

A Cheap and Effective Anti-Mdr/Xdr/Tdr Tb Drug is Already Available

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Abbreviations: MDR: Multi-drug Resistant; XDR: Extensively Drug Resistant; TDR: Totally Drug Resistant

The recently released WHO global Tuberculosis (TB) report, pictures an optimistic view on the developments in TB control: the incidence of new cases has shown a decrease for several years now, and fell in the period 2010/2011 with 2.2%. The TB mortality rate has decreased with 41% since 1990, and the world is on track to meet the target of a 50% reduction in the global incidence, by the year 2015. Mortality and incidence rates are currently falling in all six WHO regions, and in most of the 22 high-burden countries that account for over 80% of the world's TB cases [1].

Nevertheless in 2011, there were still an estimated 8.7 million new cases of TB, of which 13% co-infected with HIV and 1.4 million people died from TB. But, this was less than previously expected by the WHO.

The development of the Multi-drug Resistant TB (MDR-TB) problem, however, shows little progress in comparison to the previous report [2], and moreover, the currently published rates may only be the tip of the iceberg, as drug resistance testing is still rare in many high prevalence settings. In any case, the WHO report shows that the level of resistance in MDR-TB cases has increased significantly since the last worldwide survey, primarily in Eastern Europe, Central Asia, China and India, where 9- 32% of all new cases of pulmonary Tuberculosis are resistant to, at least, INH and rifampicin. Comparison of this data to the previous WHO report even indicates a 50% increase in the overall notification of MDR-TB. Strikingly, in the report nothing was mentioned on the occurrence of Extensively Drug Resistance (XDR-TB), or on the ill-defined Totally Drug Resistant TB (TDR-TB). Therefore, the increase in the level of resistance in MDR-TB cases so far remains hidden. Although, it is clear from the WHO 2012 report that some progress has been made, with respect to worldwide overall incidence rates and mortality, effective therapy in MDR-TB cases is still a rarity in most hot spot regions, and restricted to efficient Stop TB and The TB Alliance programmes.

Even more alarming is the situation in particular large countries that contribute significantly to the worldwide MDR-TB notification, like India. The latter country, together with China and the Former Soviet Union States, account for almost 70% of the MDR-TB cases that occur worldwide annually. The WHO report estimated that approximately 64,000 cases (44,000 - 84,000) of MDR-TB emerge annually among the pulmonary TB cases in India, and although this in absolute terms represents a high number of cases, in comparison to the total load of TB in this huge country, it may give the comfortable impression that TB control is on the right track. The report also indicates on the basis of drug resistance surveys in the states of Gujarat, Maharashtra, and Andhra Pradesh that the estimated prevalence of MDR-TB in India was 2-3% in new cases, and 12-17% in retreatment cases. Moreover, the report states the prevalence of MDR-TB is not increasing in India. However, it is conceivable that the problem of MDR-TB in India is

much larger than assumed, and in fact, may be overlooked because it is doubtful whether the official Indian MDR-TB data are representative of the country.

First of all, the WHO data is based on a very small sample of sentinel centers where program performance presumably exceeds those in routine locations, by far. Moreover, there is an important political factor influencing the low estimate of the MDR-TB problem in India; the figure of 3% MDR-TB among new cases, and 15% in retreatment cases have almost become part of a policy dogma. Many physicians actually involved in treatment of MDR-TB would beg to work in a situation with such a low prevalence of MDR-TB situation in their setting. In reality, most feel overwhelmed by a huge burden of complicated MDR-TB cases.

Harper rightly questioned the reliability of the current figures in India and referred to the term "statistico-tuberculosis". The Indian program and the politicians welcome the theoretical low prevalence figures because of the 'feel good effect', as they comply with 'manageable' global levels. Any deviation from these levels is therefore, dismissed as unrealistic.

Data on MDR prevalence from other regions in India, not included in the WHO estimations, reveals completely different figures, with MDR-TB prevalence rates ranging from 20-50% in new and retreated patients. At our institution, a tertiary TB hospital with a modern laboratory and located in the metropol of Mumbai, as many as 30% of the new cases, and 60% of the retreated cases, are currently labeled as MDR-TB. This true and valid data are understandably critiqued as unrepresentative, due to the purposive sampling of patients from non-responders accessing our referral hospital. However, already the fact that even a single center routinely sees MDR-TB rates of such magnitude belies the official data that the MDR-TB problem is under control in India.

