Pharmacokinetics of tuberculosis drugs in HIV-infected patients from Irkutsk, Russian Federation: redefining drug activity

To the Editor:

The Russian Federation has the third highest burden of multidrug-resistant (MDR) tuberculosis (TB) in the world, accounting for 10.5% of cases worldwide [1]. Management of the drug-resistant TB epidemic in the Siberian province of Irkutsk is further complicated by high rates of HIV co-infection [2], which leads to early mortality and risk for acquired *Mycobacterium tuberculosis* drug resistance [3]. Such poor treatment outcomes may be in part a consequence of pharmacokinetic variability rendering subtherapeutic drug concentrations [4–6]. Serum area under the concentration curve (AUC) is the pharmacokinetic parameter correlative with efficacy for most concentration-dependent TB drugs [7, 8] and AUC/minimum inhibitory concentration (MIC) ratio can be further used to predict treatment response [9]. However, relatively few studies have examined the pharmacokinetics of MDR-TB drugs, and none from HIV-infected patients in the Russian Federation. The following prospective cohort study of HIV-TB co-infected patients in Irkutsk was performed to describe pharmacokinetic variability and MIC ranges, and determine if drug activity associates with treatment response. The setting was hypothesised to be particularly informative given the high incidence of MDR- and extensively drug-resistant (XDR)-TB and routine use of novel treatment strategies, including high-dose isoniazid.

Consecutive HIV-infected patients initiating TB treatment at the Irkutsk Regional TB Referral Hospital were recruited, with an aim of 70 patients to enrol at least 30 patients treated for MDR-TB. All eligible patients provided written informed consent and the protocol was approved by the institutional review boards of the Scientific Centre for Family Health and Human Reproduction Problems in Irkutsk, and of the University of Virginia (Charlottesville, VA, USA). After 2 weeks of treatment, medications were directly administered and plasma samples collected at 2 h and 6 h after administration. Pyrazinamide was dosed separately from morning medications and only 2-h concentrations were measured. Samples were immediately centrifuged and the serum stored at −80°C prior to a batched dry-ice shipment to the University of Florida Infectious Disease Pharmacokinetics Laboratory (Gainesville, FL, USA). Drug concentrations were measured using validated liquid chromatography-mass spectrometry assays. Peak concentration (C_{max}) was defined as the highest value obtained in the dosing interval, and AUC from 0 to 6 h ($AUC_{0–6}$) was calculated using Phoenix WinNonlin software v.7.0 (Certara, Princeton, NJ, USA). Conventional *M. tuberculosis* drug susceptibility results that the clinicians used for initial drug regimens were obtained by chart review. MIC testing was performed for study purposes using the MYCOTB Sensititre plate (Trek Diagnostic Systems, Oakwood Village, OH, USA) [9]. For redefining drug activity, a drug was classified as active when C_{max} was greater than individual isolate MIC, or when C_{max} was greater than the median MIC for the cohort when the individual isolate MIC was not available. Outcomes were reported as treatment success in the event of a cure or completion of treatment with symptomatic and radiographic improvement. Treatment failure was defined as death or inability to complete treatment.

Data were entered into Microsoft Excel and analysed using SPSS v22 (IBM Corp., Armonk, NY, USA). Comparisons of means and medians were by two-sample t-test and Kruskal–Wallis respectively. Tests of significance were two-tailed. For hypothesis generation of the effects of drug activity with treatment

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TABLE 1 Pharmacokinetics and susceptibilities for tuberculosis (TB) drugs in HIV-TB co-infected patients from Irkutsk

