Shorter drug regimen of multidrug-resistant tuberculosis and the ambiguity in the World Health Organization recommendations

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Abstract

Organizations all over the world are trying to shift towards making healthcare intervention more acceptable to the consumers at large, but any intervention made has its cost-effective and cost-beneficial implications which should be taken into consideration while incorporating changes. A recent change of switching to shorter regimen for multidrug-resistant tuberculosis (MDR-TB) can be a landmark step in the treatment of the disease but it has its own limitations which need to be addressed.

Keywords: Drug regimen, multidrug-resistant tuberculosis, tuberculosis, World Health Organization

BACKGROUND

It has been a trend to make health-care intervention more acceptable to the consumers at large, but any intervention made has its cost-effective and cost-beneficial implications which should be taken into consideration while incorporating changes. A recent change of switching to shorter regimen for multidrug-resistant tuberculosis (MDR-TB) can be a landmark step in the treatment of the disease. The World Health Organization (WHO) is in a switch phase from the earlier 20-month (intensive phase of 8 months followed by continuation phase of 12 months) MDR-TB treatment as against the new short regimen of 9–12-month standardized alternative (shorter MDR-TB regimen) which includes an intensive phase of 4 months followed by a continuation phase of 5 months which contains kanamycin, moxifloxacin (or gatifloxacin), prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol. It achieved success in 83.7% of patients evaluated in a meta-analysis used to inform new WHO guidelines that recommended the shorter MDR-TB regimen.[1]

First, the guidelines leave considerable uncertainty about the recommendations made which are conditional with very low certainty of evidence. All the recommendations made are purely on the basis of observational studies which hold low credibility in the hierarchy of evidence. Individual patient data from Bangladesh (n = 493; supported by the Damien Foundation),[2] Uzbekistan (n = 65; supported by Médecins sans Frontières)[3] as well as aggregated data from Cameroon (n = 150),[4] Niger (n = 65),[5] and seven sub-Saharan African countries (n = 408; supported by the International Union Against Tuberculosis and Lung Disease [UNION]) were included in the

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analysis (total number of observations = 1205, of whom 89 cases were lost to follow-up and were therefore excluded in certain analyses). These were compared with the outcomes of patients without previous exposure to second-line TB drugs who were included in the adult individual patient data analysis (n = 7665).[6] The standard outcomes used in the intervention and comparator arms largely complied with the standardized outcomes used by TB programs.[7,8] The analyses performed for the evidence assessment showed that patients who met specific inclusion criteria for receiving the shorter MDR-TB treatment regimens had a statistically significant higher likelihood of treatment success than those who received longer regimens – 90% versus 78% when success was compared with treatment failure/relapse/death and 84% versus 62% when compared with treatment failure/relapse/death/loss to follow-up but the sample size of these studies was lower and the power of the study was not apt for the inferences being utilized at such a large scale. The number of relapses was very low, but this might be again due to the relatively small number of patients followed up. As expected, treatment success was lower among patients with additional resistance to pyrazinamide and/or fluoroquinolones on shorter MDR-TB regimens, even if in general, it remained high and exceeded that in the patients on longer regimens (although the differences were not statistically significant). The shorter regimen of MDR treatment Guidelines Development Group themselves consider the studies of supporting evidence as the one with very low quality of evidence. Therefore, weakening the explanation of switching to a shorter regimen of treatment. All data analyzed for the shorter regimen were derived from observational studies. The results of randomized controlled trial were not expected before the end of 2017. Either the WHO should come up with results of such trials or modify the shorter regimen treatment due to the lack of certainty of evidence and bias in the studies which inferred in favor of shorter regimen of MDR treatment.[9] The evidence for the effectiveness and safety of the shorter MDR-TB regimen derives from studies where this treatment was administered under fairly standardized conditions with relatively little variation in the content and duration. Thus, the recommendation on the use of the shorter MDR-TB regimen is made under the premise that it is implemented as per the composition and duration used in the observational studies and therefore is not necessary to be implemented in all settings of the globe. Replacement of medicines and prolongation/shortening of the duration would only be permissible within the parameters applied in these studies (e.g., gatifloxacin replaced by moxifloxacin; prothionamide replaced by ethionamide; intensive phase prolonged up to 6 months in case of no sputum conversion).

