Counting Pyrazinamide in Regimens for Multidrug-Resistant Tuberculosis

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Abstract

Rationale: For treatment of multidrug-resistant tuberculosis, World Health Organization (WHO) guidelines recommend four likely effective drugs plus pyrazinamide (PZA), irrespective of the likely effectiveness of PZA in an individual patient. Whether this regimen should be supplemented in the absence of likely PZA effectiveness is an open question.

Objectives: The objectives of this study were to examine (1) whether individuals receiving four likely effective drugs (based on documented susceptibility or no prior exposure) experienced higher mortality during the intensive phase of treatment than those receiving five likely effective drugs and (2) whether the WHO-recommended regimen (four likely effective drugs plus PZA) may be compromised in individuals in whom PZA is not likely effective.

Methods: Among 668 patients, we compared the hazard of death across regimen groups characterized by the number of likely

effective drugs and whether pyrazinamide was one of the likely effective drugs.

Measurements and Main Results: Relative to five likely effective drugs, regimens of four likely effective drugs and the WHO-recommended regimen used in individuals in whom PZA was not likely effective were associated with higher mortality rates (respectively, adjusted hazard ratio [HR], 2.87; 95% confidence interval [CI], 1.35–6.09 and adjusted HR, 2.76; 95% CI, 0.92–8.27). The mortality rate for a regimen of five likely effective drugs with likely effective PZA was similar to that for the regimen of five likely effective drugs without PZA (HR, 1.00; 95% CI, 0.12–8.00).

Conclusions: Mortality may be reduced by the inclusion of five likely effective drugs, including an injectable, during the intensive phase of treatment. If PZA is unlikely to be effective in an individual patient, these results suggest adding a different, likely effective drug.

Keywords: drug resistance; mortality; tuberculosis drug therapy

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Few randomized or prospective studies exist to guide the optimal composition of regimens for multidrug-resistant (MDR) tuberculosis (TB). Treatment guidelines therefore are based on expert opinion and the experience of retrospective observational cohorts (1–4). For the intensive phase of

treatment, current World Health Organization (WHO) guidelines recommend that MDR-TB regimens comprise four second-line TB drugs likely to be effective—based on documented susceptibility or no prior exposure—plus pyrazinamide (PZA) (5). Issued in 2011, this

was a conditional recommendation based on evidence that the WHO Guidelines Development Group judged to be of very low quality using standard criteria according to the GRADE methodology (6, 7).

Several recent studies have examined the effect of an “aggressive” regimen

(i.e., one containing at least five likely effective TB drugs, including an injectable agent during the intensive phase) on different treatment endpoints. In Peru, individuals who received aggressive regimens experienced lower rates of mortality (8) and recurrent TB (9) and faster rates of sputum conversion (10). In Russia, patients who received aggressive regimens also had significantly reduced rates of death and treatment failure (11). Although the aggressive regimen definition overlaps with WHO guidelines for regimen design, the two treatment strategies differ slightly regarding the inclusion of PZA. WHO guidelines recommend using PZA in MDR-TB regimens irrespective of its likely effectiveness in an individual patient (6) because of limited reliability and reproducibility of drug susceptibility testing for PZA (12–15). The WHO-recommended strategy can, therefore, result in a regimen of five likely effective drugs for individuals with true PZA susceptibility and four likely effective drugs for individuals with true PZA resistance. In contrast, the aggressive regimen definition considered the likely effectiveness of PZA, and all other drugs, based on drug susceptibility testing and prior exposure; patients must have received five likely effective drugs for the regimen to be classified as aggressive.

The objectives of this study were (1) to examine whether individuals receiving four likely effective drugs experienced a higher mortality rate during the intensive phase of treatment than those receiving five likely effective drugs and (2) to study whether the WHO-recommended regimen (four likely effective drugs plus PZA) may be compromised in individuals in whom PZA is not likely effective.

Methods

Study Population

We conducted a retrospective cohort study among 673 consecutive patients who initiated a first individualized MDR-TB treatment between February 1, 1999 and July 31, 2002 in Lima, Peru. This cohort included patients with extensively drug-resistant TB. Characteristics and outcomes of this cohort have been described previously (8–10, 16, 17). Treatment regimens were tailored to individual drug susceptibility test results and prior treatment exposure as previously described

(4). We excluded patients who had received prior individualized MDR-TB treatment and patients for whom detailed regimen data were not available.

