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Editorial

What is new in the WHO consolidated guidelines on drug-resistant tuberculosis treatment?

The burden of isoniazid-resistant tuberculosis (Hr-TB) and multidrug- and/or rifampicin mono-resistant tuberculosis (MDR/RR-TB) is increasing worldwide, and the high TB burden countries are the worst affected[1,2]. Ideally, early identification and treatment of Hr-TB is important to prevent progression to MDR-TB, poly-drug resistant (DR) TB, extensively drug-resistant (XDR) TB and worse treatment outcomes[3]. The term XDR-TB will likely need to be re-defined in view of the injectables no longer being recommended as the frontline treatment for MDR-TB[4]. Although both solid and liquid culture methods are invaluable tools for the laboratory diagnosis of DR-TB, they are time-consuming to detect drug resistance and drug susceptibility. Rapid molecular methods such as GeneXpert and/or first-and second-line line probe assay (SL-LPA), when performed in tandem, can provide valuable information about early diagnosis and drug susceptibility testing (DST)-guided treatment of DR-TB[3,5]. In this context, it is also essential to offer universal DST to all TB patients at baseline and during follow up. For this, national TB control programmes must have adequate laboratory infrastructure, trained healthcare workers and quality-assured laboratory DST reporting for both first-and second-line drugs to facilitate DST-guided treatment. As annual national DR-TB surveys are time-consuming and expensive, national surveys should be carried out periodically to ascertain trends in DR-TB.

The WHO recommends, albeit based on weak evidence, substitution of isoniazid with levofloxacin (Lfx) for the treatment of laboratory-confirmed Hr-TB (rifampicin-susceptible) and use of the drug regimen consisting of ERZ (ethambutol, rifampicin, pyrazinamide)-Lfx for a duration of six months without a split of intensive and continuation phases[6]. It further advises against the addition of streptomycin or any other injectable agent in the regimen. Treatment may be extended up to nine months depending upon the clinical, radiological and microbiological response and especially in extrapulmonary TB involving bone, brain/meninges and/or miliary TB. Substitution of a drug in case of additional drug resistance or intolerance can be effected by, in order of preference with linezolid (Lzd), clofazimine (Cfz) or cycloserine (Cs). High-dose isoniazid (15-20 mg/kg/day) may not be useful in Indian patients with Hr-TB since the *kat*G gene mutation conferring high-dose INH resistance is present in >90 per cent of isolates[7]. According to the first National Anti-Tuberculosis Drug Resistance Survey (NDRS) in India, resistance to any fluoroquinolone (FQ) was found in about eight per cent of Hr-TB and resistance to Lzd was uncommon in MDR/RR-TB and even less in H mono/poly-DR-TB (personal communication with RNTCP). Cultures should be done at the end of 2-3 months and thereafter as expropriate[8].

Although Mfx may arguably be more potent than Lfx[9], the main advantage of the latter is less QTcF prolongation, which has obvious advantages when combined with other QTcF-prolonging agents, such as bedaquiline (Bdq) and Cfz in regimen. Peak plasma concentration and exposure to Mfx significantly decreases with concurrent administration of rifampicin[9]; this is another advantage of using Lfx, which does not require dosage adjustment. Unlike Mfx, Lfx requires dose modification in patients with advanced stages of chronic kidney disease (CKD).

The recently published consolidated guidelines on MDR/RR-TB[9] are based on evidence synthesized from a recently completed Phase III clinical trial of delamanid (Dlm)[10,11], an individual patient data

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meta-analysis (IPD-MA) of longer[12] and 9-12-month shorter MDR-TB regimens[13,14] and efficacy and pharmacokinetic data from Dlm and Bdq-related clinical trials[15]. There are no changes in the timing of antiretroviral drugs administration in people living with HIV (PLHIV) with MDR/RR-TB, use of surgery and models of MDR-TB care (ambulatory care/ hospitalization)[16].

A new feature in the guidelines is that the second-line anti-TB drugs used for designing individualized MDR-TB regimens have been re-grouped into A, B and C and the drug ranking is based on their estimated efficacy profiles[9]. The group A drugs include FQ, Lfx or Mfx; Bdq and Lzd; group B includes Cfz and Cs or terizidone and group C contains ethambutol (E), Dlm, pyrazinamide, imipenem-cilastatin (Imp-Cln) or meropenem (Mpm), amikacin (Am) or streptomycin (S), ethionamide (Eto), or prothionamide and *p*-aminosalicylic acid (PAS). Lack of efficacy in the Dlm phase III study has resulted in its classification as a group C drug though this was based on a six-month culture conversion outcome[10,11].

While designing the individualized longer (18-20 month) MDR-TB regimen, a strong recommendation has been made to include all three drugs from group A, and to complete the regimen, the fourth drug should be from group B (and if it is not possible, then the fourth drug may be selected from the group C). A fully oral long-term regimen is the preferred option and the injectable agents, kanamycin and capreomycin, are no longer recommended because these were associated with higher treatment failure, relapse rates and mortality and toxicity[9]. The long-term Bdq-containing drug regimen should have at least four drugs for initial six months and subsequently three drugs to be continued for rest of the duration of treatment. Although the optimal number of drugs for the regimen is uncertain, we recommend a minimum of four but ideally five likely effective drugs[12]. The individualized, longer MDR-TB regimen is to be administered for a total duration of 18-20 months, and the duration is primarily based on patient's response to treatment or 15-17 months after culture conversion. However, the optimal treatment duration remains unclear. The WHO recommendations have emphasized monthly sputum cultures along with smear microscopy[9].

