techniques to assess activation used in the present paper by Fleury Curado and colleagues (positron emission tomography and magnetic resonance imaging) to measure effect on airway dimensions may be helpful to determine optimal delivery of chemogenetic receptors. At long last, it does seem hopeful that we are palpably closer to an elusive drug therapy for obstructive sleep apnea. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Sigrid Veasey, M.D.
Department of Medicine at the Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

References

1. Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep apnoea. *Eur Respir J* 1995;8:1161–1178.
2. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90:47–112.
3. Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). *J Clin Invest* 1992;89: 1571–1579.
4. Phillipson EA. Regulation of breathing during sleep. *Am Rev Respir Dis* 1977;115:217–224.
5. Horner RL, Hughes SW, Malhotra A. State-dependent and reflex drives to the upper airway: basic physiology with clinical implications. *J Appl Physiol (1985)* 2014;116:325–336.
6. Decker MJ, Haaga J, Arnold JL, Atzberger D, Strohl KP. Functional electrical stimulation and respiration during sleep. *J Appl Physiol (1985)* 1993;75:1053–1061.
7. Smith PL, Eisele DW, Podszus T, Penzel T, Grote L, Peter JH, *et al*. Electrical stimulation of upper airway musculature. *Sleep* 1996;19(Suppl):S284–S287.
8. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, *et al*.; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139–149.
9. Fleury Curado T, Pho H, Freire C, Amorim MR, Bonaventura J, Kim LJ, *et al*. Designer receptors exclusively activated by designer drugs approach to treatment of sleep-disordered breathing. *Am J Respir Crit Care Med* 2021;203:102–110.
10. Fleury Curado T, Pho H, Berger S, Caballero-Eraso C, Shin MK, Sennes LU, *et al*. Sleep-disordered breathing in C57BL/6J mice with diet-induced obesity. *Sleep (Basel)* 2018;41:zsy089.
11. Hendricks JC, Kline LR, Kovalski RJ, O'Brien JA, Morrison AR, Pack AI. The English bulldog: a natural model of sleep-disordered breathing. *J Appl Physiol (1985)* 1987;63:1344–1350.
12. Magnus CJ, Lee PH, Bonaventura J, Zemla R, Gomez JL, Ramirez MH, *et al*. Ultrapotent chemogenetics for research and potential clinical applications. *Science* 2019;364:eaav5282.

Operational Research on the Treatment of Drug-Resistant Tuberculosis: Exciting Results That Need to Be Protected

Despite worldwide efforts to improve tuberculosis (TB) control, including the introduction of molecular diagnostics, and a global focus on treatment of diagnosed patients, many high-burden TB countries will not meet 2020 milestones for TB control (1). An important underlying reason for failure to meet these targets is the challenge to successfully treat drug-resistant (DR) TB. Until recently, second-line TB regimens have been poorly active, requiring prolonged duration, with high pill burden including routine inclusion of injectable agents and substantial severe adverse effects (2).

Over the past 10 years, the introduction of new antimycobacterial drugs has facilitated the construction of innovative new regimens for the treatment of DR-TB. Critical new drugs include bedaquiline (World Health Organization Class A), a novel diarylquinoline antibiotic that acts to inhibit the mycobacterial ATP synthase proton pump, and delamanid (World Health Organization Class C), a nitroimidazole, which interferes with the production of the mycobacterial cell wall through inhibition of mycolic acid synthesis (1).

These new regimens allow for significantly shorter treatment duration compared with older-generation second-line regimens and have revolutionized DR-TB therapy by achieving substantially higher cure rates, with improved adverse effect profiles, and are more amenable to decentralized outpatient administration (1, 3).