Treatment and Monitoring

Baseline evaluation, drug susceptibility testing, and treatment monitoring were performed as described previously (18). In addition to routine drug susceptibility testing to the first-line drugs (isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin), testing for susceptibility to the following second-line drugs was performed in an isolate from more than 75% of patients: amikacin, capreomycin, cycloserine, ethionamide, kanamycin, and *para*-aminosalicylic acid; ciprofloxacin or ofloxacin; and either gatifloxacin, levofloxacin, or moxifloxacin. Drug susceptibility testing for pyrazinamide was conducted on a liquid medium using BACTEC (Becton Dickinson, Franklin Lakes, NJ) and testing a concentration of 100 µg/ml. Outpatient treatment was directly observed, and adverse events were managed according to established algorithms (19, 20).

Data Collection

Data were collected and recorded in a web-based electronic medical record during treatment (21). A standardized paper chart abstraction was conducted to complete the dataset.

Primary Exposure

The primary exposure was regimen composition during the intensive phase of treatment. It was constructed based on (1) the number of likely effective first- or second-line drugs received in the treatment month and (2) whether PZA was contained in this regimen. Likely effectiveness was determined by information on prior exposure and *in vitro* susceptibility results as previously described (8). We classified regimens into the following mutually exclusive groups: group A included five likely effective drugs, one of which was PZA; group B included four likely effective drugs plus not likely effective PZA; group C included five likely effective drugs, none of which was PZA; group D included four likely effective drugs, exclusive of group B; group E included fewer than four likely effective drugs; and group F included six or more likely effective drugs. All six groups contained a likely effective injectable during the intensive phase. Group G regimens

contained any number of likely effective drugs but not a likely effective injectable. Groups A and B corresponded to the 2011 WHO-recommended regimen of four likely effective drugs plus PZA.

Regimen group was determined by treatment day because regimen adjustments could change exposure status. Regimen changes occurred occasionally by design (regimens were started empirically and then adjusted when baseline drug susceptibility test results became available) and in response to adverse events, nonresponse to therapy, and drug stock-outs. For each treatment month, we identified the regimen category received for the majority ($\geq 75\%$) of regimen days in that month.

Covariate Data

We collected information on the following covariates: age, sex, previous anti-TB regimens received, health district, year of treatment initiation, chest X-ray findings, low body mass index (<18.5 in women and <20 in men), a clinical diagnosis of malnutrition, low hematocrit ($\leq 30\%$ in women and $\leq 36\%$ in men; when missing, we used hemoglobin ≤ 10 in women and ≤ 12 in men), tachycardia, respiratory difficulty (a clinical diagnosis of dyspnea or resting respiratory rate $>26/\text{min}$), extrapulmonary TB, drug susceptibility test results, a history of resective surgery, and comorbidities including HIV infection, cardiovascular disease, diabetes mellitus, hepatitis or cirrhosis, epilepsy/seizures, renal insufficiency, psychiatric disorder, history of smoking, and history of use or abuse of alcohol or another substance.

Statistical Analyses

We modeled the association between regimen group and the hazard of death from any cause during the intensive phase of treatment, using Cox proportional hazards analyses with the Anderson Gill formulation, stratified by treatment month (22, 23). Consistent with current WHO guidelines, the first 8 months of treatment represented the intensive phase. Data were censored when an outcome other than death (i.e., treatment default, transfer-out) was recorded or after 8 months of treatment. We adjusted for age, sex, and variables that were previously found to be confounders or predictors of death in a related analysis examining the relationship between an aggressive regimen and time to death (8). We calculated hazard

ratios (HRs) to compare the mortality rates for regimens of four likely effective drugs (group D) and four likely effective drugs, plus not likely effective PZA (group B), with that for regimens of five likely effective drugs (groups A and C).

In secondary analyses, we compared group A with group C. Lastly, to explore possible synergy between PZA and other drugs, we calculated HRs that compared group C regimens with PZA with those without PZA. For group C, PZA was not considered a likely effective drug; however, if PZA were potentiating effects of a likely effective drug, regimens with PZA might confer a protective effect, although it did not meet the definition of “likely effective.” Missing baseline covariate values were multiply imputed using Markov Chain Monte Carlo methods to complete the dataset (24). Analyses were conducted using SAS version 9.12 (SAS Institute, Cary, NC).