Pyrazinamide is to be used for MDR/RR-TB only when DST reveals susceptibility[9] (though this is not readily available and is technically challenging). Every dose of Imp-Cln or Mpm is administered with clavulanic acid (available only as amoxicillin clavulanic acid) and this combination is counted as single drug. In selected patients where a regimen cannot be constructed because of resistance profiles or drug-specific toxicity, Am or streptomycin is to be used only in patients >18 yr of age, and when high-quality audiometry monitoring for hearing loss is available. Am is to be substituted with streptomycin only if it is not available or some other contraindication exists, and when DST confirms susceptibility to streptomycin (phenotypic DST is required for streptomycin as molecular DST with SL-LPA does not detect it)[9].

It should be noted that thiacetazone, gatifloxacin and high-dose isoniazid were not included in the IPD-MA for longer regimens because of an inadequate number of patients[12] (both gatifloxacin and thioacetazone are no longer available). Evidence on the safety and efficacy of the following drugs was insufficient for review: use of Bdq beyond six months and below the age of six years and Dlm use beyond six months and below the age of three years; concomitant use of Bdq and Dlm. It was observed that the use of Lzd for at least six months showed increased efficacy and using it for the entire duration would likely be better[12]; however, one needs to balance this against the high rates of drug toxicity with prolonged use.

The new WHO guidelines has left open the option of using the longer 18-20 month group A-based regimen or the standardized shorter MDR-TB regimen containing an injectable which is given for 9-11 months[9]. Which regimen should preferably be used? In the recently published STREAM trial, the shorter injectable containing 9-11 month regimen was found to be non-inferior to the conventional 18-20 month older WHO regimen (also contained an injectable)[14]. However, bacteriologic outcomes were worse with the shorter regimen and there was a trend to worse outcomes in HIV-infected persons in both arms. Given these considerations, the toxicity and tolerability profiles (including months of painful injections), our personal recommendation is that the longer pan-oral regimen is preferable and that the standardized shorter MDR-TB regimen containing an injectable should only be used as an exception (for example, if drugs are not readily accessible) and provided (*i*) there is no proven or likely resistance to any component of the regimen (except isoniazid), (*ii*) there is access to baseline and longitudinal monitoring for hearing loss, (*iii*) FQ and second line injectable

drug (SLID) resistance has been excluded, and (*iv*) patients have been counselled about the risks of this regimen and agree to receive it. There should be clear plans within the programme or provider setting to transition to an all-oral group A-based regimen because the shorter WHO injectable-based regimen is likely to be an inferior one from an efficacy and mortality point of view (though there are no head-to-head trials yet), and Am is toxic and associated with chronic painful injections driving poor adherence.

Active TB drug-safety monitoring and management (aDSM)[17] should be an integral part of MDR-TB management as several drugs have additive toxicities. Bdq, Dlm, FQ (Mfx>Lfx) and Cfz have the potential to prolong QTcF. It is advised that deficiencies of potassium, calcium and magnesium should be corrected first, and if QTcF >500 ms persists, then the likely offending drug(s) should be stopped. Similarly, several drugs (Lzd, ethambutol and INH) in the regimen, when given in combination, can produce optic neuropathy[17].

Lzd is a potent drug with potential toxicity when used on long-term basis in MDR-TB regimens[18]. Haematological toxicity occurs early, whereas peripheral and optic neuropathy occurs late[18]. Lactic acidosis is a rare complication. Pyridoxine (100 mg daily) can be administered to decrease the risk of haematological toxicity. Lzd is very rarely associated with serotonin syndrome when administered with selective serotonin re-uptake inhibitors and other medicines known to increase serotonin concentration in the central nervous system[19,20]. In this specific context, patients should be instructed to avoid foods and liquids rich in tyramine concentration.

Proposed Indian recommendations for the fully oral longer regimen include five drugs in the intensive phase and four drugs in the continuation phase [Bdq(6 months) Lfx Lzd Cfz Cs]. After the drug procurement, implementation will start in a phased manner. If resistance to the FQ class is detected on the SL-LPA, then preferably two drugs (or at least one) from group C, *e.g.* Dlm and/or PAS, should be added to the regimen. In some cases high-dose Mfx (Mfx^h) could be useful provided there is no resistance to Mfx^h (1.0 µg)[21] on LC-DST[17] [though specific mutations of the SL-LPA, *i.e.* A90V, S91P, D94A (*gyrA*) suggest low level Mfx resistance in many settings]. Baseline SL-LPA should be performed for all patients with MDR/RR-TB to clarify whether there is additional FQ class resistance, which varies from 10 to 40 per cent in India (personal communication with RNTCP). A fully oral Bdq-containing shorter regimen remains a good prospect for the treatment of MDR-TB in future.

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