The WHO Shorter MDR-TB Regimen: Who Will Benefit With It?

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ABSTRACT

Current treatment of multidrug-resistant tuberculosis (MDR-TB) is challenging since it requires the use of more expensive and toxic drugs that must be administered for a much longer time to achieve relapse free-cure and with much less satisfactory outcomes. Early results from observational studies in Bangladesh, Cameroon and Niger using regimens lasting 12 months or less have shown a much higher likelihood of treatment success compared with longer conventional regimens. Given the published data and potential impact of shorter regimens on treatment cost and affordability, the World Health Organization (WHO) is now recommending in its 2016 MDR-TB guideline a new short-course regimen that consists of a 4-6 month intensive phase including kanamycin, moxifloxacin, ethionamide, clofazimine, pyrazinamide, high-dose isoniazid and ethambutol and a 5-month continuation phase that includes moxifloxacin, clofazimine, pyrazinamide, and ethambutol. There are very clear criteria regarding what MDR-TB patients would benefit from this regimen. WHO recommends that patients are 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. However, in the absence of such testing, patients who are highly unlikely to be infected with resistant strains based on history of exposure, use of second-line medicines at country level or recent representative surveillance data may also be eligible for the shorter MDR-TB regimen. Recently published data on patients with MDR-TB from Europe suggest that actually, less than eight percent of patients with MDR-TB in the region would be eligible for the short-course treatment regimen proposed by WHO due to the presence of resistance to other drugs in the regimen besides rifampin and isoniazid. The empirical implementation of this short-course regimen in patients with undiagnosed greater resistance than that for isoniazid-rifampin will surely lead to an extension of resistance to other drugs in the regimen, and to high rates of treatment failure. Comprehensive drug susceptibility testing for first and second-line drugs should be carried out in every MDR-TB patient that will be treated with a short-course regimen.

Key words: Drug-resistant; Tuberculosis; Short-course; Treatment; WHO

TOPIC HIGHLIGHT

Multi-drug-resistant tuberculosis (MDR-TB), a disease that is resistant at least to isoniazid and rifampicin, is much more difficult to treat than pan-susceptible TB. Current treatment of MDR-TB is challenging since it requires the use of more expensive and toxic drugs that must be administered for a much longer time (up to 24 months) to achieve relapse free-cure and with much less satisfactory outcomes: lower cure rate, higher mortality and higher loss to follow-up rates[1]. An individual patient data meta-analysis of 9,153 MDR-TB...
TB patients from 32 observational studies conducted in 23 countries, treated with conventional MDR-TB drug regimens showed a disappointing 54% treatment success rate[3].

According to the World Health Organization (WHO), globally, an estimated 3.3% of new cases and 20% of previously treated TB cases have MDR-TB; these levels have remained virtually unchanged in recent years. In 2014, there were an estimated 480,000 new cases of MDR-TB worldwide and approximately 190,000 deaths from MDR-TB. Globally in 2014, only 123,000 patients with MDR -TB or rifampicin-resistant tuberculosis (RR-TB) were notified (25% of those estimated by WHO) and just 111,000 patients were started on MDR-TB treatment during the same year (23% of total estimated cases)[3]. This treatment gap may be due, at least in part, to the absence of an accessible and simple treatment regimen. WHO most recent guideline for the treatment of MDR-TB[4] recommends for the conventional treatment of patients with MDR-TB, a regimen with at least five effective TB medicines during the intensive phase (four core second-line drugs, plus pyrazinamide); the intensive phase, that includes a second line injectable, should be maintained for 8 months in most patients; a total treatment duration of 20-24 months is suggested for most cases. The guideline emphasizes that all these recommendations are conditional, with very low certainty in the evidence.

Early results from observational studies in Bangladesh, Cameroon and Niger using regimens lasting 12 months or less, have shown a much higher likelihood of treatment success compared with longer conventional regimens when treating patients that meet specific inclusion criteria[5-7].

In light of these encouraging results, the STREAM trial (evaluation of a Standardized TREATment regimen of anti-tuberculosis drugs for patients with Multi-drug-resistant tuberculosis) was developed with the objective of evaluating a nine-month regimen in a randomized controlled trial to determine whether these promising results can be replicated in other settings, and to compare outcomes to those obtained with the WHO recommended regimen (STREAM Stage 1). Recruitment to stage 1 was completed in June 2015; follow-up is ongoing and results are expected early in 2018. STREAM Stage 2 includes two short course regimens. One is a fully oral 9-month regimen in which bedaquiline replaces the second line injectable and is prescribed throughout the 9 months. The second regimen in Stage 2 is a 6-month regimen where bedaquiline, clofazimine, pyrazinamide and levofloxacin are prescribed for 28 weeks, supplemented by isoniazid and kanamycin for the first 8 weeks. Recruitment for stage 2 started in 2016, with enrollment expected to continue for 3 years. Primary results are expected in 2020, with secondary results available the following year[8-9].

