Editorial

WHO consolidated guidelines on tuberculosis 2020 moving toward fully oral regimen: Should country act in hurry?

WHO consolidated guidelines published in March 2020 recommends fully oral regimens for drug-resistant tuberculosis (DR-TB) that is isoniazid-resistant TB, rifampicin-resistant TB (RR-TB), multi-DR-TB (MDR-TB), and extensively DR-TB (XDR-TB). These regimens are said to be game changer for these resistant forms of TB and for those who do not tolerate or respond to MDR-TB treatment.[1] Since the discovery of rifampicin in 1965, we did not have any new anti-TB drug for many years. The US Food and Drug Administration approved Bedaquiline in 2012.[2] Delamanid was approved by the European Medical Agency in 2014, by Pharmaceutical and Medical Device Agency, PMDA in 2008.[3,4] Pretomanid has been approved by the WHO in 2020 for the treatment of XDR-TB under operational research conditions.[1]

The availability of three new drugs to treat DR-TB along with effectiveness of repurposed anti-TB drugs such as linezolid and clofazimine had led WHO to develop these new consolidated guidelines for DR-TB.[1]

The likelihood of success in DR-TB patients depends upon patient's severity of disease, resistance patterns and comorbidities, as well as access to good health care (i.e. regimens with sufficient effective agents, their availability and management of comorbidities, and adverse events with patient's support.[5,6] The new regimens are recommended using primarily the estimates of effect for 2018 Individual Patient Data Meta-analysis (IPD-MA),[7] trial 213 Delamanid[8] and success of bedaquiline-containing short-drug regimen[9] and NIX-TB trial results from South Africa.[10]

The WHO has acted quite fast looking to the growing problem of DR TB and has also urged all the countries to enable access to these drugs and fully oral regimens (WHO, June 2020),[11] however, India should have considerable thought before implementing them in hurry because of following reasons.

1. The IPD-MA (2018) included 50 studies, and almost all the studies were observations and the majority described results with individualized treatment regimens. Selection biased is an important limitation for these studies because patients with more extensive disease or drug resistance may have been more likely to receive more potent drugs. There always remains a strong risk of bias in observational/nonrandomized studies.[11-13] Further, high proportions of individuals were lost to follow-up during treatment, which might bias estimates of effects. Further, WHO 2020 recommendations of fully oral regimens are conditional with very low certainty in the estimates of effects[1]
2. The Current 2020 Recommendations of WHO have discarded Short-MDR (so called Bangladesh Regimen) based on Kanamycin, mainly on the ground of toxicity (mainly ototoxicity). The regimens currently recommended are no less toxic, combinations of bedaquiline plus clofazimine, linezolid and pretomanid used in these regimens are no less toxic and even QT Prolongation deaths have been reported with bedaquiline and cloazimine combination.[13-18] It is possible that bedquiline and clofazimine have a synergistic effect and together are more likely to cause QT prolongation, especially if they are additionally combined with drugs causing QT wave prolongation.[19] In such combination, the safety of bedaquiline and delamanid may be substantially improved if clofazimine is omitted.[16,20] The NIX-TB trial 2019[10] recommended for XDR-TB is also not safe, and Grade 3 or 4 adverse events are observed in 58/109 (53%) of patients and serious adverse events in 17% (19/109).[10] The inclusion of only three drugs in the regimen might lead to increase risk of resistance amplification if there is undiagnosed resistance or intolerance to just one of three drugs.[21] Indeed the 24 month failure rate in bedaquiline treated patients with XDR was 37%.[22] WHO degrades the injections; as the IPD-MA of 2018 showed that its use associated with toxicity and higher mortality, ignoring its association with prevention of acquired fluoroquinolone resistance.[23] Moreover, within low- and middle-income countries, Kanamycin has not been associated with worst outcomes. This recommendation is therefore disputed.[24] Ototoxicity due to Kanamycin has been reported with its longer use for 6–8 months in long 24 months conventional MDR-Regimen.[25] The short MDR regimen uses this drug for 4–6 months only compared to 8 months or longer use in conventional MDR regimen. In Niger, using short-MDR regimen including Kanamycin with rigorous surveillance and replacing Kanamycin with linezolid as soon as hearing impairment is detected since the implementation of this measure, not a single patient treated with short-MDR regimen developed severe hearing loss.[26] Further, when using an injectable, it is recommended by pharmacologists to give thrice weekly at the normal 15 mg/kg dose that also makes the painful injections more acceptable to patients, while remaining equally effective treatment.[27] In our Country, most of the chest physicians are well acquainted with aminoglycoside use and management

