Applicability of the shorter ‘Bangladesh regimen’ in high multidrug-resistant tuberculosis settings

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1 Introduction

The World Health Organization (WHO) recently published its End TB Strategy, stressing the importance of diagnosing, treating, and preventing both multidrug-resistant (MDR-)- and extensively drug-resistant (XDR-) tuberculosis (TB).1–3 MDR-TB is defined as resistance to at least rifampicin and isoniazid, the two most effective anti-TB drugs, while XDR-TB is a more severe form of MDR-TB with additional resistance to any fluoroquinolone and to injectable second-line drugs (amikacin, capreomycin, kanamycin).

The Strategy also states the possibility of eliminating TB through the implementation of specific interventions that are currently recommended for low TB incidence countries.4,5 Among the eight core interventions, the management of MDR-TB has an important role.4,5

MDR- and XDR-TB represent a growing clinical and public health concern, with over 480 000 cases and 190 000 deaths estimated to have occurred globally in 2014.1 In spite of the progress achieved,6 only a proportion of existing MDR- and XDR-TB cases have access to quality diagnosis1,7 and treatment, with treatment being long (up to 24 months), expensive, and complicated by severe adverse events.2,3,6–12 Furthermore, treatment outcomes are still unsatisfactory, with treatment success...
rates remaining suboptimal, and success rates decreasing progressively from 50% in MDR-TB cases to 40% in XDR-TB cases and less than 20% in cases with resistance patterns beyond XDR-TB.2,3,13,14

Following more than 40 years of neglect since the launch on the market of the last TB-specific drug (rifampicin), the available armamentarium of anti-TB drugs currently includes two new drugs (delamanid and bedaquiline) and a few repurposed compounds.9,13–23 As clinical experience with these new drugs and some of the repurposed drugs is still limited, and the number of drugs for which susceptibility is confirmed is often very limited,20–22 clinicians face more and more difficulties in designing effective regimens as per WHO guidelines.16

Recent evidence suggests that a 9 to 12-month regimen (known as the ‘Bangladesh regimen’) may be effective in treating MDR-TB cases (Table 1).26–28

As part of the ALAT/ERS LATSINTB project (a research coordination project), the present article describes the rationale for the introduction of the Bangladesh or ‘shorter regimen’ to treat MDR-TB, the principles of the new 2016 WHO recommendations, and the main operational issues related to their implementation under programmatic conditions in high MDR-TB prevalence settings.

2. Rationale for the shorter regimen and the new WHO guidelines

The rational composition of this new regimen is similar to that of the traditional 24-month one, with a consistent number of drugs and the inclusion of a fluoroquinolone, a second-line injectable drug, and two other ‘companion’ drugs (e.g., drugs supporting the core drugs to prevent the selection of drug-resistant mutants).13,15,16 However, in the new regimen moxifloxacin is the fluoroquinolone, while clofazimine replaces cycloserine. The Bangladesh regimen includes an initial phase of 4 to 6 months of kanamycin, gatifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by 5 months of gatifloxacin, clofazimine, pyrazinamide, and ethambutol.13,14,16

Based on the available evidence, the WHO has recommended this shorter MDR-TB regimen in its new 2016 MDR-TB guidelines, with moxifloxacin replacing gatifloxacin (originally used in the Bangladesh regimen).

The new regimen, which is much cheaper than longer ones (<1000 dollars),2,16 is indicated only for “adults and children with rifampicin-resistant and MDR-TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents have been excluded or considered highly unlikely”.16 The indication also includes people living with HIV/AIDS.16 A summary of the composition of the regimen and a list of the recommended exclusion criteria for the shorter TB regimen in favour of the longer regimen are given in Table 2.

The same WHO guidelines recommend a diagnostic tool designed to speed up the detection of TB resistance – the rapid molecular MTBDRsl test.16 The promotion of broader and quicker molecular testing will ensure the appropriate selection of patients who will benefit from the shorter MDR-TB regimen, while reducing the ‘infectious period’ and the subsequent transmission of resistant strains of Mycobacterium tuberculosis within the community. Furthermore, the rapid initiation of an adequate regimen will minimize the possible development of additional drug resistance (‘super-resistance’), which is among the criteria defining ‘treatment failure’ in the 2015 WHO definitions.1

3. Operational issues and evidence of eligibility for the shorter regimen

This is a concrete demonstration of the genuine efforts being made to provide wider access to quality MDR-TB diagnostic and