A recent study by D'souza et al. [3], was the first representative study, attempting to determine the true prevalence of MDR-TB in Mumbai. She selected four centrally located TB wards in Mumbai, covering a total of 38 DOTS centers and a three million population, to establish the MDR rates both in new- and treatment failure patients.

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In total, 724 sputum positive patients were studied between 2004-2007. Whilst 231 were first line treatment failures with positive smears, despite five months of treatment, 493 represented new patients with their initial sputum studied, and prior to initiation of TB treatment. A major strength of this study was that the quality was assured by all samples being sent single blinded to the WHO SNRL in Sweden, for external quality assurance. Alarming high levels of resistance were observed in this study, with a 41% MDR-TB rate in first line treatment failures. More worryingly, a 24% MDR rate was encountered in newly diagnosed, previously untreated patients.

Whilst indeed this data, coming from a hyper-endemic area like Mumbai will not represent the average situation in the diverse and huge India, it does serve to point out that MDR-TB rates in such pockets in the country exceed the national averages depicted in the WHO report for the whole of India. Knowing there are multiple metropolises like Mumbai in India with similar human density and health situations, it is conceivable that a considerable part of the population in India unfortunately suffers from a much higher rate of MDR-TB, than reflected in the current WHO document. This is apart from the fact that for several reasons, there may be a major part of the Indian population not seeking adequate health care, when confronted with symptoms of TB.

What is urgently needed is a national and representative resistance survey in India, as has been conducted in China, where a first nationwide survey was organized in 2007, and confirmed previously published estimates based on extrapolation from sub national level data [4]. Whether the RNTCP (Revised National TB Control Program) will have the political courage and the funds to undertake this huge undertaking is unclear, but without this, the true extent of India's MDR-TB crisis will remain obfuscated.

Moreover, the magnitude of the resistance problem in India may not be restricted to MDR-TB.

In 2011, TB patients with an extreme form of drug-resistance were encountered in our MDR-TB clinic at the Hinduja Hospital and Research Center in Mumbai, and provisionally indicated as Totally Drug Resistant TB (TDR-TB). The first four of these cases were reported in a short letter to *Clinical Infectious Disease* [5], as the *Mycobacterium tuberculosis* isolates of the respective patients were resistant to all the 12 drugs our *mycobacterial* laboratory was performing DST on: isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, both the older and newer fluoroquinolones (ofloxacin and moxifloxacin), three injectable second-line drugs (kanamycin, amikacin, capreomycin), and the two most commonly used Group 4 drugs: ethionamide and Para-amino Salicylic acid (PAS). Second-line drugs had been misused in India for several decades, hence, this amplified form of drug resistance was not unexpected, but yet confronting. It was the choice of the author's terminology 'Totally Drug Resistant' that stirred up an unprecedented storm of international attention and controversy in the lay press and the medical literature. However, such cases of 'extremely' or 'totally' drug resistant TB were not really new. In practice, the terminology follows the actual situation with a delay of several years. While in 2006, the term 'Extensively Drug Resistant TB' (XDR-TB) was introduced as a new phenomenon in Europe. In the period 2003-2006, already 10% of the MDR-TB cases were already XDR-TB, as retrospective analysis confirmed [6]. Even before that, in 2006, Migliori already reported two TDR-TB cases, like the one reported in India in 2011 [7], in immigrants to Italy [8]. Both had failed to respond to any drug and died after a protracted course. The next description of cases with this pattern of resistance was from Velayati, who reported 15 cases in Teheran, Iran,

of whom 43% were immigrants [9]. No details are available on the outcome of these cases.

The Indian government, initially, very critical and then defensive about these TDR-TB cases, was eventually galvanized into action, partly as a response to all the international attention this topic had been receiving in the press. They put into motion a number of promising measures. Notification of Tuberculosis became compulsory from May 2012. The staff and budget for TB control in Mumbai increased six-fold. The Union TB budget increased by 70%, and large sums of money were spent to upgrade infrastructure, and to strengthen the laboratory capacity in the city and the state of Maharashtra. The WHO response was even more immediate. Within a week after the publication on TDR-TB, they published a set of frequently asked questions and answers on this new terminology, on their web site. A few months later, at a meeting of experts in Geneva, they reached the consensus that whilst patterns of TB with resistance worse than XDR-TB, were clearly increasing and represent a formidable challenge, a new definition of resistance beyond XDR could not be recommended, in view of the huge impact this would have on lab capacity. Moreover, also the definition of XDR-TB in itself was already doubtful, as the extent of drug resistance in such cases and the prognosis of the concerned patients already differs significantly [10]. They also stressed that the reliability, reproducibility of DST and correlation with the *in vivo* consequences was unclear. In fact, the magnitude of the problem of increasing drug resistance in TB cases in hot spots worldwide is therefore, not monitored and will remain hidden, until we will be forced into investment in visualizing the cruelty of this vastly incurable disease, by increasing mortality. After all, this may be a natural, evolutionary response of *M. tuberculosis* to the increased and uncontrolled exposure to anti *tuberculosis* drugs, and once created, this monster may be hard to control [11].

