(300–600 mg per day). However, it recommends that the safety profile of linezolid does not warrant its use in cases where there are other, safer, alternatives [7]. Furthermore, use of linezolid in improper dosage and duration have been associated with increased risk of acquired drug resistance and adverse effects/outcome may be more in those patients of XDR-TB infected with linezolid resistant strains when treated with regimens containing linezolid [8].

We have already lost the two most important first-line drugs, *i.e.* rifampicin and isoniazid to MDR-TB, and the two most important second-line drugs, *i.e.* fluoroquinolone and injectable anti-TB drugs, to XDR-TB and now it would not be wise to lose one of the key drugs in the treatment of XDR-TB, *i.e.* linezolid to the imminent "resistance beyond XDR-TB" [9]. Several clinicians refer to this dreaded condition as total drug resistance, although this terminology has not yet been recognised by WHO. Hence, at this juncture, it would be sensible to restrict the use of linezolid in XDR-TB and complicated drug-resistant TB cases only, as per the WHO guidelines, rather than in all cases of drug-resistant TB. It is well known that treatment outcomes, even under optimal conditions, are relatively poor for MDR-TB and are even worse for XDR-TB [10]. Treatment options for these XDR-TB patients are extremely limited and often rely on a set of drugs with poorly established efficacy and severe adverse events profile. Therefore, the drugs in the armamentarium for XDR-TB should be used judiciously and with utmost care, lest we run out of ammunition in the battle field of XDR-TB.

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The use of linezolid should be preserved for XDR-TB and complicated drug-resistant-TB only
http://ow.ly/Tzg66

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Received: July 19 2015 | Accepted: Aug 04 2015

Conflict of interest: None declared.

References

1 Hughes J, Isaakidis P, Andries A, *et al.* Linezolid for multidrug-resistant tuberculosis in HIV-infected and –uninfected patients . *Eur Respir J* 2015; 46: 271–274.
2 Sotgiu G, Centis R, D'Ambrosio L, *et al.* Efficacy, safety and tolerability of Linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; 40: 1430–1442.
3 World Health Organization. Companion handbook to the WHO guidelines for programmatic management of drug resistant tuberculosis. WHO/HTM/TB/2014.11. Geneva, WHO, 2014. Available from: http://www.who.int/tb/publications/pmdt_companionhandbook/en/
4 Caminero JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. *Int J Tuberc Lung Dis* 2010; 14: 382–390.
5 Revised National Tuberculosis Control Program. Guidelines on the programmatic management of drug resistant tuberculosis (PMDT) in India. Central TB Division Ministry of Health and Family Welfare, New Delhi, 2012. Available from: http://www.tbcindia.nic.in/pdfs/Guidelines%20for%20PMDT%20in%20India%20-%20May%202012.pdf
6 Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2012; 16: 447–454.
7 Migliori GB, Eker B, Richardson MD, *et al.* A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. *Eur Respir J* 2009; 34: 387–393.
8 Zhang L, Pang Y, Yu X, *et al.* Linezolid in the treatment of extensively drug-resistant tuberculosis. *Infection* 2014; 42: 705–711.
9 Migliori GB, Sotgiu G, Gandhi NR, *et al.* Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J* 2013; 42: 169–179.
10 Jacobson KR, Tierney DB, Jeon CY, *et al.* Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis* 2010; 51: 6–14.

From the authors:

We thank Bhuniya and colleagues for highlighting these common concerns regarding the use of linezolid in drug-resistant tuberculosis (DR-TB). We confirm that patients in our cohort were initially started on treatment with standardised regimens following diagnosis of rifampicin and isoniazid resistance (multidrug-resistant tuberculosis (MDR-TB)). We did have access to drug susceptibility testing (DST) for

first- and second-line drugs (rifampicin, isoniazid, ethionamide, fluoroquinolones and injectable agents) and regimens were only individualised following detection of second-line drug (SLD) resistance or failure of standardised regimens.

