Matthew Maddocks, Ph.D.
King's College London
London, United Kingdom

Morag Farquhar, Ph.D.
University of East Anglia
Norwich, United Kingdom

Derek Bell, M.D.
Jadwiga A. Wedzicha, M.D.‡
Imperial College
London, United Kingdom

William D.-C. Man, M.D.
Royal Brompton & Harefield NHS Foundation Trust
London, United Kingdom
and
Imperial College
London, United Kingdom

*Corresponding author (e-mail: r.barker2@rbht.nhs.uk).
‡J.A.W. is Editor-in-Chief of *AJRCCM*. Her participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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ATS/CDC/ERS/IDSA Clinical Practice Guidelines for Treatment of Drug-Resistant Tuberculosis: A Two-edged Sword?

To the Editor:

On the basis of individual patient data (IPD) meta-analysis of observational studies (1), the World Health Organization released the consolidated guidelines on drug-resistant tuberculosis (TB) treatment in 2019 (2). Shortly afterward, using a data set modified from the aforementioned IPD, the American Thoracic Society (ATS)/CDC/European Respiratory Society (ERS)/Infectious Diseases Society of America (IDSA) published their official clinical practice guidelines for the treatment of drug-resistant TB (3). The ATS/CDC/ERS/IDSA have recommended the use of linezolid and bedaquiline to treat all patients with multidrug-resistant TB (MDR-TB), regardless of the drug-susceptibility testing results. Although the present guidelines have substantiated the role of linezolid and bedaquiline in the treatment of fluoroquinolone-resistant MDR-TB, the IPD meta-analysis findings might have been overextrapolated (4), with findings regarding the use of linezolid and bedaquiline for the management of fluoroquinolone-resistant MDR-TB applied to fluoroquinolone-susceptible MDR-TB. Retrospective analysis of linezolid in better-defined cohorts with MDR-TB have suggested that linezolid would be useful largely in the treatment of more complicated MDR-TB (5). Whether adding bedaquiline to fluoroquinolone would improve treatment outcomes of fluoroquinolone-susceptible MDR-TB is still being evaluated in stage 2 of the STREAM (Evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with Multidrug-Resistant Tuberculosis) trial. Furthermore, selection bias and inadequate control of confounding in the IPD meta-analysis might have yielded some findings that cannot be readily explained on a biologically plausible basis. Although the ATS/CDC/ERS/IDSA have explicitly stated that their guidelines were based on evidence of very low certainty (3), their categorical recommendation regarding use of linezolid and bedaquiline may pose a two-edged sword for TB control programs worldwide.

Intuitively, the pros of including linezolid and bedaquiline in a standard regimen for all types of MDR-TB may be greater simplicity for programmatic implementation and lesser need for drug-susceptibility testing. However, the major cons probably lie in the concern for patient safety and tolerance, especially when the standard regimen is universally applied to many patients with MDR-TB worldwide. The first global report of surveillance of adverse events in the treatment of drug-resistant TB has suggested a substantial risk of serious adverse events related to the use of linezolid and, possibly, bedaquiline (6). The underlying mechanism, clinical impact, and optimal monitoring of some potentially serious toxicities, such as those pertaining to the cardiovascular and neurological systems, are not yet fully understood. Furthermore, the expertise and resources required for monitoring such adverse drug reactions likely overwhelm capacity in a large number of MDR-TB programs with high disease burdens, particularly when comorbidities such as diabetes mellitus and HIV infection prevail. It cannot be overemphasized that suboptimal management of drug toxicities significantly contributes to poor treatment adherence and eventually contributes to unfavorable treatment outcomes.

Linezolid resistance is now mounting in many parts of the world. Rapid emergence of resistance against bedaquiline would be formidable for global TB control. Use of linezolid and bedaquiline in selected patients with MDR-TB may facilitate the optimal use of resources in a programmatic setting for management of drug adverse reactions and curtailment of drug resistance.