Ethics Statement

This retrospective study was approved by the Committee on Human Studies at Harvard Medical School and by the Ministry of Health of Peru.

Results

Of the 673 patients who initiated individualized MDR-TB treatment during the study period, we excluded two patients who had previously received individualized treatment and three patients for whom detailed data on regimen composition were not available. Baseline characteristics for the 668 patients, which have been previously described (8), are shown in Table E1 in the online supplement. Briefly, patients were resistant to a mean of 5.4 drugs (SD = 1.7), and more than half had bilateral cavitary disease. Other indicators of disease severity were also common: 39% of patients had a low body mass index or a diagnosis of malnutrition, 72% had respiratory difficulty, and 30% had tachycardia. Ninety-nine percent of patients had prior exposure to at least 1 month of PZA.

We identified 133 participants (20%) in whom PZA was likely effective at the start of treatment. All but two of these patients had a drug susceptibility test result confirming PZA susceptibility. Among those in whom PZA was not likely effective, 276 (51%) had a drug susceptibility test result

demonstrating resistance to PZA. The 668 patients contributed 4,992 person-months of treatment exposure during the intensive phase. The distribution of person-months by regimen type is shown in Figure 1. The most common regimen composition—five likely effective drugs of which none was PZA (group C)—was administered during 28% of all person-months. Regimen groups A and B, the regimens consistent with the 2011 WHO guidelines, accounted for nearly 9% of person-months. Among the 440 person-months of exposure to these regimen groups, just under half (n = 188; 43%) occurred in individuals in whom PZA was likely effective (group A). More than one third (n = 498; 35%) of the 1,414 group C person-months corresponded to regimens that included PZA, although it was not likely effective. Final outcomes were previously reported (8); during the first 8 months of treatment, 59 deaths occurred.

We found that both regimen groups including only four likely effective drugs (groups B and D) were associated with higher mortality relative to regimens containing five likely effective drugs (groups A and C) (Table 1). In multivariable analyses, patients receiving a regimen of four likely effective drugs (group D) experienced nearly three times the rate of death during the intensive phase of treatment (adjusted HR [aHR], 2.87; 95% confidence interval [CI], 1.35–6.09; $P = 0.006$) relative to individuals receiving five likely effective drugs (groups A and C) (Table 1). A similar relative increase in mortality was observed for regimens of four likely effective drugs plus PZA when PZA was not likely effective (group B) (aHR, 2.76; 95% CI, 0.92–8.27), although this was not statistically significant.

In a secondary analysis, we stratified person-months of exposure to a regimen of five likely effective drugs (groups A and C) according to whether PZA was one of the likely effective agents (group A). The hazard of death for a regimen of five likely effective drugs with PZA counted among them (group A) was indistinguishable from that for regimens of five likely effective drugs without likely effective PZA (group C; aHR, 1.00; 95% CI, 0.12–8.00). We then further stratified the person-months corresponding to a regimen of five likely effective drugs of which none was PZA (group C), according to whether PZA was included in the regimen, although it was not likely effective.

The hazard of death associated with group C regimens that did not include PZA was lower than group C regimens that contained PZA (aHR, 0.10; 95% CI, 0.01–0.85).

Discussion

The present study findings suggest that regimens of five likely effective drugs may reduce the rate of death relative to four likely effective drugs in some patient populations and that the likely effectiveness of PZA is an important consideration in the design of MDR-TB regimens. Regimens containing five likely effective drugs were associated with lower mortality in the intensive phase of MDR-TB treatment than regimens containing four likely effective drugs. They also showed a nonsignificant trend toward lower mortality than regimens containing four likely effective drugs plus PZA that is not likely effective. In contrast, the mortality rate among individuals who received a regimen of four likely effective drugs plus likely effective PZA was indistinguishable from that for regimens of five likely effective drugs without PZA. The relevance of a sensitive PZA drug susceptibility test result was also highlighted in two observational studies of MDR-TB treatment, which found that a PZA-containing regimen in patients with PZA susceptibility was positively associated with culture conversion (25) and treatment success (25, 26) relative to a PZA-containing regimen in patients with PZA resistance.

