

SHORT-COURSE REGIMEN FOR MULTIDRUG-RESISTANT TUBERCULOSIS: MYTH OR REALITY!

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Tuberculosis (TB) is a slowly progressive disease and its treatment is prolonged and difficult. For decades it is a major global health problem. An important landmark towards eradication of TB was the development of short course chemotherapy. But with emergence of drug resistant TB, especially Multidrug-resistant TB (MDR-TB), it has taken a different course and has become a public health crisis. It is threatening TB control worldwide. Globally about 580,000 new cases of rifampicin-resistant (RR) or MDR-TB occurring every year.¹

The conventional treatment for MDR-TB lasts 20–24 months, is often toxic and half of the treated patients have poor outcomes.² Due to this long duration of treatment and side effects of the drugs, many patients failed to complete the treatment or stopped the treatment before completion. Implementation and continuation of this long duration of treatment especially in high burden countries like Pakistan results in tremendous burden on the health system of the country.

Development of new and more efficient diagnostic technology and new drugs, is the response required for control of MDR-TB. With the introduction of

rifampicin (RMP) into TB drugs for drug sensitive TB, new era of its treatment began has “short-course treatment strategy”.³ Such a strategy for MDR-TB was long overdue. It is encouraging to observe this progress with development of a short-course treatment strategy for MDR-TB referred to as the 'Bangladesh' regimen, also acknowledged by the World Health Organization (WHO) in May 2016. This WHO recommended shorter regimen is a for 9-12 months duration, aiming for higher effectiveness, tolerability, adherence and completion rates.⁴

This short regimen consists of kanamycin (KM) (an injectable agent), moxifloxacin (Mfx), prothionamide (Pto), clofazimine (Cfz), isoniazid (INH) (high dose), pyrazinamide (PZA), and ethambutol (EMB), given together in an initial phase of 4 months (with the possibility to extend to 6 months in case of sputum-smear remaining positive at the end of month 4), and followed by 5 months of treatment with four of the medicines (Mfx, Cfz, PZA, EMB). The newly discovered drugs Bedaquiline and delamanid are not recommended till date to be included in the shorter regimen of MDR-TB treatment.⁵ The dosage schedule for shorter regimen of MDR-TB is summarized in Figure 1.

Figure 1: Summary of shorter regimen for MDR-TB



Table 1: Dosage schedule according to body weight used in shorter regimen for MDR-TB

Drug	Weight Group		
	Less than 30Kg	30 Kg to 50Kg	More than 50Kg
Gatifloxacin	400mg	600mg	800mg
Moxifloxacin	400mg	600mg	800mg
Clofazimine	50mg	100mg	100mg
Ethambutol	800mg	800mg	1200mg
Pyrazinamide	1000mg	1500mg	2000mg
Isoniazid	300mg	400mg	600mg
Prothionamide	250mg	500mg	750mg
Kanamycine *	15mg per kilogram body weight (maximum 1g)		

* For adult over 59 years of age, the dose will be reduced to 10mg/kg (max dose 750mg)

The recommended doses of drugs (Table 1) in this regimen is based on dosage by weight published by the Global Drug-resistant TB Initiative in 2015 and the “standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis” (STREAM) trial.^{6,7} All the medicines are taken once a day, all days of the week. In case of prolonged intensive phase, the injectable agent is only given three times a week after the 4th month.

For this treatment strategy recommendations were based on the promising results of large observational cohorts in Asia and Africa. There were several studies being conducted to shorten the duration of regimen for MDR TB.⁵ Different studies pointed out that this shorter regimen give relapse free cure rate in more than 85% of selected cohort of MDR TB patients.⁸⁻¹¹

For the support of this new shorter regimen, studies referenced by WHO started with the Bangladesh Regimen, a Damien Foundation study based on the pioneering work of Dr Armand Van Deun. They used a nine-month treatment regimen to treat 515 patients between 2005-2011. The success rate was 84.5%, compared with the 24-month standard treatment of around 50%.¹⁰ This was followed by the Union-coordinated West and Central Africa Francophone study. This was the first multi-country MDR-TB patient cohort treated using the nine-month regimen in nine countries (Benin, Burkina-Faso, Burundi, Cameroon, Cote d'ivoire, Central African Republic, Niger, Democratic Republic of Congo and Rwanda). The study was funded by the French 5% Initiative, through the national agency Expertise France, and had similarly high success rates 82.1%. Currently ongoing is the STREAM trial which is supported by US Agency for International Development (USAID), this is a Union-sponsored multi-centre international

randomized control trial to evaluate shortened regimens for patients with MDR-TB. The first trial has been on-going in Ethiopia, South Africa, Vietnam and Mongolia and has recently expanded to test two additional shortened treatment regimens using bedaquiline, a new medicine from Janssen Pharmaceuticals. This stage will evaluate a nine-month all-oral regimen, that does not require painful injections, and a simplified six-month regimen.

