XDR-TB resulted in improved radiology at 6 months in 70% of patients with no serious adverse events [10]. Adjunct therapies may additionally improve treatment success rates, shorten treatment regimens, enhance immunity and prevent recurrence [11]. These data suggest that adjunct therapeutic options need to be further explored if

we are to achieve better clinical outcomes and accelerate the control of drug-resistant TB.

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