Table 1

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Setting/number of cases</th>
<th>Study results</th>
<th>Conclusions</th>
<th>Comments</th>
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<tr>
<td>Piubello et al. Int J Tuberc Lung Dis 2014 (26)</td>
<td>Niger National Tuberculosis Programme; 65 MDR-TB patients</td>
<td>Cure was achieved in 58 patients (89.2%; 95% CI 81.7–96.7%; 6 died and 1 defaulted; all 49 patients assessed at the 24-month follow-up after cure remained smear- and culture-negative</td>
<td>Standardized 12-month treatment for MDR-TB was highly effective and well tolerated in patients not previously exposed to second-line anti-TB drugs in Niger</td>
<td>The main adverse events were vomiting (26.2%) and hearing impairment (20%), but no treatment had to be stopped; 1 patient HIV-infected (1.7%)</td>
</tr>
<tr>
<td>Van Deun et al. Am J Respir Crit Care Med 2010 (27)</td>
<td>Prospective observational study conducted over a 12-year period in this large TB control program in Bangladesh; 427 MDR-TB patients</td>
<td>206/427 (48.2%) patients received the most effective treatment regimen; a minimum of 9 months of treatment with GFX, CFZ, EMB, and PZA throughout the treatment period, supplemented by PTO, KM, and high-dose INH during an intensive phase of a minimum of 4 months, giving a relapse-free cure of 87.9% (95% CI 82.7–91.6); 1 patient HIV-infected (1.7%)</td>
<td>Serial regimen formulation guided by overall treatment effectiveness resulted in treatment outcomes comparable to those obtained with first-line anti-TB treatment; confirmatory formal trials in populations with high levels of HIV co-infection and in populations with a higher initial prevalence of resistance to second-line anti-TB drugs are required</td>
<td>Major adverse drug reactions were infrequent and manageable. Compared with the 221 patients treated with regimens based on OFX and commonly PTO throughout, the hazard ratio of any adverse outcome was 0.39 (95% CI 0.26–0.59)</td>
</tr>
<tr>
<td>Aung et al. Int J Tuberc Lung Dis 2014 (28)</td>
<td>Bangladesh National Tuberculosis Programme; prospective, observational study of a GFX-based directly observed regimen, mainly with initial hospitalization; 515 MDR-TB patients</td>
<td>515 patients were recruited from 2005 to 2011, 84.4% had a bacteriologically favourable outcome; due to extensive disease with delayed sputum conversion, only half of the patients completed treatment within 9 months; 95% completed treatment within 12 months; 11 patients failed or relapsed, and 93.1% of the 435 patients who were successfully treated completed at least 12 months of post-treatment follow-up</td>
<td>The excellent outcome of the Bangladesh regimen was largely maintained; bacteriological treatment failures and relapses were rare, except among patients with high-level GFX resistance, notably in the presence of PZA resistance</td>
<td>The strongest risk factor for a bacteriologically unfavourable outcome was high-level FX resistance, particularly when compounded by initial PZA resistance. Low-level FX resistance had no unfavourable effect on treatment outcome. Amplification of drug resistance occurred only once, in a patient strain that was initially only susceptible to KM and CFZ</td>
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| CFZ, clofazimine; CI, confidence interval; EMB, ethambutol; FQ, fluoroquinolone; GFX, gatifloxacin; INH, isoniazid; KM, kanamycin; MDR-TB, multidrug-resistant tuberculosis; OFX, ofloxacin; PTO, prothionamide; PZA, pyrazinamide; TB, tuberculosis. |
Table 2
Composition of the shorter regimen (known as the Bangladesh regimen) to treat multidrug-resistant tuberculosis, and the main contraindications suggesting prescription of the longer regimen 

<table>
<thead>
<tr>
<th>Composition</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>4–6 Km–Mfx–Pro–Cfz–Z–H$_{\text{high-dose}}$–E/5 Mfx–Cfz–Z–E: 4 to 6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol</td>
<td>Evaluation of the drug resistance pattern of all patients with rapid diagnostic methods is recommended</td>
</tr>
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**Contraindication** | **Comments**
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Confirmed resistance to or suspected ineffectiveness of a drug in the shorter MDR-TB regimen (except isoniazid resistance) | Intolerance to a drug composing the regimen is, in practice, equivalent to resistance to the drug |
Exposure to ≥1 second-line drugs in the shorter MDR-TB regimen for >1 month | Insufficient evidence available |
Intolerance to ≥1 drugs in the shorter MDR-TB regimen or risk of toxicity (e.g., drug–drug interactions) | Insufficient evidence available |
At least one drug in the shorter MDR-TB regimen not available | |
Pregnancy | |
Extrapulmonary disease | |

MTR-TB, multidrug-resistant tuberculosis.

$^a$ Note: The emergence of treatment failure, drug intolerance, return after an interruption >2 months, or emergence of any other exclusion criterion implies interruption of the shorter regimen and a move to the longer one.

...
A core factor in facilitating the appropriate use of the new regimens will be the systematic use of rapid MTBDRsl testing, so that the regimen is prescribed to the correct patients.

The increasing possibility of dosing blood levels of the different drugs through therapeutic drug monitoring (TDM) will further improve the tolerability of the shorter regimen (as well as that of the longer one) in the coming future, while increasing treatment adherence.

Importantly, the role of expert discussion (cohort discussion and ‘consilium’) to support clinical decisions in difficult-to-treat cases needs, once more, to be emphasized.11

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References