In this issue of the *Journal*, Franke and colleagues (pp. 111–119) report on rates of 6-month sputum TB culture conversion using new treatment regimens in a large multinational DR-TB prospective cohort (4). Eligible patients were acid-fast bacilli smear positive at baseline and were initiated on bedaquiline, delamanid, or both as key components of the treatment regimen. In this study, 6-month TB culture conversion was used as the primary outcome, which has been previously used as a surrogate for end-of-treatment outcome in patients with DR-TB treated with older second-line regimens (5). Strengths of this study include its large sample size, with patients recruited in 17 geographically diverse, low- and middle-income countries, primarily Kazakhstan, Georgia, Bangladesh, and Pakistan, the prospective enrollment of patients, inclusion of HIV-infected and HIV-uninfected patients, and the statistical analyses and operational study design. Because diagnostics and DR-TB treatment and care were provided as per routine practices, study results should be considered generalizable to clinical DR-TB programs in high-burden settings.

Compared with earlier operational studies of DR-TB treatment using older second-line DR-TB regimens, which demonstrated

Originally Published in Press as DOI: 10.1164/rccm.202007-2974ED on August 21, 2020

6-month culture conversion of 34–78% (6, 7), the percentage experiencing TB culture conversion (85%) in this study is impressive and comparable to 6-month culture conversion rates reported in the randomized controlled trials of bedaquiline (79%) and delamanid (87%) (8, 9). These results therefore give the global TB community reason for much enthusiasm. However, limitations inherent to the study design may reduce generalizability of the results.

Among the major limitations of this study are the lack of monitoring for baseline and emergent drug resistance, particularly to bedaquiline and delamanid, and absence of information on adherence support measures and loss to follow-up or retention in care during treatment.

Drug resistance arises by a combination of spontaneous mutation and selection and has been reported for virtually every antituberculosis drug used clinically. Once acquired, DR *Mycobacterium tuberculosis* mutants can rapidly spread via transmission. In cohorts from Europe, South Africa, and China, 3–5% of existing DR-TB isolates exhibit reduced susceptibility to bedaquiline, with an additional 5–11% developing emergent resistance during treatment (10–12). Comparable data for delamanid are currently lacking, but it is highly likely that baseline and emergent resistance are also occurring, including resistance to both delamanid and bedaquiline (12). It would therefore be useful to know baseline and rates of emergent resistance during treatment of DR-TB with new regimens. But it is also important for a well-resourced international group such as this to establish the operational importance for routine drug-susceptibility testing to bedaquiline and delamanid. Molecular diagnostics, including the recent GeneXpert MTB/XDR cartridge, do not include genetic targets that correlate with phenotypic bedaquiline or delamanid resistance. However, increasing availability of genomic and phenotypic data will help shape the much-needed next generation of rapid tests.

Medication adherence is a key predictor of outcomes in DR-TB treatment; however, it is understudied in high-burden TB settings (13). Although the demands of new bedaquiline- and delamanid-based regimens are presumably lower owing to decreased pill burden and treatment duration, loss to retention in care (formerly termed as "default") has not been significantly reduced in operational cohorts of patients with DR-TB treated with bedaquiline-containing regimens.

Loss to retention in care and decreased medication adherence are known to lead to reduced drug levels, leading to selection for resistant *M. tuberculosis* isolates, and may be particularly problematic in a medication with a long half-life such as bedaquiline. Therefore, enhanced patient-centered treatment support is needed to improve outcomes, protect new drugs and regimens, and prevent the transmission of DR isolates (14).

Other limitations in the study are a lack of data disaggregated by country and treatment regimen (bedaquiline, delamanid, or both). The low- and middle-income countries included in this study are heterogeneous in their health systems that include type and intensity of medication adherence support provided. Similarly, bedaquiline may have different rates of culture conversion than delamanid, and the combination may be more effective than either. TB culture was performed on a mix of solid (35%) and liquid (65%) culture media. Because solid agar media is less sensitive to detect mycobacteria, this may have the effect of overestimating culture conversion compared with liquid culture media. Overall, 6-month TB culture conversion is a reasonable surrogate for durable end-of-treatment results; however, specificity is limited by culture reversion and loss to retention in care.