Individualised regimens were designed based on prior history of antituberculosis drug use and results of first- and second-line DST, as endorsed by World Health Organization (WHO) guidelines; all available drug options, including clofazimine, high-dose isoniazid, amoxicillin/clavulanate and bedaquiline, were used where possible. We emphasise that for all patients in this cohort, the recommended standardised MDR-TB regimens in either country were not considered adequate to provide treatment with at least four likely effective drugs, which is one of the WHO's basic principles of treatment [1].

While we agree with Bhuniya and colleagues that it is important to preserve the efficacy of newer and repurposed antituberculosis drugs such as linezolid (LZD), we also advocate greater access to these drugs in regimens containing at least two other likely effective drugs, within optimally administered treatment programmes with sufficient monitoring and adherence support [2]. Treatment outcomes are poor for MDR-TB, with <50% treatment success globally and in both settings included in our study [3, 4]; outcomes are even worse for patients infected with strains with additional second-line resistance [5]. Persistent use of standardised regimens that are potentially inadequate in cases with known SLD resistance, or where standardised treatment has already failed, is likely to contribute to the emerging extensively drug-resistant tuberculosis (XDR-TB) epidemic due to further acquisition of SLD resistance through selective drug pressure [6], particularly in high-burden settings. This defines the need for strengthened treatment regimens including new TB drugs, both to improve individual patient outcomes and to prevent undertreatment on a programmatic level that drives further resistance.

As ours was a small, retrospective study among DR-TB patients offered treatment with LZD in high-burden programmatic settings, and not a randomised controlled trial to prove the efficacy of LZD; there was no clear control group to allow comparison of our findings. Given their poor prognosis, we optimised treatment using any available medications thought to be effective, in order to offer patients a reasonable chance of cure. There have been very few reports of LZD use for tuberculosis/HIV-coinfected patients; our interim outcomes appear more favourable than previous reports on XDR-TB treatment outcomes for predominantly HIV-uninfected patients treated with standardised regimens [7].

Bhuniya and colleagues suggest that use of LZD at improper dosages and duration is associated with acquired resistance. The article they refer to in support of their argument in fact reports a high proportion of LZD resistance among isolates taken prior to any LZD treatment and emphasises the need to assess resistance early [8]; this is not a reason to avoid LZD in DR-TB treatment. While 11% of patients in a recent randomised controlled trial of LZD in XDR-TB developed linezolid resistance, those patients were effectively receiving monotherapy, unlike our cohort [9]. Furthermore, there is *in vitro* evidence that LZD resistance occurs at lower frequency than what is observed with other tuberculosis drugs [10]. Drug exposure of LZD is highly variable, as is drug susceptibility, with wild-type minimum inhibitory concentration ranging from <0.125 to 0.5 $mg \cdot L^{-1}$. While there is no existing evidence to suggest that therapeutic drug monitoring (TDM) for LZD improves treatment outcomes, it is possible that TDM-guided dosing may prevent toxicity and development of acquired drug resistance. Although TDM of tuberculosis drugs may be challenging in resource-limited programmatic settings, this could be facilitated by innovations such as dried blood spot testing [11, 12].

LZD is still classified as a group 5 drug by WHO and is often only recommended for XDR-TB; however, there is substantially more evidence supporting the effectiveness of LZD than currently exists for many other SLDs used routinely in standard DR-TB treatment regimens [9]. Despite the frequency of adverse events associated with long-term use of LZD, these can be appropriately monitored, and we support wider use of this drug precisely due to the lack of "other, safer alternative" treatment options that would still be effective. The risk of toxicity and the demonstrated clinical effectiveness of LZD should be carefully weighed against the adverse events and monitoring requirements associated with other, less effective SLDs. Joint collaboration between tuberculosis practitioners is necessary to encourage and optimise appropriate use of effective drugs and their potential impact on overall DR-TB treatment outcomes, rather than severely restricting their use and limiting their potential wider public health benefit.

