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1 **Has the time come for systematic therapeutic drug monitoring of first-line and WHO group-A anti-**
2 **tuberculosis drugs?**

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12

13 **Abstract:**

14 Purpose:

15 Tuberculosis (TB) is a major global health issue, with around 10 million people being infected each year
16 and is the leading cause of mortality from infectious disease with 1.5 million death each year. Optimal
17 TB treatment requires drugs combination for an adequate treatment duration due to persistent
18 organisms, hardly accessible infection sites and high risk of resistance selection. This multidrug, long-
19 term therapy raises the risk of patients' loss of adherence, adverse drug reaction and drug-drug
20 interactions potentially leading to treatment failure. The high inter-patient variability of TB drugs
21 exposure is another point eliciting the interest of therapeutic drug monitoring (TDM) to optimize
22 treatment. Studies reported clinically relevant exposure thresholds, which might be proposed as
23 targets to take a step in treatment personalization are discussed. Practical TDM strategies have also
24 been reported to circumvent issues related to delayed drug absorption and the need for multiple
25 samples when evaluating area under the curve of drug concentrations. The arisen of multi-drug

26 resistant TB or extensively-drug resistant TB advocates as well for treatment individualization. Finally,
27 the willingness to shorten the treatment duration while maintaining success is also a driver of ensuring
28 adequate exposure to TB drugs with TDM. The aim of the present review is to underline the role of
29 TDM for drug-susceptible and World Health Organization group-A TB drugs.

30

31 **Keywords:** antituberculous; pharmacokinetics; pharmacodynamics; exposure; rifampicin ; isoniazid ;
32 ethambutol ; pyrazinamide ; fluoroquinolones; linezolid; bedaquiline

33

34 **Introduction:**

35 Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, is a major global health
36 issue, with around 10 million people being infected each year and is the leading cause of mortality
37 from infectious disease with 1.5 million death each year (1). Optimal TB treatment requires the
38 association of anti-TB drugs for an adequate treatment duration due to persistent organisms, hardly
39 accessible infection sites and high risk of resistance selection. Usual treatment relies on isoniazid,
40 rifampicin, pyrazinamide and ethambutol (HRZE) combination, which can be formulated into fixed-
41 dose association. This long-term, multidrug therapy makes the adherence difficult for patients and
42 threatens drug treatment exposure, which might be related to treatment outcome. These drugs also
43 display pharmacokinetic variability leading to hardly predictable plasma drug exposure and finally drug
44 exposure at the site of infection. For example, in a large cohort of tuberculosis patients identified sex,
45 weight adjusted-dosage, drug formulation, liver parameters, HIV-status and albumin as related sources
46 of pharmacokinetic variation for one or more of the HRZE drugs (2). Besides, TB treatment can lead to
47 significant drug-drug interactions both within the TB therapy and towards drugs prescribed to patients
48 outside of this indication. Therapeutic drug monitoring (TDM) can then be a tool to optimize TB
49 treatment offering a strategy to maximize drug efficacy while limiting the onset of concentration-

50 dependent adverse drug reaction (ADR). TB treatment is not limited to these four drugs used in
51 susceptible infection. As drug resistance grows in the spectrum of *Mycobacterium tuberculosis*
52 resulting in multi-drug resistant TB (MDR-TB) or extensively-drug resistant TB (XDR), second-line agents
53 including fluoroquinolones, clofazimine, cycloserine, ethionamid, linezolid, aminoglycosides and p-
54 amino salicylic acid joined the therapeutic armamentarium and are added or replaced drugs in the
55 HRZE treatment. Recently approved drugs, bedaquiline, delamanid and pretomanid also showed
56 promising results. These agents may as well benefited from TDM. Globally, with a rate of treatment
57 success reported to be approximately 85% for sensitive-TB but which can be as low as 57% with MDR-
58 TB, TB treatment can still be improved and TDM is one of the levers allowing take a step in optimizing
59 outcome (3). Shortening the TB treatment is now a commonly accepted objective and ensuring an
60 adequate drug exposure with the use of TDM appears crucial in such strategies.

61 The aim of the present review is to underline the role of therapeutic drug monitoring during TB
62 treatment. This review will be limited to the drugs used for drug-susceptible TB and World Health
63 Organization (WHO) group A drugs for drug-resistant TB (table 1).