Drug	Patients n	Dose mg·kg^{-1}	Recommended dose	C_{max} μg·mL^{-1}	Expected C_{max} μg·mL^{-1}	AUC_{0-6} μg·mL^{-1}	MIC[#] μg·mL^{-1}	Susceptible by DST[¶]	Susceptible by C_{max} or MIC
Isoniazid	38	9.7 (8.9-10.0)	4–6 mg·kg^{-1}	3.1 (trace–5.47)	3–6	15.5 (6.2–24.5)	2.0 (0.81–4)	14 (36.8)	22 (57.9)
Levofloxacin	30	9.3 (8.7–11.2)	750–1000 mg	3.7 (0.05–6.47)	8–12	16.5 (0.2–33.5)	0.5 (0.5–1.0)	26 (86.7)	19 (63.3)
Moxifloxacin	7	9.7 (7.8–10.7)	400–800 mg	0.46 (trace–4.39)	3–5	11.1 (4.0–15.2)	0.25 (0.12–0.37)	6 (85.7)	4 (57.1)
Ofloxacin	19	7.6 (5.7–8.9)[+]	800–1000 mg	4.3 (2.3–5.6)	8–12	23.0 (10.4–28.0)	0.5 (0.5–1.0)	13 (68.4)	15 (78.9)
Amikacin	8	15.0 (13.6–17.6)	15 mg·kg^{-1}	35.9 (18.1–38.5)	35–45	158.8 (87.7–183.6)	0.5 (0.25–0.63)	7 (87.5)	5 (62.5)
Kanamycin	22	16.6 (14.1–20.0)	15 mg·kg^{-1}	32.9 (15.1–49.1)	35–45	173.6 (93.5–208.7)	1.2 (1.2–15.0)	19 (86.4)	12 (54.5)
Capreomycin	18	16.5 (15.7–18.3)	15 mg·kg^{-1}	11.1 (5.6–15.8)	35–45	47.7 (6.5–74.8)	NA	17 (94.4)	17 (94.4)
Pyrazinamide	54	26.9 (25.8–31.3)	25 mg·kg^{-1}	19.8 (6.9–34.9)	20–60	NA	NA	47 (87.0)	30 (55.6)

Data are presented as median (interquartile range) or n (%), unless otherwise stated. C_{max}: peak concentration; AUC_{0-6}: area under the concentration curve from 0 to 6 h; MIC: minimum inhibitory concentration; DST: drug susceptibility testing; NA: not available. [#]: MIC testing for isoniazid, levofloxacin, ofloxacin and amikacin was available for 34 patients, and for moxifloxacin and kanamycin for 33 patients; capreomycin and pyrazinamide MICs were not performed as they were not part of the version of the MIC plate. [¶]: DST by conventional phenotypic test per hospital protocol and/or chart review. [+]: ofloxacin was administered at this dose twice a day.

outcome, a decision tree method, classification and regression tree (CART), was applied (RStudio, Inc., Boston, MA, USA). Treatment outcome was the dependent variable while predictors included demographics, the presence of central nervous system (CNS) TB, cavitary disease on chest imaging, treatment with antiretrovirals prior to TB treatment initiation, C_{max} and AUC values for individual drugs and the redefined total number of active drugs in a patient's regimen based on the pharmacokinetic data.

A total of 69 patients with HIV had pharmacokinetic testing at 2 weeks after treatment initiation. Mean ±SD age was 34±6.2 years, 45 (65.2%) were male. Mean±SD CD4 count was 180±202 cells·mL^{-1}, median HIV viral load was 182 686 (interquartile range (IQR) 5200–822 067). Only 19 (27.5%) patients were on antiretrovirals at TB treatment initiation. 36 (52.2%) patients had prior TB treatment, 51 (73.9%) were smokers, 31 (44.9%) used intravenous drugs, 11 (15.9%) had CNS TB and 25 (36.2%) had cavitary disease. Of the total, 36 (52.2%) were classified as having drug-susceptible TB, 10 (14.5%) MDR-TB, 17 (24.6%) pre-XDR-TB and six (8.7%) XDR-TB. MIC testing was performed on 34 patients' *M. tuberculosis* isolates. All patients were inpatients for the duration of the study procedures.