@ERSpublications
Collaboration is needed to encourage and optimise use of effective drugs and their impact on overall DR-TB treatment http://ow.ly/TRkcu

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Received: Aug 18 2015 | Accepted: Oct 24 2015

Conflict of interest: None declared.

References

1 World Health Organization. Companion Handbook to the WHO Guidelines for Programmatic Management of Drug Resistant Tuberculosis. WHO/HTM/TB/2014.11. Geneva, WHO, 2014.
2 Cox HS, Furin J, Mitnick CD, *et al.* The need to accelerate access to new drugs for multidrug-resistant tuberculosis. *Bull World Health Organ* 2015; 93: 491–497.
3 Isaakidis P, Cox HS, Varghese B, *et al.* Ambulatory multi-drug resistant tuberculosis treatment outcomes in a cohort of HIV-infected patients in a slum setting in Mumbai, India. *PLoS One* 2011; 6: e28066.
4 Cox HS, Hughes JA, Daniels J, *et al.* Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. *Int J Tuberc Lung Dis* 2014; 18: 441–448.
5 Dheda K, Shean K, Zumla A, *et al.* Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet* 2010; 375: 1798–1807.
6 Cegielski JP, Dalton T, Yagui M, *et al.* Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2014; 59: 1049.
7 Pietersen E, Ignatius E, Streicher E, *et al.* Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *The Lancet* 2014; 383: 1230–1239.
8 Zhang L, Pang Y, Yu X, *et al.* Linezolid in the treatment of extensively drug-resistant tuberculosis. *Infection* 2014; 42: 705–711.
9 Lee M, Cho SN, Barry CE III, *et al.* Linezolid for XDR-TB – final study outcomes. *N Engl J Med* 2015; 373: 290–291.
10 Hillemann D, Rusch-Gerdes S, Richter E. *In vitro*-selected linezolid-resistant *Mycobacterium tuberculosis* mutants. *Antimicrob Agents Chemother* 2008; 52: 800–801.
11 Robijns K, Harteveld AR, Greijdanus B, *et al.* An interlaboratory quality control programme for the measurement of tuberculosis drugs. *Eur Respir J* 2015; 46: 268–271.
12 Daskapan A, de Lange WC, Akkerman OW, *et al.* The role of therapeutic drug monitoring in individualised drug dosage and exposure measurement in tuberculosis and HIV co-infection. *Eur Respir J* 2015; 45: 569–571.

Eur Respir J 2015; 46: 1844–1846 | DOI: 10.1183/13993003.01374-2015 | Copyright ©ERS 2015

Mediastinoscopy after negative endoscopic mediastinal nodal staging: can it be omitted?

To the Editor:

We read with great interest the study by Vilmann *et al.* [1], proposing new guidelines for diagnosis and staging of lung cancer, particularly discussing the role of combined endobronchial ultrasound (EBUS) and endoscopic oesophageal ultrasound (EUS) in mediastinal nodal staging. We have several comments on this paper.

Various other guidelines have recently already been published on this matter, from the American College of Chest Physicians (ACCP) in 2013 [2] and the European Society of Thoracic Surgeons (ESTS) in 2014 [3]. When comparing these three guidelines, specifically on invasive mediastinal nodal staging, notable differences are few. However, it is interesting to see the fluctuating role of mediastinoscopy after negative endoscopic staging through EBUS and/or EUS. The ESTS guidelines have stated that mediastinoscopy is indicated after negative endoscopic staging. Then again, mediastinoscopy has a much more optional character in the ACCP guidelines [2], emphasising the thoroughness with which the procedure is performed rather than which test is used. It would seem that, the fewer surgeons are involved in the development of the guideline, the more non-committal mediastinoscopy becomes in the diagnostic algorithm of the mediastinum. In the new guidelines by Vilmann *et al.* [1], a combined effort between surgeons, respiratory physicians and endoscopists, mediastinoscopy after negative endoscopic staging is