64

65 **2. Summary of pharmacokinetics and pharmacodynamics of drugs used to treat TB**

66 **2.1 Rifampicin:**

67 Rifampicin (RFP) is a rifamycin drug used to treat susceptible *Mycobacterium tuberculosis* infections.
68 The drug is usually given once a day (QD) at the dose of 10 mg/kg or 600 mg QD either orally (on an
69 empty stomach) or intravenously but increased dosage up to 35 mg/kg/day reduces the time to
70 sputum conversion (4). The drug presents a large inter-individual variability of its concentrations, a
71 short half-life and is a potent metabolism inducer including its own metabolism (5). Among factors
72 resulting in decrease exposure, sex, fixed-dose combination (FDC) and HIV-status can be cited. On the
73 opposite, increase in weight-adjusted drug dosage and bilirubin level can lead to increase RFP exposure

74 (2). The time to maximal concentration (T_{max}) is usually reached in 2 hours but with some patients and
75 circumstances where delayed absorption and longer T_{max} can be elicited for example by food intake
76 or diabetes mellitus (6). RFP inhibits DNA-dependent RNA polymerase bacterial enzymes and is active
77 against extracellular and intracellular *Mycobacterium tuberculosis*. Peak concentration (C_{max}) and area
78 under the curve of drug concentrations (AUC) correlates with the bactericidal efficacy and resistance
79 onset of rifampicin in models (7,8). Rifampicin trough concentration (C_{min}) is frequently low / below
80 the limit of quantification of method assays and then correlates poorly with the drug exposure (9).

81

82 **2.2 Isoniazid:**

83 Isonicotinyl hydrazine or isoniazid (INH) is a potent bactericidal drug against *Mycobacterium*
84 *tuberculosis* acting as an inhibitor of mycolic acid synthesis, which are major constituents of the
85 mycobacteria wall. The drug is administered at the dose of 4-5 mg/kg QD but some *in-vitro* data
86 suggest that doses up to 10-15 mg/kg may be needed for resistant strains (10). INH is rapidly resorbed
87 and C_{max} occurs 1-2h after drug intake. INH is a substrate of the N-acetyltransferase 2 (NAT2) and
88 cytochrome P450 2E1 (CYP2E1) metabolic enzymes. These enzymes are encoded by polymorphic
89 genes, which can lead to different phenotypes. NAT2 produces acetylhydrazine which can then be
90 transformed by CYP2E1 into hepatotoxins (11). Slow metabolizers for NAT2 are then at higher risk of
91 hepatotoxicity (12). On the other hand, rapid acetylators might be at higher risk of treatment failure
92 as suggested by a randomized controlled trial where early failure where reduced in this sub-population
93 of patients with the use of a pharmacogenetic-guided approach (13). Sex and FDC contribute to
94 exposure decrease while age, weight-adjusted drug dosage increase, and increase in gamma-glutamyl
95 transferase level increase drug exposure (2). The efficacy and resistance onset prevention has been
96 shown to be related to the AUC/Minimum Inhibitory Concentration (MIC) and the C_{max} /MIC ratios in
97 pre-clinical models (14).

98

99 **2.3 Pyrazinamide:**

100 Pyrazinamide (PZA) is a prodrug converting *in vivo* into its active component pyrazinoic acid. It inhibits
101 semi-dormant, persisting microorganisms and has the ability to remain active in an acidic environment
102 like inside macrophages, which makes its mechanism of action distinctive from other TB drugs. PZA is
103 administered at the dose of 25 mg/kg/d QD. The dosage can be increased up to 35 mg/kg/d in some
104 situations (notably in children) as the usual dosage may result in significant underexposure. Median
105 C_{max} obtained is usually around 50 µg/mL but can be lower in HIV patients particularly in case of
106 profound immunodeficiency (15). On the opposite, weight-adjusted dosage increase and bilirubin
107 elevation are reported factors associated with increase in drug exposure (2). A
108 pharmacokinetic/pharmacodynamics (PK/PD) approach using a hollow-fiber infection model revealed
109 the EC_{90} for PZA to be reached for a AUC_{0-24}/MIC ratio above 209 (16). The safety profile of PZA is
110 dominated by the risk of hepatotoxicity and hyperuricemia.

111

112 **2.4 Ethambutol:**

113 Ethambutol (ETH) is considered as the fourth antituberculosis drug used in the prevention of RFP
114 resistance in INH resistant strains. It is a bacteriostatic drug inhibiting the synthesis of the
115 mycobacterial cell wall. The drug is usually administered at the dose of 15-20 mg/kg QD and up to 25
116 mg/kg. ETH presents a large PK variability but with few delayed absorption profiles (17). Sex, HIV-
117 status, increase in albumin level and ETH retreatment are associated with decrease in drug exposure.
118 Higher weight-adjusted doses and older patients had increased exposure (2). In models, the drug
119 efficacy is best predicted by both C_{max}/MIC and AUC/MIC ratios (18). Optical neuropathy (i.e the most
120 concerning adverse effect with the drug) seems to occur with a higher frequency in patients treated
121 with higher dosage, suggesting an impact of exposure on toxicity (19).