Second, there is no reliable data available on the costs of shorter TB regimens and its impact on health equity which still remains unanswered. In order to reproduce the high cure rates achieved by the studies included in the reviews for the shorter regimen guidelines, all efforts need to be made to avoid the acquisition of additional resistance, through careful selection of patients to be enrolled, and effective patient support to enable full adherence to treatment. Hitherto, the issue with treatment of TB has been the compliance and adherence to the treatment, if the shorter regimen again requires a strict adherence to treatment, failing which would invite a rapid and new emergence of drug-resistant organisms which will be even more difficult to treat and leading to increased burden of Extensively Drug Resistance (XDR) globally and thus increasing the socioeconomic burden across the globe. It is recommended that patients be tested for susceptibility or resistance to fluoroquinolones and to the second-line injectable agent used in the regimen before being started on a shorter MDR-TB regimen. This has again increased the complexity of treatment in the already existing algorithms. Patients with strains resistant to any of the two groups of medicines should be transferred to treatment with a longer, individualized regimen. The availability of reliable and rapid tests would be essential to decide which patients would be eligible for shorter MDR-TB regimens, and what modifications to longer MDR-TB regimens are necessarily based on the resistance detected. All these modifications, just increase the complexity and feasibility of treatment which is questionable in the resource settings where MDR TB is more prevalent such as African and Asian regions. It is essential to mention here that the resistance toward XDR will increase due to such modifications. The recommendations suggest that representative drug-susceptibility testing surveillance data may be used to indicate populations of eligible patients. However, they fail to expand to which drugs and at what prevalence of resistance the shorter MDR-TB regimen can be given or should be avoided. In patients with confirmed rifampicin-resistant TB or MDR-TB, the MTB DR/assay may be used as the initial test, over culture and phenotypic Drug Susceptibility Testing (DST), to detect resistance to fluoroquinolones and to the second-line injectable drugs (conditional recommendations; certainty of evidence for direct testing of sputum from low to moderate). This applies to testing in both children and adults.
Indirect testing may include biological samples from extrapulmonary sites. While resistance-conferring mutations to fluoroquinolones detected by the MTB DRsl assay are highly correlated with phenotypic resistance to ofloxacin and levofloxacin, the correlation with moxifloxacin and gatifloxacin is less clear, and the inclusion of moxifloxacin or gatifloxacin in an MDR-TB regimen is best guided by phenotypic DST results. In patients with confirmed rifampicin resistant (RR)-TB or MDR-TB, WHO now recommends that the GenoType Mycobacterium tuberculosis drug-resistant second-line assay (MTBDRsl) be used as an initial direct test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones and second-line injectable drugs (conditional recommendation; the certainty of evidence low to moderate).[10,11] This applies to test in both children and adults. While resistance-conferring mutations to fluoroquinolones detected by the MTBDRsl assay are highly correlated with phenotypic resistance to ofloxacin and levofloxacin, the correlation with moxifloxacin and gatifloxacin is less clear, and the inclusion of moxifloxacin or gatifloxacin in an MDR-TB regimen is best guided by phenotypic DST results.

Third, in settings in which laboratory capacity for DST to fluoroquinolones and injectable agents is not yet available, the clinician and the TB program manager would need to decide on the basis of the likelihood of resistance to these medicines, informed by the patient's clinical history and recent representative surveillance data. This would depend on the expertise of the individual in a particular setting leading to the failure of implementation of the guidelines.

Fourth, people living with HIV need to be given the same consideration for treatment with the shorter MDR-TB treatment regimen as people who are HIV seronegative. Children were generally excluded from studies of shorter MDR-TB treatment regimens. However, given that the same medicines have been in use in pediatric MDR-TB regimens for many years, there was no plausible biological reason to believe that these regimens would be less effective or safe in children than in adults without actually ascertaining the facts before execution at such a wide scale.

Fifth, pregnancy was an exclusion criterion for the shorter MDR-TB treatment regimen studies. Two of the core components of the shorter MDR-TB regimens – the injectable agent and ethionamide (or prothionamide) – are usually contraindicated in pregnancy.[12] Withholding these medicines from the shorter MDR-TB treatment regimen could seriously compromise its effectiveness. Thus, for pregnant women, it is recommended that a longer individualized regimen be used which can allow the inclusion of four or more effective second-line TB medicines with no known teratogenic properties. This conditional recommendation further increases the complexity of treatment algorithms.