Given promising results from Bangladesh and Africa, and the potential impact of shorter regimens on treatment cost and affordability, WHO proceeded to evaluate the existing evidence by an expert panel. 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 conventional regimens. Overall treatment success (cured or treatment completed vs. failure/relapse/death) in patients treated with a shorter MDR-TB regimen (> 1,100 patients) was 90.3% vs. 78.3% for patients (> 5,800 patients) treated with conventional regimens; in patients whose strains were fluoroquinolone and pyrazinamide susceptible, treatment success for short regimens was even better: 96.8% vs 83.5% for conventional regimens 10.

Based on this evidence WHO is now recommending in its 2016 MDR-TB guideline a new short-course regimen that consists of a 4-6 month intensive phase including kanamycin, moxifloxacin, ethionamide, clofazimine, pyrazinamide, high-dose isoniazid and ethambutol and a 5-month continuation phase that includes moxifloxacin, clofazimine, pyrazinamide, and ethambutol.

There are very clear criteria regarding what MDR-TB patients would benefit from this regimen:

1. RR-TB and MDR-TB. All patients – children or adult - with rifampicin-resistant TB and MDR-TB that have not received treatment with second-line drugs in the past may be treated with the shorter MDR-TB treatment regimen. WHO recommends that the shorter MDR-TB regimen should not be used in patients who have been previously treated with second-line drugs for more than one month or who have documented or likely resistance to medicines included in the regimen. Patients infected with strains known or strongly suspected of being resistant to one or more drugs in the shorter MDR-TB treatment regimen (except for isoniazid) should not be treated with the short-course regimen.

2. Since the regimen include potential teratogenic drugs (kanamycin, moxifloxacin, and ethionamide), pregnancy is an exclusion criterion for the shorter MDR-TB treatment regimen as well as extrapulmonary tuberculosis (due to lack of evidence for this later group)[9].

WHO warns that in order to reproduce the high cure rates in clinical trials, all efforts need to be made to avoid the acquisition of additional resistance, through the careful selection of patients and strict directly observed therapy.

In the implementation considerations section of the guideline, WHO recommends that patients are 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. However, in a previous paragraph, the guideline states: “In the absence of such testing, patients who are highly unlikely to be infected with resistant strains based on history of exposure, use of second-line medicines at country level, or recent representative surveillance data may also be eligible for the shorter MDR-TB regimen”[10]. This might send the wrong message to countries with limited diagnostic resources, who usually are those with the highest rates of drug resistance; due to the lack of diagnostic resources, country surveillance data on drug resistance will seldom be available for the clinician to make an educated guess on the likelihood and magnitude of resistance in a particular case. The empirical implementation of this short-course regimen in patients with undiagnosed greater resistance than that for isoniazid-rifampin will surely lead to an extension of resistance to other drugs in the regimen, and to high rates of treatment failure.

In a recent publication that reviewed the potential eligibility for the MDR-TB short-course treatment in patients from Europe, based on drug susceptibility testing data from more than eleven hundred patients (from Austria, France, Germany, Portugal and the TBNET that includes data from 16 countries), only 7.8% of MDR patients in this database from Europe would be eligible. Thirty-three percent of the patients had resistance to a fluoroquinolone, 36.8% to a second line injectable, 64.4% to ethionamide/prothionamide, 59.5% to ethambutol and 66.8% to pyrazinamide. This data suggest that less than eight percent of patients with MDR-TB in Europe would actually be eligible for the short-course treatment regimen proposed by WHO in May 2016[10].

To save this treatment regimen from becoming obsolete due to drug resistance, comprehensive drug-susceptibility testing (DST) for first and second-line drugs should be carried out in every MDR-
TB patient that is considered a candidate for treatment with a short-course regimen. Molecular testing for rifampicin, isoniazid, second-line injectables and fluoroquinolone drug resistance (e.g. by line probe assays) are reliable enough tools to screen optimal candidates and start treatment, while we wait for the results of conventional DST. Deciding if our patient is a good candidate for this regimen based just on the history of previous exposure will not do. Let’s be coherent with one of the core components of WHO post-2015 End Strategy, which recommends universal drug susceptibility testing [3]. Drug-resistant TB is necessarily a laboratory-based diagnosis; this will certainly require an increase in laboratory capacity in every country to allow the detection of drug resistance to first and second line drugs in every case of TB.

It is important to emphasize that worldwide, only 12% of new bacteriologically-confirmed and 58% of previously treated TB cases was tested for drug resistance in 2014. Besides the fact that the traditional diagnosis strategy for drug-resistant TB (phenotypically-based DST) can take up to 16 weeks [3], in most high-burden countries, there are very few (and in many countries there is none) reference laboratories that can carry out DST for second line drugs and/or molecular biology testing [10]. Laboratory capacity needs to be urgently increased at a global level, especially in high-burden countries to reach a larger number of TB patients screen them for drug resistance at an earlier stage [11] and determine if they could benefit from a short-course treatment for MDR-TB.

REFERENCES


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