Reply: Roll out of bedaquiline without drug susceptibility testing leads to emergence of bedaquiline-resistance in high burden countries with tuberculosis - Danger of losing a novel drug

Dear Sir,

In response to the correspondence by Udwadia Zarir and Jennifer,[1] “India should speed up access to bedaquiline based all-oral regimens, not procrastinate further,” I would like to submit that my key message in the Editorial was grossly misinterpreted by authors. The article “WHO consolidated guidelines on tuberculosis 2020 moving towards fully oral regimens: Should country act in hurry?”[2] have been written with concern to save bedaquiline for long-term use in the management of drug-resistant tuberculosis. The article does not question the efficacy of bedaquiline in the management of drug-resistant tuberculosis with its judicious use.

The same concern has been expressed internationally too, on rolling out WHO consolidated guidelines, Kranzer et al.[3] have written “New World Health Organization Treatment Recommendations for Multidrug-Resistant Tuberculosis: Are We Well Enough Prepared?” and Andres et al.[4] have commented, “Bedaquiline Resistant-Tuberculosis: Dark Clouds on the Horizon” both the articles published in prestigious American Journal of Respiratory and Critical Care Medicine.

The same enthusiasm was there when rifampicin was discovered for treatment for tuberculosis. Drug-resistant tuberculosis (DR-TB) was not a major problem till year 1997–2000 when RNTCP was rolled out with weaker regimens, as a result of which India has become home to 24% of world’s Multi DR-TB (MDR-TB)[5] problem, second highest in the world within 20 years of its implementation (WHO Global TB Report 2019).

The Editorial[2] answers almost all the questions raised by Udwadia and Furin, however for the sake of clarity I would like to respond further. Udwadia and Furin write about touting of Bangladesh regimen, there is no question of touting it, there are enough published data on the efficacy of this regimen in programmatic management of DR-TB in many countries, over 80 countries are implementing short MDR-regimen maintaining a cure rate of over 80%[6-10] and the same has been proven in well-controlled clinical study STREAM (a trial of Shorter Regimen for Rifampicin-Resistant Tuberculosis).[11] This regimen has been suggested to buy time awaiting results of large number of clinical trials in pipeline including TB-PRACTECAL.[12]

SIMPICI-TB,[13] ZeNIX,[14] NEXT-TB,[15] STREAM II,[16] END-TB,[17] MDR-END,[18] and BEAT TB[19] the results of which will be available by end of 2022. By this time country can establish a strong infrastructure of DST laboratories for DST to bedaquiline, clofazimine, linezolid, and delamanid as WHO validated accurate reliable and reproducible methods have been established for these drugs (WHO consolidated guidelines on Drug-Resistant TB, 2020).[20]

Currently, bedaquiline DST is available at only 3 national reference laboratories, rolling out of WHO Consolidated Guidelines 2020 in such situation without the establishment of DST methods for drugs used in the regimen (s) may result in the development of bedaquiline-resistant TB which will be a disaster for the nation.

Primary bedaquiline-resistance exists in 5%–6% of drug-resistant TB cases[21-23] and insufficient protection of bedaquiline-clofazimine (BDQ/CFZ) by the remaining companion drugs because of resistance or drug toxicity especially to fluoroquinolone and linezolid, amplification of resistance to BDQ/CFZ is likely to occur.[4]

Many countries that have rolled out bedaquiline containing regimens largely in the absence of programmatic drug-susceptibility testing (DST) are facing problems of high frequency of acquired resistance to bedaquiline (15%–45%).[24-26] Andres et al., in 2020[4] have proposed monthly phenotype and genotype testing to determine the emergence of resistance to drugs used and in an early view, Chesov et al.[27] in European Respiratory Journal (2021), have expressed that in high burden countries of tuberculosis bedaquiline resistance can emerge in more than 15% of mycobacterial TB complex strains obtained from follow-up isolates of MDR-TB patients and globally emerging resistant strains threaten the effectivity of novel MDR-TB treatment regimens. It is rightly written by Köser et al. that “THOSE WHO CANNOT REMEMBER THE PAST ARE CONDEMNED TO REPEAT IT.”[28]

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Correspondence

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Correspondence

Nirmal Kumar Jain
Department of Respiratory Medicine, JNU Medical College, Jaipur, Rajasthan, India
E-mail: jainmkdr1971@gmail.com

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