The findings from studies of shorter MDR-TB regimens were limited to patients with pulmonary disease, and they cannot be extrapolated directly to extrapulmonary TB cases. No recommendation is thus possible at this stage to use the shorter regimen in patients with extrapulmonary MDR-TB. Therefore, again reducing the uniformity of treatment in the settings where it is not feasible to go for a change as of now.

Sixth, to reproduce the high cure rates achieved by the studies included in the reviews for this guidance, all efforts need to be made to avoid the acquisition of additional resistance, by ensuring careful selection of patients to be enrolled, and effective patient support to enable full adherence to treatment. It is recommended that patients be tested for susceptibility or resistance to fluoroquinolones and to second-line injectable agents used in the regimen before being started on a shorter MDR-TB regimen. Patients with strains resistant to any of the two groups of medicines are to be transferred to a longer MDR-TB regimen. The availability of reliable and rapid tests would be valuable in deciding (within a few days) which patients would be eligible for the shorter MDR-TB regimen, and what modifications to longer, individualized MDR-TB regimens are necessary based on the resistance detected. Rigorous application of the resistance-and exposure-based criteria would require culture-based drug-susceptibility testing. The Hain MTBDRsl test, recommended for eligibility screening for the short regimen, is not widely available and has suboptimal sensitivity for fluoroquinolones and second-line injectable drugs.[10] Moreover, there is no validated test to rapidly identify resistance to the other drugs.

Seventh, considered eligible are “patients with rifampicin-resistant or MDR-TB in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely”.[8] Later, the document indicates that “the shorter MDR-TB regimen” should not be used in patients who “have documented or likely resistance to medicines in the regimen.”[9] This refinement, however, does not explicitly form part of the recommendation or eligibility criteria.

The uncertainty around this inconsistency affects a large proportion of patients with MDR-TB. As documented in a large meta-analysis, 50% of patients with MDR-TB have isolates resistant to pyrazinamide and 61% to ethambutol.[13]
Although most rifampicin-resistant strains are resistant to isoniazid, at least at low concentrations, this alone does not constitute a threat to the regimen. The specific isoniazid-resistance-conferring mutation, however, has implications for resistance to other drugs in the shortened regimen: Mutation in katG is the most frequent mutation in isoniazid-resistant isolates (66%) and is linked to resistance to high-dose isoniazid; mutations in inhA (21%) may also confer resistance to ethionamide.\[^{[14]}\]

Finally, we address the prior exposure criterion: Eligibility is restricted to patients with rifampicin-resistant or MDR-TB “who have not been previously treated with second-line drugs.”\[^{[1]}\] We note that the vast majority of MDR-TB is due to transmission rather than acquisition (median: 95.9% [95% uncertainty range, 68.0–99.6] of all incident MDR-TB cases).\[^{[18]}\] Their disease may be caused by *M. tuberculosis* strains that have been exposed to second-line drugs before transmission to the patient. Thus, the disease caused by these bacilli may harbor more resistance to other drugs in the regimen. This may be one of the reasons for poorer outcomes in the cohort reported from Uzbekistan (64% of favorable outcomes\[^{[13]}\] vs. 80% in settings with less population exposure to second-line drugs), despite the exclusion of patients with resistance to fluoroquinolones or second-line injectables and patients with previous exposure to second-line drugs. Whether the strain has been exposed to second-line drugs is unknowable, so patients with this risk factor will, inevitably, be included under the current guidance.

Strict application of the exposure and resistance-based criteria would require culture-based drug-susceptibility testing. The Hain MTBDRsl test, recommended for eligibility screening for the short regimen, is not widely available and has suboptimal sensitivity for fluoroquinolones and second-line injectables.\[^{[10]}\] Moreover, there is no validated test to rapidly identify resistance to the other drugs. Although there is tremendous enthusiasm for shorter, more effective MDR-TB treatment, the current WHO guidance on exclusion and practical selection of eligible patients should be refined and clarified. In the absence of such changes, there is considerable risk that, in settings where resistance to other drugs included in the regimen is common among patients with MDR-TB, the shorter regimen will be administered to patients whose profile is very different from those who experienced high proportions of successful treatment in the cohort\[^{[11]}\] studies that led to these recommendations.

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Conflicts of interest
There are no conflicts of interest

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