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1 2	Has the time come for systematic therapeutic drug monitoring of first-line and WHO group-A anti- 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 organisms, hardly accessible infection sites and high risk of resistance selection. This multidrug, long-18 term therapy raises the risk of patients' loss of adherence, adverse drug reaction and drug-drug 19 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 resistant TB or extensively-drug resistant TB advocates as well for treatment individualization. Finally,
 the willingness to shorten the treatment duration while maintaining success is also a driver of ensuring
 adequate exposure to TB drugs with TDM. The aim of the present review is to underline the role of
 TDM for drug-susceptible and World Health Organization group-A TB drugs.

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Keywords: antituberculous; pharmacokinetics; pharmacodynamics; exposure; rifampicin ; isoniazid ;
 ethambutol ; pyrazynamide ; 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 from infectious disease with 1.5 million death each year (1). Optimal TB treatment requires the 37 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 fixeddose association. This long-term, multidrug therapy makes the adherence difficult for patients and 41 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 outside of this indication. Therapeutic drug monitoring (TDM) can then be a tool to optimize TB 48 49 treatment offering a strategy to maximize drug efficacy while limiting the onset of concentration50 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.

The aim of the present review is to underline the role of therapeutic drug monitoring during TB treatment. This review will be limited to the drugs used for drug-susceptible TB and World Health 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**:

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

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

81

82 **2.2 Isoniazid**:

Isonicotinyl hydrazine or isoniazid (INH) is a potent bactericidal drug against Mycobacterium 83 tuberculosis acting as an inhibitor of mycolic acid synthesis, which are major constituents of the 84 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 cytochrome P450 2E1 (CYP2E1) metabolic enzymes. These enzymes are encoded by polymorphic 88 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).

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 situations (notably in children) as the usual dosage may result in significant underexposure. Median 104 105 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 AUC₀₋₂₄/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 efficacy is best predicted by both C_{max}/MIC and AUC/MIC ratios (18). Optical neuropathy (i.e the most 119 120 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).

123 2.5 Fluoroquinolones:

124 Levofloxacin and moxifloxacin are the fluoroquinolnes 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 AUCO-131 24/MIC 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) AUC₀₋₂₄/MIC 134 ratio of 146 might maximize bactericidal effect while an AUC₀₋₂₄/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**

Limited data exists for other second-line agents. Among these drugs, linezolid and bedaquiline belong to the WHO group A classification, that is the most effective treatments for TB (table 1). Bedaquiline is an inhibitor of the subunit c and the subunit ε of the mycobacterial ATP synthase of *Mycobacterium tuberculosis*. The drug has a T_{max} at 5h and is a CYP3A4 substrate with a long terminal half-life (around 170h). It requires then a 2-week loading dose to reach therapeutic steady-state concentrations. Its main metabolite M2 has a limited antimycobacterial activity (25). The drug is associated with Qtc prolongation. Svensson and Karlsson have modeled PK and PD data obtained from phase IIb revealing
a probable relationship between drug exposure and culture conversion. In this study, the estimated
EC₅₀ was 1.42 mg/L but should be considered informative only for MDR-TB patients (i.e the population
of the phase IIb study) (26).

Linezolid is an oxazolidinone drug and a recent option for MDR and XDR-TB. The AUC₀₋₂₄/MIC is the best PK/PD parameter related to LNZ efficacy. During log-phase growth, a free linezolid AUC₀₋₂₄/MIC of 35.6 has been reported as a target for resistance suppression in a hollow fiber infection model. To reach a 1.0 Log CFU/mL kill relative to baseline in the acidic phase, a free AUC₀₋₂₄/MIC of 88.8 is proposed (22). These values, given the protein binding of the drug, are closed to another PK/PD study showing that EC₈₀ is obtained with an AUC₀₋₂₄/MIC of 119 and a 1.0 Log CFU/mL kill with an AUC₀₋₂₄/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 µg/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 the 20 mg/kg did not reach the RIF C_{max} threshold of 8 µg/mL. Fifty percent of the patients had INH 167 168 and ETH below 2.3 μg/mL and 1.7 μg/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 µg/mL (30). The large pharmacokinetic 171 variability reported in the previous part explained at least partly these frequent low drug exposures. Besides, a number of studies explored the impact of TB drug exposure on treatment efficacy or drug-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 μ g/mL followed by a RFP peak > 6.6 μ g/mL and a INH peak > 8.8 μ g/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 where 363 µg.h/mL for PZA, 13 µg.h/mL for 190 RFP, and 52 μ g.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 patients in Uganda showed that patients with at least one TB-drug with a low C_{max} (<3 μ g/mL for INH, 193 194 <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 with patients having no TB-drugs below the recommended C_{max} threshold. Despite a high proportion
 of patients with low exposure, the treatment failure rate in this study was low (4.4%).

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

In a small (n=41) randomized study comparing linezolid 600 mg versus 300 mg in chronic resistant tuberculosis, Lee and colleagues did not find any relationship between peak or trough concentration and time to culture conversion. However, the group taking 600 mg had an 2.7 times increased risk of adverse events when compared to the 300 mg group (35). A post-hoc analysis of the data obtained from this study identified a threshold of C_{min} of 2 µg/mL for ADR. Every patients presenting a Cmin above 2 µg/mL had ADRs, a rate falling to 58% of patients when C_{min} was below 2 µg/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 µg.h/mL, AUC_{0-12h} of 1156 µg.h/mL 218 and a C_{max} of 22 μ g/mL (36).

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

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

222

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.

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Table 1. Drug-susceptible and group-A drugs according to the WHO classification

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

393 Table 2. Exposure threshold with clinically demonstrated relevant impact to guide TB treatment

394 using TDM.

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TB Drugs	Exposure index threshold		
	Cmin (μg/mL)	Cmax (µg/mL)	AUC (μg.h/mL)
Rifampicin		8 (22) ¹	13
Isoniazid		3	52
Pyrazinamide		35	363
Linezolid	< 2 ²		

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