122

123 **2.5 Fluoroquinolones:**

124 Levofloxacin and moxifloxacin are the fluoroquinolones recommended by WHO in case of drug-resistant
125 TB (table 1). Moxifloxacin is also an attractive alternative to INH, ETH or as an add-on to HRZE therapy
126 to shorten drug-susceptible TB treatment to a 4-month regimen but there are concerns that such a
127 strategy might lead to increase relapses. These drugs are orally well resorbed and their T_{max} are usually
128 obtained 1 hour post-dose. As for other TB drugs, fluoroquinolones exhibit a large inter-individual
129 variability of plasma exposure. For example, the moxifloxacin plasma exposure for patients treated
130 with 400 mg/d can range up to nine-fold (20). Hollow fiber infection models show that a free AUC_{0-24}/MIC
131 ratio of 132.9 allows achieving 1.0 Log CFU kill relative to baseline for moxifloxacin in the
132 acidified pH environment. Data from this model also suggest that increasing moxifloxacin dosage to
133 800 mg/d might influence the resistance emergence (16). For levofloxacin, a (total drug) AUC_{0-24}/MIC
134 ratio of 146 might maximize bactericidal effect while an AUC_{0-24}/MIC ratio of 360 should be targeted
135 to avoid resistance selection (21,22). A dosage regimen of 750-1000 mg/d and 1500-1750 mg/d might
136 be needed to reach PK/PD objectives with levofloxacin when MIC are 0.5 mg/L or 1 mg/mL, respectively
137 (23). Safety concerns with fluoroquinolones include: phototoxicity, tendinopathy, neurotoxicity and,
138 mainly for moxifloxacin, QTc prolongation which can lead to arrhythmia. Some of these adverse drug
139 reactions can be related to drug accumulation in patients (24).

140

141 **2.6 Other WHO group A drugs**

142 Limited data exists for other second-line agents. Among these drugs, linezolid and bedaquiline belong
143 to the WHO group A classification, that is the most effective treatments for TB (table 1). Bedaquiline is
144 an inhibitor of the subunit c and the subunit ϵ of the mycobacterial ATP synthase of *Mycobacterium*
145 *tuberculosis*. The drug has a T_{max} at 5h and is a CYP3A4 substrate with a long terminal half-life (around
146 170h). It requires then a 2-week loading dose to reach therapeutic steady-state concentrations. Its
147 main metabolite M2 has a limited antimycobacterial activity (25). The drug is associated with Qtc

148 prolongation. Svensson and Karlsson have modeled PK and PD data obtained from phase IIb revealing
149 a probable relationship between drug exposure and culture conversion. In this study, the estimated
150 EC_{50} was 1.42 mg/L but should be considered informative only for MDR-TB patients (i.e the population
151 of the phase IIb study) (26).

152 Linezolid is an oxazolidinone drug and a recent option for MDR and XDR-TB. The AUC_{0-24}/MIC is the
153 best PK/PD parameter related to LNZ efficacy. During log-phase growth, a free linezolid AUC_{0-24}/MIC
154 of 35.6 has been reported as a target for resistance suppression in a hollow fiber infection model. To
155 reach a 1.0 Log CFU/mL kill relative to baseline in the acidic phase, a free AUC_{0-24}/MIC of 88.8 is
156 proposed (22). These values, given the protein binding of the drug, are closed to another PK/PD study
157 showing that EC_{80} is obtained with an AUC_{0-24}/MIC of 119 and a 1.0 Log CFU/mL kill with an AUC_{0-}
158 $_{24}/MIC$ of 73.6 (27).