Currently, we have a cohort of 16 patients with TDR-TB in our hospital in Mumbai. They are all from poorer walks of life, and with an average age of 32, they are the young bread earners of their families. They are male and female in equal ratio, and have seen an average of four doctors in the public and private sectors, and received a mean of 9.33 drugs for an average period of 26 months, before being labelled 'TDR-TB' by us. Indeed, each TDR-TB patient holds a mirror to the way MDR-TB is mismanaged in India. Each TDR-TB patient represents a collective failure of all the players involved in health care in the country.

The WHO report also presents MDR-TB therapies championed by the Stop TB and TB Alliance, none of which are completely effective. However, there is a cheap, safe and inexpensive drug, which has the promise to cure any pulmonary TB infection, regardless of its degree of antibiotic resistance. This drug is the old neuroleptic phenothiazine, Thioridazine (TZ), which has been confirmed to have *in vitro* activity against MDR [12,13], and XDR *M. tuberculosis* clinical isolates [14]. Although the *in vitro* concentrations of TZ that completely inhibit replication of *M. tuberculosis* are well beyond clinical reach, concentrations that are quite low and routinely present in the serum of psychotic patients moderately treated with TZ, promote the killing of intracellular *M. tuberculosis* by non-killing macrophages [14-16]. Moreover, when used as a sole drug, TZ significantly reduces the number of pansusceptible and MDR-TB bacilli in pulmonary infections, in a well established mouse model [17,18]. In addition, it enhances the effectiveness of first line antibiotics in the same model, when used in combination [18]. Moreover, TZ has also been successfully applied in compassionate use in 17 XDR-TB patients in Buenos Aires, in combination with other drugs [19]. When used as a

sole drug, it rapidly improved the quality of life of an XDR-TB patient [11], suggesting that TZ should be considered as a 'salvage drug'. Both studies have shown that no dramatic side effects theoretically could be induced by TZ therapy, namely cardio-pathology, have been noted [11,19]. Thereby, TZ in combination with antibiotics to which the initial infecting micro-organisms were resistant to seems to increase the intracellular concentration of these compounds to a level intracellular killing can be achieved [14-16]. Because of its dual action of TZ that enhances killing of intracellular *M. tuberculosis* via the indirect activation of phagolysosomal hydrolases [15,16], and its ability to inhibit efflux pumps of these organisms, which extrude the antibiotic(s), prior to reaching their intended targets [20], this drug seems highly valuable, especially in the therapy of TDR-TB, in which almost all other drugs fail [21-23]. Targeting the macrophage for activation of its killing machinery is believed to by-pass any mutational response by the micro-organism [21-23].

As of this writing, the WHO, neither TB Alliance nor Stop TB organizations, have shown any direct interest in pursuing the possibility of using TZ as an effective adjunct in the therapy of antibiotic resistant pulmonary TB infections. Rather, the therapies presented in the 2012 WHO report, are limited to those of the latter two organizations alone. This we believe is a disservice to those patients who are non-responsive to the available therapeutic modalities, especially when these afflicted cases are in regions of the world that are economically limited. An effective anti-MDR/XDR and probably TDR drug that is extremely cheap and safe to use in hands of a competent physician, could shortly have a major impact on the survival rates. How many more TB patients will needlessly suffer and die from an infection that in fact can be cured by an existing, cheap drug?

