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Short Communication

Shorter Regimen to Treat Multidrug Resistant Tuberculosis and Rifampicin Resistant Tuberculosis

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Multidrug resistant-tuberculosis (MDR-TB) is defined as disease due to *Mycobacterium tuberculosis* resistant to atleast rifampicin and/or isoniazid, two main drugs in the armamentarium against tuberculosis (TB). Rifampicin resistant-TB (RR-TB) is defined as mono-resistance to rifampicin detected using genotypic or phenotypic techmiques with or without resistance to other anti-TB drugs. RR-TB is emerging as a major health problem due to poor management of drug sensitive as well as drug resistance TB. MDR-TB is treatable but involves very high health-care costs with an extended duration of the treatment (usually 2 years) and contains potentially toxic drugs.[1-4]

The Global Tuberculosis Report 2016 estimated that of 3.9% newly diagnosed and 21% of previously treated TB cases had MDR-TB. It has been estimated that almost 6 lakh cases have RR-TB globally in 2015; of whom approximately 5 lakh cases had MDR-TB and with a significant mortality of 2.5 lakh patients. Out of these 6 lakh cases only 23% were detected and 50% cases were able to complete the treatment successfully with anti-TB therapy (ATT).

In India, estimated prevalence of MDR-TB among new and previously treated patients was 2.5% and 16%, respectively.[5,6] It is estimated that there was a total of 1.30 lakh cases of MDR-TB in India in 2015, out of which 79,000 were notified cases of TB. Out of these 79,000 notified cases 30,000 were diagnosed with a treatment success rate of 46%.[5] The reasons for poor outcome are possibly due to lengthy, expensive and toxic regimens leading to poor compliance.[7] World Health Organization update 2016 for drug-resistant TB has introduced a shorter treatment regimen for MDR-TB/RR-TB with an aim to reduce the cost of treatment, thereby improving the compliance and cure rate.[8] In patients with RR-TB or MDR-TB who have not been previously treated with second-line drugs and in whom resistance to flouroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen for a duration of 9-12 months may be used instead of a conventional regimen of usually two years duration.

Shorter MDR-TB regimen consists of intensive phase of four months (extended upto 6 months in case of non-conversion of sputum smear) with gatifloxacin or moxifloxacin, kanamycin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol followed by a continuation phase of five months with gatifloxacin or moxifloxacin, clofazimine, ethambutol, and pyrazinamide. Doses of each drug in shorter MDR-TB regimen are given in the table below.

Table. Anti-tuberculosis drugs and doses used in shorter MDR-TB regimen

Antituberculosis Therapy	Weight Band (in Kg/day)		
	<33	33 to 50	>50
Moxifloxacin	400 mg	600 mg	800 mg
Clofazimine	50 mg	100 mg	100 mg
Ethambutol	800 mg	800 mg	1200 mg
Pyrizinamide	1000 mg	1500 mg	2000 mg
Isoniazid	300 mg	400 mg	600 mg
Prothionamide	250 mg	500 mg	750 mg
Kanamycin	15 mg per kilogram body weight (maximum 1000 mg)		

Short-course regimens can be given to children, adults and people living with human immuno-deficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS) who are smear positive, but these may not be used in patients having extra-pulmonary TB and in pregnant females.[9-13] Under the Damien Foundation pilot programme, using a 9-month treatment regimen in Bangladesh (n=515), cure rate of 82.1% and overall success rate of 84.5% was reported.[9-13] Whether the shorter MDR-TB regimen will work in all settings and especially outside trial conditions needs further research.

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However, the fundamental approach of the shorter regimen is practically the same as of conventional 24 months treatment. Shorter regimen is using the same number of drugs including flouroquinolones, a second-line injectable and two other drugs. The only difference is that fluoroquinolone used is gatifloxacin or moxifloxacin instead of levofloxacin and replacement of cycloserine with clofazimine.[13]

This study was followed by The Union coordinated first multi-country MDR-TB patient cohort study of 1000 patients in 9 countries of West Africa (Benin, Burkina-Faso, Burundi, Cameroon, Côte d'Ivoire, Central African Republic, Niger, Democratic Republic of Congo and Rwanda), treated with modified Bangladesh regimen.[14] Interim analysis of 408 patients showed a treatment success rate of 82.1%, thereby demonstrating that the 9-month regimen can be successful in other environment settings than Bangladesh, and also in settings with high HIV prevalence. They also showed that shorter MDR-TB treatment regimens given in patents who met specific inclusion criteria had a statistically-significant higher likelihood of treatment success than those received longer conventional regimens (89.9% *versus* 78.3%). It will improve adherence, drug safety, tolerability, and reduces cost of treatment to approximately half of the conventional MDR-TB regimen. Shorter MDR-TB regimen will be the useful tool in the fight against drug-resistant TB, if properly utilised.

An important issue which may need to be addressed is whether management of MDR-TB with a shorter regimen in large-scale national prgrammes will lead to XDR-TB. Currently, there is no evidence to this dilemma as shorter regimen has produced excellent results under the operational research conditions in some settings.[13] Presently, the strongest risk for unfavourable outcome with shorter MDR-TB treatment regimen is high level of fluoroquinolone resistance, especially when associated with initial pyrazinamide resistance.[13]

If resistance is present for one or more drugs in the shorter regimen, these could be replaced with linezolid, delamanid or bedaquiline and maintain shorter treatment duration. The resistance to pyrizinamide, even if evident by reliable drug susceptibility testing (DST) is not an absolute contraindication for the shorter regimen; unless there are indications that one or other drugs in the regimen are also resistant. Currently, Union-sponsored and United States Agency for International Development (USAID) supported Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB (STREAM) stage 1 study (multi-center international randomised controlled trial), started in July 2012 to evaluate shortened regimens for patients with MDR-TB is underway and results are expected in 1st quarter of 2018.[14-16] STREAM has recently expanded (stage 2) to test two additional shorter treatment regimens using bedaquiline.[16] This expanded arm will evaluate a 9-month all-oral regimen without injections and an even shorter simplified 6-month regimen. It will finish enrollment of patients in 2018 and initial results are expected by 2020.

In conclusion, shorter and successful treatment for MDR-TB is now with us, especially in high burden countries like India. The decision makers of high TB burden countries need to make use of this new WHO recommended shorter MDR-TB regimen to treat MDR-TB/RR-TB cases, and fulfil the goal of "End TB strategy by 2030".[17]

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