159

160 **3. Concentration-controlled studies in patients**

161 Low exposure to anti-TB drugs is a frequent situation. Globally, using 2-hour post-dose as an indicator
162 of exposure and a threshold of 8, 3, 2 and 35 $\mu\text{g}/\text{mL}$ for RFP, INH, ETH and PZA, respectively, a meta-
163 analysis of 41 studies showed that low exposure to be 67, 43, 27 and 12% for these drugs, respectively
164 (28). In a large phase II, triple-blind, randomized, placebo-controlled, dose-ranging clinical trial
165 comparing RFP delivered orally at 10, 15, or 20 mg/kg combined with weight-based INH, PZA and ETH,
166 Peloquin and colleagues reported that 67% of patients in the 10 mg/kg group and 19% of patients in
167 the 20 mg/kg did not reach the RIF C_{max} threshold of 8 $\mu\text{g}/\text{mL}$. Fifty percent of the patients had INH
168 and ETH below 2.3 $\mu\text{g}/\text{mL}$ and 1.7 $\mu\text{g}/\text{mL}$ respectively (29). This low drug exposure can also be common
169 in specific population such as HIV patients where, in patients receiving 600 mg daily, 77% of patients
170 of small cohort presented a RFP peak concentration below 8 $\mu\text{g}/\text{mL}$ (30). The large pharmacokinetic
171 variability reported in the previous part explained at least partly these frequent low drug exposures.

172 Besides, a number of studies explored the impact of TB drug exposure on treatment efficacy or drug-
173 related adverse events.

174 In a randomized controlled trial comparing RFP 10 mg/kg, 15 mg/kg and 20 mg/kg, Velazquez and
175 colleagues showed that in the *per protocol* population, but not in the intention-to-treat population,
176 that RIF AUC_{0-6h} correlated with the Log colony forming unit in the sputum of patients (31). Considering
177 INH, a retrospective study conducted in patients treated with drug-susceptible TB during continuous
178 treatment phase with once weekly INH/RFP or twice-weekly INH/rifapentine evaluated the impact of
179 INH exposure on treatment efficacy. In the INH/rifapentine group only, INH exposure was lower in
180 patients with treatment failure (AUC_{0-12h} = 36.0 µg.h/mL vs 55.9 µg.h/mL in the cure group). Exposure
181 was not different in the INH/RFP arm (32).

182 In a South-African study conducted in patients hospitalized during the first 2 months and treated for
183 TB with RFP (600 mg or 450 mg if bodyweight was less than 50 kg), INH (300 mg/d), PZA (20–35
184 mg/kg/d) and ETH (15 mg/kg/d), Pasipanodya and colleagues explored the predicting factors for
185 sputum conversion at month-2 as well as long-term outcomes. Using a CART analysis, they identified
186 the PZA peak > 58.3 µg/mL followed by a RFP peak > 6.6 µg/mL and a INH peak > 8.8 µg/mL to be the
187 main factors for sputum conversion (33). Regarding long-term outcomes, 25% of patients had poor
188 outcome (mainly relapses or failures) and AUC₀₋₂₄ of PZA, RFP, and INH were the most predictive
189 factors of patients' clinical course. Thresholds associated were 363 µg.h/mL for PZA, 13 µg.h/mL for
190 RFP, and 52 µg.h/mL for INH. Having all the 3 drugs exposure above these thresholds was associated
191 with a 88% chance of treatment success while success was just 48% in patients with only 1 drug above
192 the threshold. Recently, a large (n=268) prospective, observational study conducted in HIV-infected
193 patients in Uganda showed that patients with at least one TB-drug with a low C_{max} (<3 µg/mL for INH,
194 <8 µg/mL for RFP, <20 µg/mL for PZA, <2 µg/mL for ETH) presented less sputum conversion during
195 treatment (34). In this study, patients had an adjusted 60% and 74% reduction chance of culture
196 conversion with one drug and two drugs below the recommended C_{max}, respectively, when compared

197 with patients having no TB-drugs below the recommended C_{max} threshold. Despite a high proportion
198 of patients with low exposure, the treatment failure rate in this study was low (4.4%).

199 Another large (n=225) study conducted in Botswana has assessed the relationship between TB-drug
200 exposure and clinical outcome in HIV (69%) and non-HIV patients. Patients received 300 mg INH, 450
201 mg RFP, 1000 mg ETH and 1500 mg PZA if their weight was below 50 kg and 400 mg INH, 600 mg RFP,
202 1200 mg ETH and 2000 mg PZA if their weight exceeded 50 kg. In this study, poor treatment outcomes
203 occurred three-times higher in patients with PZA C_{max} below 35 $\mu\text{g}/\text{mL}$ (50.0 versus 15.7%, $p < 0.01$)
204 regardless of HIV infection status (15).

205 In a small (n=41) randomized study comparing linezolid 600 mg versus 300 mg in chronic resistant
206 tuberculosis, Lee and colleagues did not find any relationship between peak or trough concentration
207 and time to culture conversion. However, the group taking 600 mg had an 2.7 times increased risk of
208 adverse events when compared to the 300 mg group (35). A post-hoc analysis of the data obtained
209 from this study identified a threshold of C_{min} of 2 $\mu\text{g}/\text{mL}$ for ADR. Every patients presenting a C_{min}
210 above 2 $\mu\text{g}/\text{mL}$ had ADRs, a rate falling to 58% of patients when C_{min} was below 2 $\mu\text{g}/\text{mL}$ (35).

