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Shorter & cheaper regimen to treat multidrug-resistant tuberculosis: A new hope

Multidrug-resistant tuberculosis (MDR-TB) is defined as a disease due to *Mycobacterium tuberculosis* that is resistant to at least both rifampicin and isoniazid with or without resistance to other anti-tuberculosis (TB) drug. Rifampicin-resistant TB (RR-TB) is defined as resistance to rifampicin detected using genotypic or phenotypic methods with or without resistance to other anti-TB drugs. MDR-TB/RR-TB is emerging as a major problem due to poor management of drug-sensitive as well as drug-resistance TB. MDR-TB is treatable but is very expensive, requires long duration of treatment (usually two years) and contains potentially toxic drugs[1-4].

The Global Tuberculosis Report 2016 estimated that 3.9 per cent newly diagnosed and 21 per cent of previously treated TB cases had MDR-TB. It has been estimated that of the 580,000 cases of TB resistant to at least rifampicin (RR-TB) globally in 2015, 480,000 were resistant to both rifampicin and isoniazid (MDR-TB) and 250,000 deaths were reported due to MDR-TB/RR-TB in 2015 globally. Of the estimated 580,000 MDR-TB/RR-TB cases, only 132,120 (23%) cases were detected and even fewer 124,990 (20%) cases were started on appropriate treatment and only 52 per cent of these were treated successfully[5]. In India, estimates showed that the prevalence of MDR-TB among new and previously treated patients was 2.5 and 16 per cent, respectively. It is estimated that 130,000 cases of MDR-TB/RR-TB emerged in India, of whom 79,000 were among notified cases of TB in 2015. Of the 79,000 MDR-TB/RR-TB cases, only 28,876 (36%) were diagnosed, 26,988 (34%) were started on treatment and treatment success rate was only 46 per cent[5].

The reasons for poor result are probably due to lengthy, expensive and toxic regimens, leading to poor compliance[6]. In May 2016, the WHO recommended the use of a shorter regimen treatment for MDR-TB which was aimed to reduce cost, improve compliance and cure rate[7]. In patients with RR-TB or MDR-TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9-12 months may be used instead of the conventional regimen of usually two years duration. To rule out resistance to second-line drugs, a prerequisite for shorter MDR regimen, the WHO recommends second-line probe assay, a rapid diagnostic test, GenoType MTBDRsL that identifies genetic mutation in MDR strains that detects resistance to fluoroquinolones and injectable second-line anti-TB drugs[8]. The shorter MDR regimen consists of an intensive phase of four months (extended to six months in case of delayed sputum smear conversion) containing high-dose gatifloxacin or moxifloxacin, kanamycin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide and ethambutol followed by a continuation phase of five months containing gatifloxacin or moxifloxacin, clofazimine, ethambutol and pyrazinamide. It can be given to children, adults and people living with HIV who meet above-specified criteria but should not be used in extrapulmonary TB and in pregnant women. This recommendation is based on results of a meta-analysis[5] of initial programmatic studies conducted by the Union, Damien Foundation, Medecins Sans Frontieres and the Antwerp Institute of Tropical Medicine in Belgium, involving 1205 patients with uncomplicated MDR-TB[9-11]. Data of 486 patients under the Damien Foundation pilot programme which was the first study, using a nine-month treatment regimen in Bangladesh, showed cure rate of 82.1 per cent and overall success rate of 84.5 per cent[9]. This study was followed by the Union coordinated first multi-country MDR-TB patient cohort study of 1000 patients in nine countries of West Africa

(Benin, Burkina-Faso, Burundi, Cameroon, Côte d'Ivoire, Central African Republic, Niger, Democratic Republic of Congo and Rwanda), treated with a modified Bangladesh regimen[12]. Interim analysis of 408 patients has demonstrated 82.1 per cent treatment success rate, demonstrating that the nine-month regimen can be successful in other environments than Bangladesh, and also in settings with high HIV prevalence[12]. They showed that shorter MDR-TB treatment regimens given in patients who met specific inclusion criteria had a significantly higher likelihood of treatment success than those who received longer conventional regimens (89.9 vs. 78.3%)[7]. Currently, Union-sponsored and USAID-supported STREAM (Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With Multi-Drug-Resistant Tuberculosis) Stage1 study (multicentre international randomized controlled trial)[13] which was started in July 2012 to evaluate shortened regimens for patients with MDR-TB, is underway and results are expected early in 2018. STREAM has been recently expanded (Stage 2)[14,15] to test two additional shortened treatment regimens using bedaquiline. This expanded study will evaluate a nine-month all-oral regimen without injections and an even shorter simplified six-month regimen. It is expected to finish enrolment of patients in 2018 and initial results are expected by 2020. There are a number of other oral regimens without injections under evaluation, of which under phase 3 evaluation are STAND (Shortening Treatment by Advancing Novel Drugs)[16] and NIX TB trials[17]. STAND trial consists of moxifloxacin, pretomanid and pyrazinamide and NIX TB trial consists of bedaquiline, pretomanid and linezolid with duration of treatment of six months.

The recently recommended shorter regimen by WHO has proven successful in developing countries like Bangladesh[9]. Hence, it should also be effective in country like India. Shorter regimen will improve compliance as it reduces duration by almost half, cost by one-third and number of adverse events which ultimately will lead improvement in treatment success rate. Decision-makers of especially high TB burden countries like India need to make use of new opportunity by adapting WHO-recommended shorter MDR-TB regimen to fulfil the goal of end TB strategy by 2030 or earlier[18] as envisaged in sustainable development goal 3.3[19].

***Conflicts of Interest*:** None.

Rajendra Prasad[1,*], Nikhil Gupta[2] & Amitabh Banka[1]

[1]Department of Pulmonary Medicine, ERA's Lucknow Medical College & Hospital & [2]Department of General Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow 226 024, Uttar Pradesh, India

[*]*For correspondence:* rprasadkgmc@gmail.com

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