Consistent with WHO guidelines, we defined likely effectiveness based on prior treatment exposure and drug susceptibility test results. Consideration of prior exposure may be especially important for PZA given the challenges associated with drug susceptibility testing for PZA. Standard culture-based tests for PZA susceptibility are subject to several technical challenges that may jeopardize reliability (13, 14). First, PZA activity requires an acidic medium, which also inhibits growth of *Mycobacterium tuberculosis* (14); this may result in misclassification of resistant isolates as sensitive. On the other hand, sensitive isolates may be misclassified as resistant because a large inoculum may release ammonia, increasing the pH of the medium and inactivating PZA (14). Tests for the presence of *pncA* mutations avoid the problems of the culture-based testing,

Figure 1. Person-time distribution of multidrug-resistant tuberculosis regimens during the first 8 months of treatment. *Consistent with an aggressive regimen (8–10). Some regimens corresponding to this category included pyrazinamide (PZA), which was not likely effective. †In one place in the WHO 2011 guidelines (6), the recommendation is for “at least four likely effective drugs, as well as PZA” (p. 19). In all others, the recommendation is for exactly “four likely effective drugs as well as PZA.” WHO = World Health Organization.

but *pncA* mutations are diverse, and, on average, 13% of PZA-resistant strains do not have detectable *pncA* mutations (15), potentially leading to further underestimation of resistance.

It is possible that PZA may confer some clinical benefit in MDR-TB regimens even if PZA resistance is confirmed. PZA has been shown in preclinical studies to have synergy with other first- and second-line anti-TB

drugs, including rifampin, levofloxacin, and bedaquiline (14, 27–30). It has been hypothesized that this synergy may—as in the reduction of relapse when PZA is combined with rifampin—be due to the unique activity of PZA against persisting *M. tuberculosis* that are not killed by other drugs (14). There has been no clinical demonstration of any benefit from adding PZA to regimens used to treat patients with

PZA-resistant isolates. In this study, we did not find evidence that PZA provided clinical benefit to patients in whom PZA was not likely effective. Among regimens of exactly five likely effective drugs of which none was PZA (group C), those including PZA (and by definition not likely to be effective) were associated with higher mortality than those that did not include PZA. This observation may be a chance

Table 1. Univariable and multivariable associations between regimen composition and time to death

Group	Regimen	Univariable Hazard Ratio (95% CI)	P Value	Multivariable* Hazard Ratio (95% CI)	P Value
A and C	5 likely effective drugs ^{†‡}	Reference		Reference	
B	4 likely effective drugs [†] plus PZA, which is not likely effective	4.40 (1.40–13.85)	0.01	2.76 (0.92–8.27)	0.07
D	4 likely effective drugs [†]	4.46 (1.87–10.60)	0.007	2.87 (1.35–6.09)	0.006
E	<4 likely effective drugs [†]	4.24 (1.61–11.14)	0.003	3.36 (1.43–7.85)	0.005
F	≥6 likely effective drugs [†]	1.51 (0.39–5.82)	0.55	1.20 (0.32–4.45)	0.80
G	Any number of likely effective drugs without a likely effective injectable agent	2.73 (1.11–6.69)	0.03	1.94 (0.83–4.53)	0.12

Definition of abbreviations: CI = confidence interval; PZA = pyrazinamide.

*Multivariable estimates adjusted for age, sex, HIV infection, number of drugs to which the isolate was resistant, presence of extrapulmonary tuberculosis, low body mass index or a clinical diagnosis of malnutrition, tachycardia (heart rate >100/min), receipt of two or fewer regimens without standardized multidrug-resistant tuberculosis treatment, and the presence of one or more comorbidities (cardiovascular disease, diabetes mellitus, hepatitis or cirrhosis, epilepsy/seizures, renal insufficiency, psychiatric disorder, ever smoked, ever used/abused alcohol or other substance).

[†]Included in the number of likely effective drugs is a likely effective injectable agent.

[‡]Included in this group is person-time corresponding to regimen groups A and C.

finding or the result of confounding by other regimen characteristics, such as the inclusion of third-line drugs. Small sample sizes and the use of PZA in multidrug regimens limited our ability to rule out synergy between PZA and other second-line drugs when infecting isolates were resistant to PZA. This, and whether higher doses of PZA could increase activity or shorten treatment without compromising efficacy (31, 32), could be further explored.