211 The case for TB meningitis may require higher drug exposure. In a randomized intensification
212 treatment study, Te Brake *et al.* explored the relationship between anti-TB drugs exposure and survival
213 in this indication. Patients received standard RFP (10 mg/kg orally) or intensified RFP (13 mg/kg
214 intravenously) treatment combined with either standard moxifloxacin (400 mg/d), high dose
215 moxifloxacin (800 mg/d) or ETH (750 mg/d). All patients also received INH 300 mg, PZA 1500 mg and
216 corticosteroids. There was a relationship between RFP exposure and survival and concentration-
217 response curves allows estimating a minimum target AUC_{0-6h} of 70 $\mu\text{g}\cdot\text{h}/\text{mL}$, AUC_{0-12h} of 1156 $\mu\text{g}\cdot\text{h}/\text{mL}$
218 and a C_{max} of 22 $\mu\text{g}/\text{mL}$ (36).

219 Finally, the field is still lacking of a randomized clinical trial aiming at comparing the benefit of a TDM-
220 guided over a standard approach.

221 Proposed exposure threshold based on clinical data are summarized in table 2.

222

223 **4. TDM implementation in clinical practice**

224 As already stated, when measuring plasma trough concentrations, observed values are frequently
225 below the limit of quantification of assay methods. This implies that C_{\min} is not an appropriate
226 surrogate for AUC and then, for drug exposure. C_{\max} can be proposed as an alternative to C_{\min} but has
227 also some disadvantages. Hence, some patients display delayed drug absorption resulting in delayed
228 T_{\max} . That is why a two sampling-time scheme (2h and 6h post-dose) has been proposed by authors to
229 maximize the probability for accessing C_{\max} in both absorption profiles (9). An intermediate sampling
230 time at 4h may also provide information as it is frequently proposed as a time-point in limited sampling
231 strategies (37,38). The best pharmacokinetic parameter for evaluating drug exposure remains AUC but
232 requires several samples along the drug interval, particularly with drugs like TB drugs with various
233 absorption profiles, and is hardly compatible with clinical practice. To circumvent this limitation,
234 limited sampling strategies have been developed for most of TB-drugs (39–43). They allow accessing
235 AUC with a limited number of samples, limiting then the burden of venipunctures for patients and
236 making it more suitable for outpatient clinic. The development of a robust limited sampling approach
237 allowing estimating AUC of antituberculosis drugs administered in combination, irrespective of the
238 route of administration and with or without food is a still a milestone to reach in the field despite
239 preliminary interesting results (44). Other recent strategies such as dried blood spots and saliva
240 measurements might also help implementing TDM of TB drugs and makes it easier evaluating drug
241 exposure (45,46).

242

243 **Conclusion:**

244 TDM is a tool of added value in the management of patients treated with anti-TB drugs. Because of the
245 high variability of drug exposure and the existence of threshold associated with treatment outcome,
246 TDM may help improving the TB treatment. While it is usually restricted to specific situation such as
247 patients having a slow treatment response with sputum smears culture positive after 2 months,
248 patients with poor drug resorption and in drug-drug interaction context, the overview of the literature
249 shows that there is a potential place for systematic TDM in that era.

