



HAL
open science

Shortened multidrug-resistant tuberculosis treatment in settings with a high prevalence of ofloxacin resistance

Lorenzo Guglielmetti, Francis Varaine, Helena Huerga, Maryline Bonnet,
Michael L. Rich, Carole D Mitnick

► To cite this version:

Lorenzo Guglielmetti, Francis Varaine, Helena Huerga, Maryline Bonnet, Michael L. Rich, et al.. Shortened multidrug-resistant tuberculosis treatment in settings with a high prevalence of ofloxacin resistance: Ofloxacin resistance and shortened MDR-TB treatment. *European Respiratory Journal*, 2017, 50 (1), Epub ahead of print. 10.1183/13993003.00598-2017 . inserm-01618338

HAL Id: inserm-01618338

<https://inserm.hal.science/inserm-01618338>

Submitted on 17 Oct 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **TITLE:**

2 Shortened MDR-TB treatment in settings with high prevalence of ofloxacin resistance

3

4 **AUTHORS:**

5 Lorenzo Guglielmetti,^{1,2} Francis Varaine,¹ Helena Huerga,³ Maryline Bonnet,^{3,4} Michael L.

6 Rich,⁵ Carole D. Mitnick⁶

7

8 1. Médecins Sans Frontières, Paris, France

9 2. Sorbonne Université, UPMC Université Paris 06, CR7, INSERM, U1135, Centre
10 d'Immunologie et des Maladies Infectieuses, CIMI, Team E13 (Bactériologie), Paris,
11 France

12 3. Epicentre, Paris, France

13 4. Institut de Recherche pour le Développement, INSERM, Université de Montpellier,
14 Montpellier, France

15 5. Brigham and Women's Hospital, Boston, Massachusetts

16 6. Harvard Medical School, Boston, Massachusetts

17

18 **AUTHOR CONTRIBUTIONS:**

19 LG, FV, HH, MB, MR, CDM contributed to the design of the manuscript

20 LG, FV, CDM wrote the first draft of the manuscript

21 LG, FV, HH, MB, MR, CDM reviewed and approved the manuscript for publication

22

23 Word count: 799

24

25 **TEXT:**

26 We have read with interest the research letter by Javaid et al. in a recent issue of the European
27 Respiratory Journal.¹ The authors aptly note some uncertainty in current World Health
28 Organization (WHO) guidelines.² Nevertheless, we question the authors' main assertion that
29 "high prevalence of ofloxacin resistance should not limit the applicability of the new shorter
30 regimen". The shortened regimen has indeed produced promising results in a number of
31 settings, in populations carefully selected for their limited exposure and resistance to second-
32 line drugs.³⁻⁵ That this should be extended to settings with high prevalence of fluoroquinolone
33 resistance, without individual, rapid molecular testing for fluoroquinolone resistance, is not
34 supported by data or WHO.

35 The present sub-national, cross-sectional study shows worryingly high levels of
36 resistance to ofloxacin and other drugs contained in the shortened multidrug-resistant
37 tuberculosis (MDR-TB) regimen. We concur with the authors on the importance of
38 strengthening the public-health response to the various sources of fluoroquinolone-resistant
39 TB in Pakistan. Nevertheless, the presence of ofloxacin resistance, tested at $2 \mu\text{g}\cdot\text{mL}^{-1}$, in
40 48.6% of patients does not support widespread applicability of the shortened regimen in this
41 population. More than 50% of the patients in Bangladesh with "high-level" resistance to
42 ofloxacin by this definition had unfavorable treatment outcomes on the shortened regimen.³
43 Moreover, it is noteworthy that the present study did not report overlapping resistance
44 among these drugs to further inform estimates of the population eligible for the shortened
45 regimen. Since rapid, reliable pyrazinamide testing is not available routinely, any use of the
46 shortened regimen in the presence of high population levels of ofloxacin resistance needs to
47 consider the frequency of concurrent pyrazinamide resistance: according to results from
48 meta-analyses that supported the development of WHO recommendations, the probability of

49 favorable outcomes on the shortened regimen is reduced from 90.3 (95% CI: 87.8-92.4%)
50 among all patients to 67.9% (95% CI: 47.5-84.1%) among patients with isolates resistant to
51 both drugs.⁶ The authors assertion that “it is not recommended to base decision-making on
52 the basis of resistance to pyrazinamide and ethambutol” is at odds with these findings and
53 with WHO guidance. The latter recommends avoiding the shortened treatment in patients
54 with “documented or likely resistance to medicines in the regimen” and “in patients infected
55 with strains known or strongly suspected of being resistant to one or more drugs in the shorter
56 MDR-TB treatment regimen (e.g. pyrazinamide) ...”.⁶

57 The authors propose to increase the applicability of the shortened regimen in this and
58 similar settings by: a) increasing the clinical breakpoint for ofloxacin from 2 to 4 $\mu\text{g}\cdot\text{mL}^{-1}$, b)
59 administering moxifloxacin at high dose, and c) considering resistance to
60 moxifloxacin/gatifloxacin, rather than ofloxacin, as an exclusion criterion for the short course
61 treatment. However, these changes neither resolve the uncertainty in the guidelines nor
62 strengthen the case for the shortened regimen in populations with high prevalence of
63 fluoroquinolone resistance. First, rationale for the proposed increase of MIC for ofloxacin,
64 presumably to serve as a better proxy for resistance to later-generation fluoroquinolones, is
65 not presented; this cut-off is higher than that used for both the national survey and the
66 observational study that demonstrated different clinical outcomes of the shorter regimen in
67 strains with low-level versus high-level fluoroquinolone resistance.^{3,7} Second,
68 moxifloxacin/gatifloxacin are already prescribed at high dose (400 to 800 mg/day according
69 to weight group) in some applications of the shortened regimen, so the results showing
70 reduced effectiveness in the presence of resistance to fluoroquinolones and pyrazinamide
71 already factor in this reinforcement.⁶ Third, while we agree in principle that usefulness of late-
72 generation fluoroquinolones is best guided by drug susceptibility testing (DST) to those