In this patient population, less than 10% of treatment-months corresponded to the currently recommended regimen of four likely effective drugs—including a likely effective injectable—plus PZA (groups A and B). This limited power for some important estimates. For example, regimens of four likely effective drugs plus PZA that was not likely effective (group B) were associated with an increase in mortality relative to regimens of five likely effective drugs (groups A and C). Although this relative increase in mortality was comparable to that associated with regimens of four likely effective drugs

(group D), it was not statistically significant ($P = 0.07$).

The small sample size also precluded the study of whether the likely effectiveness of PZA influenced other outcomes, such as TB recurrence, and whether results differed among individuals in whom the likely effectiveness of PZA was determined by drug susceptibility testing versus by prior exposure. Nearly all individuals in this cohort had prior exposure to PZA for more than 1 month, and, in the absence of drug susceptibility testing, this history of exposure to PZA resulted in the classification of PZA as not likely effective. This definition may have misclassified some patients in whom PZA retained effectiveness despite prior exposure. Provided that the probability of misclassification was similar between outcome groups, it would likely attenuate the HR. Misclassification would not explain our study finding that four likely effective drugs were associated with higher mortality than five likely effective drugs. In spite of imprecise estimates for some comparisons, we believe these results contribute importantly to existing

knowledge regarding the design of regimens for patients with MDR-TB and that these findings are generalizable to other patient populations in which advanced TB disease and/or extensive previous treatment is common.

In conclusion, our results provide strong evidence that the rate of death can be significantly reduced by the inclusion of five likely effective drugs, including an effective injectable, during the intensive phase of MDR-TB treatment. We urge consideration of the likely effectiveness of PZA when designing MDR-TB regimens. Individuals who receive a regimen of four likely effective drugs plus PZA when PZA is not likely effective may require an additional TB drug to achieve the lower mortality rate observed among patients receiving five likely effective drugs. ■

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

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References

- Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, Becerra MC, Benedetti A, Burgos M, Centis R, *et al.*; Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012;9:e1001300.
- Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, Gandhi NR, Galvani AP. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:153–161.
- Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PLoS ONE* 2009;4:e6914.
- Mukherjee JS, Rich ML, Soggi AR, Joseph JK, Virú FA, Shin SS, Furin JJ, Becerra MC, Barry DJ, Kim JY, *et al.* Programmes and principles in treatment of multidrug-resistant tuberculosis. *Lancet* 2004;363:474–481.
- World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis, 1st ed. Geneva, Switzerland: WHO; 2006.
- World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update. Geneva, Switzerland: WHO; 2011.
- Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–926.
- Mitnick CD, Franke MF, Rich ML, Alcantara Viru FA, Appleton SC, Atwood SS, Bayona JN, Bonilla CA, Chalco K, Fraser HSF, *et al.* Aggressive regimens for multidrug-resistant tuberculosis decrease all-cause mortality. *PLoS ONE* 2013;8:e58664.
- Franke MF, Appleton SC, Mitnick CD, Furin JJ, Bayona J, Chalco K, Shin S, Murray M, Becerra MC. Aggressive regimens for multidrug-resistant tuberculosis reduce recurrence. *Clin Infect Dis* 2013;56:770–776.
- Tierney DB, Franke MF, Becerra MC, Alcantara Viru FA, Bonilla CA, Epifanio Sanchez E, Guerra D, Munoz M, Llaro K, Palacios E, *et al.* Time to culture conversion and regimen composition in multidrug-resistant tuberculosis treatment. *PLoS One* 2014;9:e108035.
- Velásquez GE, Becerra MC, Gelmanova IY, Pasechnikov AD, Yedilbayev A, Shin SS, Andreev YG, Yanova G, Atwood SS, Mitnick CD, *et al.* Improving outcomes for multidrug-resistant tuberculosis: aggressive regimens prevent treatment failure and death. *Clin Infect Dis* 2014;59:9–15.
- World Health Organization. Framework for implementing new tuberculosis diagnostics. Geneva, Switzerland: WHO; 2010.
- Dormandy J, Somoskovi A, Kreiswirth BN, Driscoll JR, Ashkin D, Salfinger M. Discrepant results between pyrazinamide susceptibility testing by the reference BACTEC 460TB method and *pncA* DNA sequencing in patients infected with multidrug-resistant *Mycobacterium tuberculosis* strains. *Chest* 2007;131:497–501.
- Zhang Y, Mitchison D. The curious characteristics of pyrazinamide: a review. *Int J Tuberc Lung Dis* 2003;7:6–21.
- Chang KC, Yew WW, Zhang Y. Pyrazinamide susceptibility testing in *Mycobacterium tuberculosis*: a systematic review with meta-analyses. *Antimicrob Agents Chemother* 2011;55:4499–4505.
- Mitnick CD, Shin SS, Seung KJ, Rich ML, Atwood SS, Furin JJ, Fitzmaurice GM, Alcantara Viru FA, Appleton SC, Bayona JN, *et al.* Comprehensive treatment of extensively drug-resistant tuberculosis. *N Engl J Med* 2008;359:563–574.
- Becerra MC, Appleton SC, Franke MF, Chalco K, Bayona J, Murray MB, Mitnick CD. Recurrence after treatment for pulmonary multidrug-resistant tuberculosis. *Clin Infect Dis* 2010;51:709–711.
- Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcántara F, Sánchez E, Sarria M, Becerra M, Fawzi MCS, *et al.* Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *N Engl J Med* 2003;348:119–128.
- Partners In Health. The PIH guide to the medical management of multidrug-resistant tuberculosis. Boston, MA: Partners in Health; 2003.