The shorter MDR-TB regimen should only be used in patients with the diagnosis of RR-/MDR-TB who have been reliably confirmed by an approved molecular (Xpert MTB/RIF) or phenotypic DST method. This treatment may be also introduced into the children and people with human immunodeficiency virus (HIV). There are few conditions for the MDR-TB patients where this treatment is not recommended;⁵

- (1). Patients with resistance to any of drugs in the shorter regimen (excluding resistance to INH)
- (2). If the patient's previous exposure (> 1 month) to a second line medicine included in the shorter MDR-TB regimen
- (3). Any intolerance to one or more medicines in the shorter MDR-TB regimen or increased risk of toxicity (e.g., drug-drug interactions, cardiotoxicity)
- (4). Pregnancy
- (5). Extrapulmonary disease
- (6). If any of the medicine in the shorter MDR-TB regimen not available in the program.

Exposure to fluoroquinolone (FQ) or any second-line injectable for more than 1 month, not included in shorter regimen but may generate cross resistance. In such condition it is necessary to perform a reliable

drug susceptibility testing (DST) for both drugs and if result show negative for both drugs then the shorter MDR-TB regimen can be used. Detection of pyrazinamide resistance at the start of treatment by using a reliable DST may also an important point for the start of this treatment strategy.

There are other circumstances where a clinician can use longer duration of regimen, for example, uncertainty about drug susceptibility; there is no access to second-line line probe assay (LPA); unavailability of one or more medicines; or the patient condition requires immediate start of treatment.

There are some instances where shorter MDR-TB regimen may be stopped and a longer, individual MDR-TB regimen may be started;

- (1). DST results taken after start of treatment fail to confirm resistance to rifampicin or even TB (i.e., initial results were not valid);
- (2). DST results show resistance to medicines in the shorter MDR-TB regimen
- (3). Lack of response to treatment (e.g., no sputum smear conversion by 6 months or clinical condition not improve despite treatment);
- (4). When somebody initiated treatment and took treatment for more than one month and then defaulted and after declared default again visited for treatment, such patient don't suitable for short regimen.

The patients on shorter MDR-TB regimen should be followed up and monitored like the patients on longer MDR-TB treatment. Response to treatment should be monitored by monthly sputum smear microscopy and DST. The shorter MDR-TB regimen is a reality, and it should be adapted by the national TB control programme in eligible group of MDR-TB patients irrespective of age and HIV status. This regimen can cut the cost burden of treating MDR-TB patients on health system of the country.

Pakistan is among the top TB/MDR-TB burden countries. According to 2015 global report, an estimated MDR/RR-TB cases in Pakistan were 14000, 4.2% new cases and 16% among previously treated cases. Out of these only 2553 (18.2%) MDR/RR-TB and 68 (0.4%) XDR-TB patients were enrolled for treatment.

A recent survey about the prevalence of MDR-TB in Pakistan conducted by Javaid et al, (2017)¹² suggest that approximately 50% of MDR-TB patients will not be eligible for the short course of MDR-TB.

Another study by Javaid et al. (2016), showed that

among 832 culture confirmed MDR-TB patients, 49% were resistant to Fluroquinolone (FQ). Moreover this study also suggest high resistance to pyrazinamide (PZA) & ethambutal (EMB), which are part of the regimen but decision about the regimen selected is not based on resistance to PZA and EMB.¹³

The fact that almost 50% of the MDR-TB in a country like Pakistan will not be eligible for this short course regimen makes the applicability of this regimen rather doubtful. It is high time that concerned health authorities through out the country adopt strict rules for rational use of drugs, ban use of FQ and antibiotics without proper prescription and stop self medication of TB.

Despite the limitations of short course regimen mentioned above and considering the potential of the short course therapy in terms of efficacy and cost effectiveness it is right time for NTP to adopt this newly recommended regimen in a high burden countries like Pakistan.

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