Directly observed treatment in the holistic patient care package likely contributed to the high treatment success rates of optimized background regimens in Trial 213 (7) and in the STREAM trial (8). With advances in rapid detection of drug resistance, optimized background regimens or shorter World Health Organization MDR-TB regimens may still have a place in the programmatic treatment of fluoroquinolone-susceptible MDR-TB in some parts of the world (8), at least currently. ■

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Kwok-Chiu Chang, M.B. B.S., M.Sc.*
The Department of Health
Hong Kong, China

Wing-Wai Yew, M.B. B.S.
The Chinese University of Hong Kong
Hong Kong, China

ORCID ID: 0000-0002-3682-5069 (K.-C.C.).

*Corresponding author (e-mail: kc_chang@dh.gov.hk).

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Reply to Chang and Yew

From the Authors:

We appreciate the letter by Drs. Chang and Yew commenting on the Official Guidelines of the American Thoracic Society (ATS)/CDC/European Respiratory Society (ERS)/Infectious Disease Society of America (IDSA) on the treatment of multidrug-resistant tuberculosis (MDR-TB) (1). Three issues are raised in the letter: first, the certainty of the evidence on the use of linezolid and bedaquiline in the management of fluoroquinolone-sensitive and -resistant MDR-TB; second, the risk of resistance to these two drugs with generalized use, suggesting focused use of these drugs in selected patients might limit this hazard and minimize acquisition of resistance and serious adverse events; and third, that with broadening availability of rapid drug susceptibility testing (DST), optimized longer and existing standardized shorter-course regimens still have value.

On the first issue, we concur that the certainty in the evidence is low. However, until such a time when randomized controlled trials in TB therapeutics are adequately funded, conducted, and completed, the propensity score (PS)-matched individual patient data meta-analysis (IPDMA) of a database of more than 12,000 patient records from 25 countries in support of the ATS/CDC/ERS/IDSA guidelines represents the best available evidence base on which to assess drugs for treatment of drug-resistant TB (1, 2). Our PS-matched IPDMA showed consistently that bedaquiline and linezolid improved treatment success and reduced mortality across all patients with drug-resistant TB (with the greatest impact noted in extremely drug-resistant TB). These benefits were substantial, with absolute reductions in mortality of 5–10% with use of bedaquiline or linezolid (2). Sensitivity analyses were also conducted across subgroups of MDR-TB patients with respect to additional resistance to any fluoroquinolone, and the results remained essentially unchanged within subgroups (1, 2). The potency of linezolid and bedaquiline, when combined with a later-generation fluoroquinolone, allows for the composition of an all-oral regimen for MDR-TB for the first time in patients with fluoroquinolone-susceptible TB. The availability of effective and injectable-free regimens is an advance that we endorse enthusiastically.

On the second issue, we concur that the development and scale-up of rapid genotypic DST for new agents are urgently needed. The ATS/CDC/ERS/IDSA guidelines recommend as a good practice statement that regimens should include only drugs to which the patient's *Mycobacterium tuberculosis* isolate has a documented or a high likelihood of susceptibility. Drugs known to be ineffective based on *in vitro* growth-based or molecular resistance should not be used given consistent findings in the IPDMA that outcomes were worse in patients who received drugs to which their isolates were resistant (2). For the settings in which these guidelines are relevant, molecular methods and, more recently, whole-genome sequencing are increasingly available and can provide information on resistance to all first-line and many second-line drugs.

On the third issue, although we concur that the standardized shorter-course regimens may still have value when susceptibility is documented for all the drugs in the regimen, we found that when applying the eligibility criteria from the World Health Organization for using this regimen (3) for the population included in our PS-matched IPDMA, fewer than 15% of individuals were eligible for the regimen. In Europe, patient eligibility for the shorter-course regimen has ranged from 8% to 17% in surveillance-based studies (4, 5). In the United States, only 10% of MDR-TB patients would have been eligible based on national data from 2011 to 2016 (6). We recommend the conduct of randomized controlled trials evaluating the efficacy, safety, and tolerability of modified

The authors are the co-chairs of the official American Thoracic Society Document entitled, "Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline."

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