Beyond randomized clinical trials, observational studies provide results that can be expected in real-world settings. This study has demonstrated that on average, treatment for highly DR forms of TB can achieve very good outcomes with these novel agents. The TB community (practitioners and patients alike) have waited nearly four decades for novel classes of antituberculosis agents, and the results presented here certainly do not disappoint and in fact approach results seen in clinical trials. Identifying key drivers of poor outcomes in programmatic settings that use these highly active agents would be a logical and much- needed follow-up. Nevertheless, based on their encouraging findings, the authors rightly advocate for widespread and rapid access to these novel agents. We would argue equally for integration of rapid phenotypic or genotypic methods for detection of baseline and emergent bedaquiline and delamanid resistance and scale-up of optimal approaches to treatment adherence to protect invaluable new agents. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Max O'Donnell, M.D., M.P.H.
Division of Pulmonary, Allergy, and Critical Care Medicine
Columbia University Irving Medical Center
New York, New York
Mailman School of Public Health
Columbia University Irving Medical Center
New York, New York
and
Centre for AIDS Programme of Research in South Africa
Durban, South Africa

Barun Mathema, Ph.D., M.P.H
Mailman School of Public Health
Columbia University Irving Medical Center
New York, New York

References

1. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: WHO; 2019.
2. Lange C, Dheda K, Chesov D, Mandalakas AM, Udwadia Z, Horsburgh CR Jr. Management of drug-resistant tuberculosis. *Lancet* 2019;394: 953–966.
3. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, *et al*.; Nix-TB Trial Team. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020;382:893–902.
4. Franke MF, Khan P, Hewison C, Khan U, Huerga H, Seung KJ, *et al*.; endTB Observational Study Team. Culture conversion in patients treated with bedaquiline and/or delamanid: a prospective multi-country study. *Am J Respir Crit Care Med* 2021;203:111–119.
5. Günther G, Lange C, Alexandru S, Altet N, Avsar K, Bang D, *et al*.; for TBNET. Treatment outcomes in multidrug-resistant tuberculosis. *N Engl J Med* 2016;375:1103–1105.
6. O'Donnell MR, Padayatchi N, Kvasnovsky C, Werner L, Master I, Horsburgh CR Jr. Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. *Emerg Infect Dis* 2013;19:416–424.
7. Kurbatova EV, Cegielski JP, Lienhardt C, Akksilp R, Bayona J, Becerra MC, *et al*. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. *Lancet Respir Med* 2015;3:201–209.
8. von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V Jr, Ticona E, Segura P, *et al*. Efficacy and safety of delamanid in combination

with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. *Lancet Respir Med* 2019;7:249–259.
9. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, *et al*.; TMC207-C208 Study Group. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014;371:723–732.
10. Nimmo C, Millard J, Brien K, Moodley S, van Dorp L, Lutchminarain K, *et al*. Bedaquiline resistance in drug-resistant tuberculosis HIV co-infected patients. *Eur Respir J* 2020;55:1902383.
11. Liu Y, Gao M, Du J, Wang L, Gao J, Shu W, *et al*. Reduced susceptibility of Mycobacterium tuberculosis to bedaquiline during antituberculosis treatment and its correlation with clinical outcomes in China. *Clin Infect Dis* [online ahead of print] 15 Jul 2020; DOI: 10.1093/cid/ciaa1002.
12. Bloemberg GV, Keller PM, Stucki D, Trauner A, Borrell S, Latshang T, *et al*. Acquired resistance to bedaquiline and delamanid in therapy for tuberculosis. *N Engl J Med* 2015;373:1986–1988. [Published erratum appears in *N Engl J Med* 373:e29.]
13. Law S, Daftary A, O'Donnell M, Padayatchi N, Calzavara L, Menzies D. Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review. *Eur Respir J* 2019;53:1801030.
14. O'Donnell MR, Daftary A, Frick M, Hirsch-Moverman Y, Amico KR, Senthilingam M, *et al*. Re-inventing adherence: toward a patient-centered model of care for drug-resistant tuberculosis and HIV. *Int J Tuberc Lung Dis* 2016;20:430–434.