250

251

252 **References:**

- 253 1. Furin J, Cox H, Pai M. Tuberculosis. *Lancet*. 2019 Apr 20;393(10181):1642–56.
- 254 2. McIlleron H, Wash P, Burger A, Norman J, Folb PI, Smith P. Determinants of rifampin, isoniazid,
255 pyrazinamide, and ethambutol pharmacokinetics in a cohort of tuberculosis patients.
256 *Antimicrob Agents Chemother*. 2006 Apr;50(4):1170–7.
- 257 3. World Health Organization. Global Tuberculosis Report [Internet]. 2017. Available from:
258 https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf
- 259 4. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, et al. High-dose rifampicin,
260 moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised
261 controlled trial. *Lancet Infect Dis*. 2017 Jan;17(1):39–49.
- 262 5. Abulfathi AA, Decloedt EH, Svensson EM, Diacon AH, Donald P, Reuter H. Clinical
263 Pharmacokinetics and Pharmacodynamics of Rifampicin in Human Tuberculosis. *Clin*
264 *Pharmacokinet*. 2019 Sep;58(9):1103–29.
- 265 6. Kumar AKH, Chandrasekaran V, Kannan T, Murali AL, Lavanya J, Sudha V, et al. Anti-tuberculosis
266 drug concentrations in tuberculosis patients with and without diabetes mellitus. *Eur J Clin*
267 *Pharmacol*. 2017 Jan;73(1):65–70.
- 268 7. Jayaram R, Gaonkar S, Kaur P, Suresh BL, Mahesh BN, Jayashree R, et al. Pharmacokinetics-
269 pharmacodynamics of rifampin in an aerosol infection model of tuberculosis. *Antimicrob*
270 *Agents Chemother*. 2003 Jul;47(7):2118–24.
- 271 8. Gumbo T, Louie A, Deziel MR, Liu W, Parsons LM, Salfinger M, et al. Concentration-dependent
272 *Mycobacterium tuberculosis* killing and prevention of resistance by rifampin. *Antimicrob Agents*
273 *Chemother*. 2007 Nov;51(11):3781–8.
- 274 9. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an
275 update. *Drugs*. 2014 Jun;74(8):839–54.
- 276 10. Lange C, Alghamdi WA, Al-Shaer MH, Brighenti S, Diacon AH, DiNardo AR, et al. Perspectives for
277 personalized therapy for patients with multidrug-resistant tuberculosis. *J Intern Med*. 2018 May
278 28;
- 279 11. Erwin ER, Addison AP, John SF, Olaleye OA, Rosell RC. Pharmacokinetics of isoniazid: The good,
280 the bad, and the alternatives. *Tuberculosis (Edinb)*. 2019 May;116S:S66–70.
- 281 12. Metushi I, Uetrecht J, Phillips E. Mechanism of isoniazid-induced hepatotoxicity: then and now.
282 *Br J Clin Pharmacol*. 2016 Jun;81(6):1030–6.
- 283 13. Azuma J, Ohno M, Kubota R, Yokota S, Nagai T, Tsuyuguchi K, et al. NAT2 genotype guided
284 regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-
285 drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-
286 based therapy. *Eur J Clin Pharmacol*. 2013 May;69(5):1091–101.
- 287 14. Gumbo T, Louie A, Liu W, Brown D, Ambrose PG, Bhavnani SM, et al. Isoniazid bactericidal
288 activity and resistance emergence: integrating pharmacodynamics and pharmacogenomics to

- 289 predict efficacy in different ethnic populations. *Antimicrob Agents Chemother.* 2007
290 Jul;51(7):2329–36.
- 291 15. Chideya S, Winston CA, Peloquin CA, Bradford WZ, Hopewell PC, Wells CD, et al. Isoniazid,
292 rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a
293 predominantly HIV-infected cohort of adults with tuberculosis from Botswana. *Clin Infect Dis.*
294 2009 Jun 15;48(12):1685–94.
- 295 16. Gumbo T, Dona CSWS, Meek C, Leff R. Pharmacokinetics-pharmacodynamics of pyrazinamide in
296 a novel in vitro model of tuberculosis for sterilizing effect: a paradigm for faster assessment of
297 new antituberculosis drugs. *Antimicrob Agents Chemother.* 2009 Aug;53(8):3197–204.
- 298 17. Zhu M, Burman WJ, Starke JR, Stambaugh JJ, Steiner P, Bulpitt AE, et al. Pharmacokinetics of
299 ethambutol in children and adults with tuberculosis. *Int J Tuberc Lung Dis.* 2004
300 Nov;8(11):1360–7.
- 301 18. Alffenaar J-WC, Gumbo T, Dooley KE, Peloquin CA, McIlleron H, Zagorski A, et al. Integrating
302 Pharmacokinetics and Pharmacodynamics in Operational Research to End Tuberculosis. *Clin*
303 *Infect Dis.* 2020 Apr 10;70(8):1774–80.
- 304 19. Hasenbosch RE, Alffenaar JWC, Koopmans SA, Kosterink JGW, van der Werf TS, van Altena R.
305 Ethambutol-induced optical neuropathy: risk of overdosing in obese subjects. *Int J Tuberc Lung*
306 *Dis.* 2008 Aug;12(8):967–71.
- 307 20. Pranger AD, van Altena R, Aarnoutse RE, van Soolingen D, Uges DRA, Kosterink JGW, et al.
308 Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience. *Eur Respir J.*
309 2011 Oct;38(4):888–94.
- 310 21. Deshpande D, Pasipanodya JG, Mpagama SG, Bendet P, Srivastava S, Koeuth T, et al.
311 Levofloxacin Pharmacokinetics/Pharmacodynamics, Dosing, Susceptibility Breakpoints, and
312 Artificial Intelligence in the Treatment of Multidrug-resistant Tuberculosis. *Clin Infect Dis.* 2018
313 Nov 28;67(suppl_3):S293–302.
- 314 22. Heinrichs MT, Drusano GL, Brown DL, Maynard MS, Sy SKB, Rand KH, et al. Dose optimization of
315 moxifloxacin and linezolid against tuberculosis using mathematical modeling and simulation. *Int*
316 *J Antimicrob Agents.* 2019 Mar;53(3):275–83.
- 317 23. Al-Shaer MH, Alghamdi WA, Alsultan A, An G, Ahmed S, Alkabab Y, et al. Fluoroquinolones in
318 Drug-Resistant Tuberculosis: Culture Conversion and Pharmacokinetic/Pharmacodynamic
319 Target Attainment To Guide Dose Selection. *Antimicrob Agents Chemother.* 2019
320 Jul;63(7):e00279-19.
- 321 24. Stahlmann R, Lode HM. Risks associated with the therapeutic use of fluoroquinolones. *Expert*
322 *Opin Drug Saf.* 2013 Jul;12(4):497–505.
- 323 25. Esposito S, Bianchini S, Blasi F. Bedaquiline and delamanid in tuberculosis. *Expert Opin*
324 *Pharmacother.* 2015;16(15):2319–30.
- 325 26. Svensson EM, Karlsson MO. Modelling of mycobacterial load reveals bedaquiline’s exposure-
326 response relationship in patients with drug-resistant TB. *J Antimicrob Chemother.* 2017 Dec
327 1;72(12):3398–405.