of adverse events and are quite satisfied with their potency in treatment of TB

3. To date, not a single publication document use bacteriological outcome of all oral longer MDR regimen in a randomized clinical trial and there is only one small randomized control clinical trial of short fully oral MDR regimen where kanamycin has been replaced by bedaquiline[9] in 162 patients, despite expected improvement in efficacy, failure or relapse will undoubtedly occur, as no regimen has ever proved 100% effective in the TB history.[23] Resistance to bedaquiline, delamanid, and clofezimine is known to occur[28-35]
4. Till date, the aminoglycoside containing short-MDR-TB regimen, so called Bangladesh regimen[36] is the only regimen with proved efficacy of 80%–95% in prospective cohort study[37-41] as was in a well-planned randomized control trial of STREAM I.[42] The success of regimen is attributed to early bactericidal activity of kanamycin and fluoroquinolones and sterilizing activity of pyrazinamide and clofazimine, isoniazid, ethambutol and ethionamide/prothionamide are included mainly for the additional protection of core drugs. Ethionamide/prothionamide is given only during the intensive phase to limit gastrointestinal adverse events.[5] The use of more drugs in the intensive phase when bactericidal burden is highest, potentially reduce the risk of amplifying drug resistance with improved adherence and lower mortality.[5] Although 2018 IPD-MA and WHO 2020 discarded kanamycin and ethionamide because of toxicity and increased mortality, a similar IPD-MA including 9153 patients,[12] treatment success, and survival were associated with the use of fluoroquinolones, ethionamide/prothionamide and longer use of injections and total number of effective drugs in continuation phase. Since 2016, the WHO recommendations of 9–11 months standard short-MDR regimen, 82 countries are implementing short-MDR regimen maintaining high cure rates of over 80%.[37-42] Further, this high success rate is also associated with very low loss to follow-up, treatment failure, death, and relapse.[23,26] Indeed, a recast modelling study assumed that short-MDR regimen would double treatment access and predicted a reduction in MDR incidence by 23% over 9 years.[43] The key criteria for the use of this regimen include the absence of resistance to drugs used (except isoniazid), lack of prior exposure for more than 1 month to any of second-line drugs in the regimen and no known drug intolerance, pregnant women, and those with severe form of extrapulmonary TB (WHO 2016)[44]
5. Even if Kanamycin is replaced by amikacin according to the WHO 2020 recommendations and using global drug facility, the cost of injectable short-MDR regimen is nearly 782 US Dollars much lower than all long oral regimen currently recommended by WHO, which costs nearly 6000 US Dollars. This low cost of standard short-MDR regimen favors sustainability in low- and middle-income countries since global fund priorities and international help may shift over time[45]
6. Country's policy-makers have adopted short-MDR regimen of 9–11 months (Indian PMDT Guidelines 2019);[46] however, relying on IPD-MA 2018 and WHO consolidated guidelines (2020)[1] along all oral regimen of 18–20 months is preferred (conditional recommendations, very low certainty in estimation of effects).[1] However, looking at high frequency of fluoroquinolones resistance of 21.82% (National Anti-Tuberculosis Drug Resistance Survey, 2018),[47] they have rightly recommended 6 drugs regimen in intensive phase and 4 drugs regimen in continuation phase instead of 5 drugs intensive phase and 3 drugs continuation phase as recommended by WHO, 2020,[1] we should wait for results of this fully oral longer regimen and resistance development pattern. In an attempt to develop shortest, safe, effective and tolerable regimens large numbers of trials are in pipeline (SIMPLICI-TB)[48] is a 4–6 months regimen of BPaMZ for drug sensitive 4 months and DR-TB 6 months. ZeNIX[49] is a 6 month regimen of different doses and duration of linezolid plus bedaquiline and pretomanid (BPaLi). TB-PRACTECAL[50] is a 6 months regimen of BPaLi plus clofazimine or moxifloxacin (BPaLi + C/M). BEAT-TB[51] is a study of 6 months BDCLeLi for RR-TB. NEXT-TB[52] is a study of 6–9 months BLeLiZ + HH/ETH/TZ. STREM II[53] is containing conventional[1] 18 months MDR regimen with 9 months fully oral regimen of BCLeEZ supplemented with 20 week INH and prothionamide and 28 week BCLeZ supplemented with 8-week Kanamycin and INH and 40 week CEZ +Le/M supplemented with 28 week BCLeZ supplemented with 8 week Kanamycin and isoniazid. END-TB[54] is study of five drug regimens of 9 months BLiMZ, BCLeLiZ, BDLiLeZ, DLiCLeZ and DCMZ with comparater, end TB regimen for DR-TB. MDR-END[55] is a study of 9–12 months DLeLiZ
7. Low market availability and high costs are important barriers to access to newer drugs like bedaquiline, delamanid, pretomanid and even repurposed drug Clofazimine. None of these newer drugs are manufactured in the country and adopting a regimen where the availability of drugs cannot be fully ensured may result in catastrophic situation under national program condition and may be beyond the resource of country's health programs. High cost of treatment is a serious impediment in scaling TB treatment with these drugs and it should be our sincere effort to protect these drugs from inappropriate use and thus emergence of drug resistance. The facility of DST for these new drugs has not still been developed at the country level despite the development of validated, agreed, reliable, and reproducible methods for new drugs bedaquiline, delamanid, and repurposed drugs linezolid, clofazimine, and pyrazinamide being approved by the WHO[56]
8. Development of new drugs bedaquiline, delamanid,

and pretomanid along with proven efficacy of repurposed drugs Linezolid and Clofazimine is a landmark in the history of TB treatment. Shorter and more tolerable regimens are desperately needed to increase adherence, reduce loss to follow-up and treat severe form of DR-TB allowing for diagnostic and management simplification. However there are concerns regarding the safety and efficacy of these new drugs. Amplification of drug resistance and cost of these new drugs will ensue if they are used in mass without informed guidance and proper evidence.[57]

Country's policy-makers should wait for the evidence which is likely to come by the end of 2022. This is high time that they should decide specifically who should be treated with these drugs so that outcomes are optimally improved without amplifying the burden of drug-resistance and other potential drawbacks like adverse events, thus, sustaining effectiveness of these new drugs for long time to come.

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