A total of 38 patients were treated with isoniazid, with a calculated median (IQR) dose of 9.7 (8.9–10.0) mg·kg^{-1} (table 1). Fluoroquinolones were used in 54 cases; of those, levofloxacin and moxifloxacin were used at standard doses while the ofloxacin median dose was 400 mg twice per day (median dose 7.6 mg·kg^{-1}) (table 1). C_{max} values were frequently below expected ranges, including trace values for the orally administered drugs. Drug activity was commonly redefined as active for those dosed with isoniazid, and more commonly redefined as inactive for those dosed with fluoroquinolones and injectable agents (table 1).

Based on the C_{max} and MIC informed drug activity, patients were treated with a significantly lower number of active drugs (3.25±1.40) compared to the number of drugs presumed to be active when initially prescribed (4.81±0.94; $p<0.001$). 50 patients had treatment outcomes that could be accurately categorised, with 16 (32.0%) experiencing treatment failure. In decision tree analysis, CNS TB was the most important predictor of treatment failure. However, when CNS TB was removed as a predictor, having <4.5 active drugs, as redefined by C_{max} and MIC testing, was the first classification of significance, correctly identifying 15 (93%) out of the 16 patients with treatment failure.

The treatment approach to drug-resistant TB has targeted shorter durations, better-tolerated regimens and drug susceptibility testing. Our findings from this HIV-infected cohort in Irkutsk with complex *M. tuberculosis* drug resistance patterns suggest that a more comprehensive definition of drug activity, which incorporates circulatory drug exposure relative to quantitative susceptibility testing of the patient's *M. tuberculosis* isolate, may further improve treatment outcomes. Potential alterations in drug and dose selection occurre across multiple drug classes.

Isoniazid was commonly prescribed despite conventional *M. tuberculosis* drug resistance, but given at a median dose of 10 mg·kg^{-1}, double that given for isoniazid-susceptible *M. tuberculosis* [10]. Despite considerable pharmacokinetic variability in estimated C_{max} and AUC for higher-dose isoniazid, many patients achieved a serum concentration that exceeded the MIC. The World Health Organization has recently approved a 9-month treatment regimen that utilises higher-dose isoniazid, hypothesised to result in increased drug concentration at the site of TB disease to overcome low-level resistance [11]. In previous studies from Irkutsk we have noted the *M. tuberculosis inhA* promoter mutation to be rare compared to the *katG* catalase mutation, those mutations conferring low- and high-level isoniazid resistance, respectively [12]. Yet the MIC data from this study suggest a greater variability in quantitative isoniazid resistance, which probably explains why higher-dose isoniazid and improved serum exposure may result in clinical efficacy.

For the fluoroquinolones, human studies have demonstrated a dose-dependent increase in concentrations in *M. tuberculosis*-infected lung lesions, suggesting that increasing serum concentrations may lead to better treatment outcomes [13, 14]. The optimal serum exposure relative to the MIC for predicting treatment efficacy has not been adequately studied, but our findings from Irkutsk would suggest that most patients were significantly under-dosed, even for patients with conventionally fluoroquinolone-susceptible *M. tuberculosis*. Similar patterns to the fluoroquinolones were observed for the injectable agents. However, given that fewer than expected patients were initiated on antiretrovirals at the time of blood collection for pharmacokinetic testing, drug–drug interactions were not investigated.

Nevertheless, our hypothesis-generating decision tree analysis found a break-point of 4.5 active drugs was most predictive of favourable outcome. In practice in Irkutsk and other drug-resistant TB endemic settings, most patients are initiated on treatment with a rapid molecular result for rifampin resistance from sputum. In order to increase the likelihood of prescribing four or more active drugs, our findings suggest an initial drug regimen in Irkutsk should include higher-dose isoniazid, later-generation fluoroquinolones

and an expanded regimen for XDR-TB, followed by serum concentration testing of medications prone to pharmacokinetic variability. Guidance for such an approach exists [15], and we recommend implementation projects to test the recommendations.

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