- 328 27. Srivastava S, Magombedze G, Koeuth T, Sherman C, Pasipanodya JG, Raj P, et al. Linezolid Dose
329 That Maximizes Sterilizing Effect While Minimizing Toxicity and Resistance Emergence for
330 Tuberculosis. *Antimicrob Agents Chemother*. 2017 Aug;61(8):e00751-17.
- 331 28. Mota L, Al-Efraij K, Campbell JR, Cook VJ, Marra F, Johnston J. Therapeutic drug monitoring in
332 anti-tuberculosis treatment: a systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2016
333 Jun;20(6):819–26.
- 334 29. Peloquin CA, Velásquez GE, Lecca L, Calderón RI, Coit J, Milstein M, et al. Pharmacokinetic
335 Evidence from the HIRIF Trial To Support Increased Doses of Rifampin for Tuberculosis.
336 *Antimicrob Agents Chemother*. 2017 Aug;61(8):e00038-17.
- 337 30. Perlman DC, Segal Y, Rosenkranz S, Rainey PM, Remmel RP, Salomon N, et al. The clinical
338 pharmacokinetics of rifampin and ethambutol in HIV-infected persons with tuberculosis. *Clin
339 Infect Dis*. 2005 Dec 1;41(11):1638–47.
- 340 31. Velásquez GE, Brooks MB, Coit JM, Pertinez H, Vargas Vásquez D, Sánchez Garavito E, et al.
341 Efficacy and Safety of High-Dose Rifampin in Pulmonary Tuberculosis. A Randomized Controlled
342 Trial. *Am J Respir Crit Care Med*. 2018 Sep 1;198(5):657–66.
- 343 32. Weiner M, Burman W, Vernon A, Benator D, Peloquin CA, Khan A, et al. Low isoniazid
344 concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and
345 rifapentine. *Am J Respir Crit Care Med*. 2003 May 15;167(10):1341–7.
- 346 33. Pasipanodya JG, McIlleron H, Burger A, Wash PA, Smith P, Gumbo T. Serum drug concentrations
347 predictive of pulmonary tuberculosis outcomes. *J Infect Dis*. 2013 Nov 1;208(9):1464–73.
- 348 34. Sekaggya-Wiltshire C, von Braun A, Lamorde M, Ledergerber B, Buzibye A, Henning L, et al.
349 Delayed Sputum Culture Conversion in Tuberculosis-Human Immunodeficiency Virus-
350 Coinfected Patients With Low Isoniazid and Rifampicin Concentrations. *Clin Infect Dis*. 2018 Aug
351 16;67(5):708–16.
- 352 35. Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for treatment of chronic
353 extensively drug-resistant tuberculosis. *N Engl J Med*. 2012 Oct 18;367(16):1508–18.
- 354 36. Te Brake L, Dian S, Ganiem AR, Ruesen C, Burger D, Donders R, et al.
355 Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin
356 and moxifloxacin for tuberculous meningitis. *Int J Antimicrob Agents*. 2015 May;45(5):496–503.
- 357 37. van Beek SW, Ter Heine R, Alffenaar J-WC, Magis-Escurra C, Aarnoutse RE, Svensson EM, et al.
358 A Model-Informed Method for the Purpose of Precision Dosing of Isoniazid in Pulmonary
359 Tuberculosis. *Clin Pharmacokinet*. 2021 Jul;60(7):943–53.
- 360 38. van den Elsen SHJ, Sturkenboom MGG, Akkerman OW, Manika K, Kioumis IP, van der Werf TS,
361 et al. Limited Sampling Strategies Using Linear Regression and the Bayesian Approach for
362 Therapeutic Drug Monitoring of Moxifloxacin in Tuberculosis Patients. *Antimicrob Agents
363 Chemother*. 2019 Jul;63(7):e00384-19.
- 364 39. Medellín-Garibay SE, Correa-López T, Romero-Méndez C, Milán-Segovia RC, Romano-Moreno S.
365 Limited sampling strategies to predict the area under the concentration-time curve for
366 rifampicin. *Ther Drug Monit*. 2014 Dec;36(6):746–51.