References

1. Global *tuberculosis* report 2012 (2012) World Health Organisation (WHO), Geneva, Switzerland.
2. WHO Report 2010-Global Tuberculosis Control (2010). World Health Organisation (WHO), Geneva, Switzerland.
3. Almeida D, Rodrigues C, Udwadia ZF, Lalvani A, Gothi GD, et al. (2003) Incidence of multidrug-resistant *tuberculosis* in urban and rural India and implications for prevention. *Clin Infect Dis* 36: e152-e154.
4. D'souza DT, Mistry NF, Vira TS, Dholakia Y, Hoffner S, et al. (2009) High levels of multidrug resistant *tuberculosis* in new and treatment-failure patients from the Revised National Tuberculosis Control Programme in an urban metropolis (Mumbai) in Western India. *BMC Public Health* 9: 211.
5. <http://www.flutrackers.com/forum/showthread.php?t=25164>.
6. Devaux I, Manissero D, Fernandez de la Hoz K, Kremer K, van Soolingen D (2010) Surveillance of extensively drug-resistant *tuberculosis* in Europe, 2003-2007. *Euro Surveill* 15.
7. Udwadia ZF, Amale RA, Ajbani KK, Rodrigues C (2012) Totally drug-resistant *tuberculosis* in India. *Clin Infect Dis* 54: 579-581.
8. Migliori GB, De Iaco G, Besozzi G, Centis R, Cirillo DM (2007) First *tuberculosis* cases in Italy resistant to all tested drugs. *Euro Surveill* 12: E070517.
9. Velayati AA, Masjedi MR, Farnia P, Tabarsi P, Ghanavi J, et al. (2009) Emergence of new forms of totally drug-resistant *tuberculosis* bacilli: super extensively drug-resistant *tuberculosis* or totally drug-resistant strains in Iran. *Chest* 136: 420-425.
10. van Ingen J, de Lange WC, Boeree MJ, Iseman MD, Daley CL, et al. (2011) XDR tuberculosis. *Lancet Infect Dis* 11: 585.
11. Udwadia ZF, Sen T, Pinto LM (2011) Safety and efficacy of thioridazine as salvage therapy in Indian patients with XDR-TB. *Recent Pat Antiinfect Drug Discov* 6: 88-91.
12. Amaral L, Kristiansen JE, Abebe LS, Millett W (1996) Inhibition of the respiration of multi-drug resistant clinical isolates of *Mycobacterium tuberculosis* by thioridazine: potential use for initial therapy of freshly diagnosed tuberculosis. *J Antimicrob Chemother* 38: 1049-1053.
13. van Ingen J, van der Laan T, Amaral L, Dekhuijzen R, Boeree MJ, et al. (2009) *In vitro* activity of thioridazine against *mycobacteria*. *Int J Antimicrob Agents* 34: 190-191.
14. Martins M, Viveiros M, Ramos J, Couto I, Molnar J, et al. (2009) SILA 421, an inhibitor of efflux pumps of cancer cells, enhances the killing of intracellular extensively drug-resistant *tuberculosis* (XDR-TB). *Int J Antimicrob Agents* 33: 479-482.
15. Ordway D, Viveiros M, Leandro C, Bettencourt R, Almeida J, et al. (2003) Clinical concentrations of thioridazine kill intracellular multidrug-resistant *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 47: 917-922.
16. Amaral L, Viveiros M, Kristiansen JE (2006) "Non-Antibiotics": alternative therapy for the management of MDRTB and MRSA in economically disadvantaged countries. *Curr Drug Targets* 7: 887-891.
17. Martins M, Viveiros M, Kristiansen JE, Molnar J, Amaral L (2007) The curative activity of thioridazine on mice infected with *Mycobacterium tuberculosis*. *In Vivo* 21: 771-775.
18. van Soolingen D, Hernandez-Pando R, Orozco H, Aguilar D, Magis-Escorra C, et al. (2010) The antipsychotic thioridazine shows promising therapeutic activity in a mouse model of multidrug-resistant tuberculosis. *PLoS One* 5.
19. Abbate E, Vescovo M, Natiello M, Cufre M, Garcia A, et al. (2012) Successful alternative treatment of extensively drug-resistant *tuberculosis* in Argentina with a combination of linezolid, moxifloxacin and thioridazine. *J Antimicrob Chemother* 67: 473-477.
20. Amaral L, Martins M, Viveiros M (2007) Enhanced killing of intracellular multidrug-resistant *Mycobacterium tuberculosis* by compounds that affect the activity of efflux pumps. *J Antimicrob Chemother* 59: 1237-1246.
21. Amaral L, Udwadia Z, Abbate E, van Soolingen D (2012) The added effect of thioridazine in the treatment of drug-resistant *tuberculosis* [Correspondence]. *Int J Tuberc Lung Dis* 16: 1706-1708.
22. Amaral L, Molnar J (2012) Why and how the old neuroleptic thioridazine cures the XDR-TB patient. *Pharmaceuticals* 5: 1021-1031.
23. Amaral L, Molnar J (2012) Why and how thioridazine in combination with antibiotics to which the infective strain is resistant will cure totally drug-resistant tuberculosis. *Expert Rev Anti Infect Ther* 10: 869-873.