- 20 Partners in Health, Harvard Medical School B& MGF. A DOTS-Plus handbook: guide to the community-based treatment of MDR-TB. Boston, MA: Harvard Medical School; 2002.
- 21 Fraser HSF, Jazayeri D, Mitnick CD, Mukherjee JS, Bayona J. Informatics tools to monitor progress and outcomes of patients with drug resistant tuberculosis in Peru. *Proc AMIA Symp* 2002;270–274.
- 22 Cox DR. Regression models and life-tables. *J R Stat Soc B* 1972;34: 187–220.
- 23 Therneau TM, Grambsch PM. Modeling survival data. New York: Springer; 2000.
- 24 Shafer J. Analysis of incomplete multivariate data. New York: Chapman and Hall; 1997.
- 25 Chang K-C, Leung C-C, Yew W-W, Leung EC-C, Leung W-M, Tam C-M, Zhang Y. Pyrazinamide may improve fluoroquinolone-based treatment of multidrug-resistant tuberculosis. *Antimicrob Agents Chemother* 2012;56:5465–5475.
- 26 Bastos ML, Hussain H, Weyer K, Garcia-Garcia L, Leimane V, Leung CC, Narita M, Penã JM, Ponce-de-Leon A, Seung KJ, *et al.*; Collaborative Group for Meta-analysis of Individual Patient Data in MDR-TB. Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first- and second-line drugs: an individual patient data meta-analysis. *Clin Infect Dis* 2014;59:1364–1374.
- 27 Sokolova GB, Semenova OV, Bogadel'nikova IV, Kunichan AD. Effect of levofloxacin on cell elements of the lung tissue and on the growth of drug resistant *Mycobacteria tuberculosis*. (In Russian.) *Antibiot Khimioter* 2002;47:12–17.
- 28 Ibrahim M, Andries K, Lounis N, Chauffour A, Truffot-Pernot C, Jarlier V, Veziris N. Synergistic activity of R207910 combined with pyrazinamide against murine tuberculosis. *Antimicrob Agents Chemother* 2007;51:1011–1015.
- 29 Tasneen R, Li S-Y, Peloquin CA, Taylor D, Williams KN, Andries K, Mdluli KE, Nuermberger EL. Sterilizing activity of novel TMC207- and PA-824-containing regimens in a murine model of tuberculosis. *Antimicrob Agents Chemother* 2011;55:5485–5492.
- 30 Veziris N, Ibrahim M, Lounis N, Andries K, Jarlier V. Sterilizing activity of second-line regimens containing TMC207 in a murine model of tuberculosis. *PLoS ONE* 2011;6:e17556.
- 31 Hall RG, Leff RD, Gumbo T; Insights from the Society of Infectious Diseases Pharmacists. Treatment of active pulmonary tuberculosis in adults: current standards and recent advances. *Pharmacotherapy* 2009;29:1468–1481.
- 32 Gumbo T, Dona CS, Meek C, Leff R. Pharmacokinetics-pharmacodynamics of pyrazinamide in a novel in vitro model of tuberculosis for sterilizing effect: a paradigm for faster assessment of new antituberculosis drugs. *Antimicrob Agents Chemother* 2009;53:3197–3204.