73 drugs—and not by DST to earlier-generation class members⁸—the proposed modification to
74 guidance to rule out moxifloxacin/gatifloxacin resistance is problematic from an operational
75 standpoint; DST to these drugs is infrequently available in high-burden settings (including
76 Pakistan, according to the authors). More practically, rapid molecular tests will be used to
77 assess eligibility. Their careful interpretation to identify individual patients eligible for the
78 shortened regimen will be especially important in settings with known high population levels
79 of fluoroquinolone resistance. Existing data from sequencing suggest that resistance caused
80 by mutations in the QRDR region of *gyrA* (except 94Ala) is associated with an important
81 increase in poor outcomes on the shortened regimen.⁹ Fortunately, there are other options:
82 the advent of delamanid and bedaquiline,¹⁰ as well as other “core” MDR-TB drugs used in
83 conventional regimens offer alternatives to using the shortened regimen in patients in whom
84 its success is likely compromised. Multiple new studies of shortened regimens containing
85 these drugs (Nix-TB [NCT02333799], TB-PRACTECAL [NCT02589782], endTB [NCT02754765])
86 may generate palatable and effective alternatives.

87 In conclusion, we recommend caution in the introduction of the shortened MDR-TB
88 treatment in settings with high prevalence of resistance to ofloxacin or pyrazinamide;
89 eligibility for shortened treatment should be evaluated individually according to rapid
90 molecular testing and available DST results.

91

92 **BIBLIOGRAPHY:**

- 93 1. Javaid, A. *et al.* Applicability of the World Health Organization recommended new shorter
94 regimen in a multidrug-resistant tuberculosis high burden country. *Eur. Respir. J.* **49** pii:
95 (2017).
- 96 2. Varaine, F. *et al.* Eligibility for the shorter multidrug-resistant tuberculosis regimen:
97 ambiguities in the World Health Organization recommendations. *Am. J. Respir. Crit. Care*
98 *Med.* **194**, 1028–1029 (2016).
- 99 3. Aung, K. J. M. *et al.* Successful ‘9-month Bangladesh regimen’ for multidrug-resistant
100 tuberculosis among over 500 consecutive patients. *Int. J. Tuberc. Lung Dis.* **18**, 1180–7
101 (2014).
- 102 4. Piubello, A. *et al.* High cure rate with standardised short-course multidrug-resistant
103 tuberculosis treatment in Niger: no relapses. *Int. J. Tuberc. Lung Dis.* **18**, 1188–1194
104 (2014).
- 105 5. Kuaban, C. *et al.* High effectiveness of a 12-month regimen for MDR-TB patients in
106 Cameroon. *Int. J. Tuberc. Lung Dis.* **19**, 517–524 (2015).
- 107 6. Dennis Falzon, Holger J. Schünemann, Elizabeth Harausz, Licé González-Angulo, Christian
108 Lienhardt, Ernesto Jaramillo, Karin Weyer. World Health Organization treatment
109 guidelines for drug-resistant tuberculosis, 2016 update. *European Respiratory Journal* Mar
110 2017, 49 (3) 1602308; DOI: 10.1183/13993003.02308-2016.
- 111 7. Zignol, M. *et al.* Population-based resistance of *Mycobacterium tuberculosis* isolates to
112 pyrazinamide and fluoroquinolones: results from a multicountry surveillance project.
113 *Lancet Infect. Dis.* **16**, 1185–1192 (2016).
- 114 8. Farhat, M. R. *et al.* Concordance of *Mycobacterium tuberculosis* fluoroquinolone
115 resistance testing: implications for treatment. *Int. J. Tuberc. Lung Dis.* **19**, 339–341 (2015).

- 116 9. Rigouts, L. *et al.* Specific *gyrA* gene mutations predict poor treatment outcome in MDR-TB. *J.*
117 *Antimicrob. Chemother.* **71**, 314–323 (2016).
- 118 10. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D’Ambrosio L, Centis R, Sotgiu G, Tiberi S,
119 Alffenaar JW, Maryandyshev A, Belilovski E, Ganatra S, Skrahina A, Akkerman O, Aleksa A, Amale
120 R, Artsukevich J, Bruchfeld J, Caminero JA, Martinez IC, Codecasa L, Dalcolmo M, Denholm J,
121 Douglas P, Duarte R, Esmail A, Fadul M, Filippov A, Forsman LD, Gaga M, Garcia-Fuertes JA,
122 García-García JM, Gualano G, Jonsson J, Kunst H, Lau JS, Mastrapa BL, Troya JLT, Manga S, Manika
123 K, Montaner PG, Mullerpattan J, Oelofse S, Orтели M, Palmero DJ, Palmieri F, Papalia A,
124 Papavasileiou A, Payen MC, Pontali E, Cordeiro CR, Saderi L, Sadutshang TD, Sanukevich T,
125 Solodovnikova V, Spanevello A, Topgyal S, Toscanini F, Tramontana AR, Udwadia ZF, Viggiani P,
126 White V, Zumla A and Migliori GB. Effectiveness and safety of bedaquiline-containing regimens in
127 the treatment of multidrug and extensively drug-resistant tuberculosis: a multicentre study. *Eur*
128 *Respir J* 2017; in press