- 367 40. Pranger AD, Kosterink JGW, van Altena R, Aarnoutse RE, van der Werf TS, Uges DRA, et al.
368 Limited-sampling strategies for therapeutic drug monitoring of moxifloxacin in patients with
369 tuberculosis. *Ther Drug Monit.* 2011 Jun;33(3):350–4.
- 370 41. Alffenaar J-WC, Kosterink JGW, van Altena R, van der Werf TS, Uges DRA, Proost JH. Limited
371 sampling strategies for therapeutic drug monitoring of linezolid in patients with multidrug-
372 resistant tuberculosis. *Ther Drug Monit.* 2010 Feb;32(1):97–101.
- 373 42. Magis-Escurra C, Later-Nijland HMJ, Alffenaar JWC, Broeders J, Burger DM, van Crevel R, et al.
374 Population pharmacokinetics and limited sampling strategy for first-line tuberculosis drugs and
375 moxifloxacin. *Int J Antimicrob Agents.* 2014 Sep;44(3):229–34.
- 376 43. Alsultan A, An G, Peloquin CA. Limited sampling strategy and target attainment analysis for
377 levofloxacin in patients with tuberculosis. *Antimicrob Agents Chemother.* 2015 Jul;59(7):3800–
378 7.
- 379 44. Saktiawati AMI, Harkema M, Setyawan A, Subronto YW, Sumardi null, Stienstra Y, et al.
380 Optimal Sampling Strategies for Therapeutic Drug Monitoring of First-Line Tuberculosis Drugs in
381 Patients with Tuberculosis. *Clin Pharmacokinet.* 2019 Nov;58(11):1445–54.
- 382 45. Vu DH, Alffenaar JWC, Edelbroek PM, Brouwers JRBJ, Uges DRA. Dried blood spots: a new tool
383 for tuberculosis treatment optimization. *Curr Pharm Des.* 2011;17(27):2931–9.
- 384 46. van den Elsen SHJ, Oostenbrink LM, Heysell SK, Hira D, Touw DJ, Akkerman OW, et al.
385 Systematic Review of Salivary Versus Blood Concentrations of Antituberculosis Drugs and Their
386 Potential for Salivary Therapeutic Drug Monitoring. *Ther Drug Monit.* 2018 Feb;40(1):17–37.
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390 **Table 1. Drug-susceptible and group-A drugs according to the WHO classification**

Groups	Drugs
Drug-susceptible	Rifampicin
	Isoniazid
	Ethambutol
	Pyrazinamide
WHO group-A drugs	Levofloxacin
	Moxifloxacin
	Bedaquiline
	Linezolid

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393 **Table 2. Exposure threshold with clinically demonstrated relevant impact to guide TB treatment**
 394 **using TDM.**

TB Drugs	Exposure index threshold		
	<i>C_{min}</i> ($\mu\text{g/mL}$)	<i>C_{max}</i> ($\mu\text{g/mL}$)	<i>AUC</i> ($\mu\text{g.h/mL}$)
Rifampicin		8 (22) ¹	13
Isoniazid		3	52
Pyrazinamide		35	363
Linezolid	< 2 ²		

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396 ¹ Result with brackets is for TB meningitis; ² Threshold to prevent adverse drug reaction