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**Pharmacokinetics and pharmacogenetics of anti-tubercular drugs: a tool for treatment optimization?**

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1 **Abbreviations:** RIF, rifampicin, RFB, rifabutin; RPT, rifapentine; INH, isoniazid; ETB,  
2 ethambutol; PZA, pyrazinamide; AUC Area Under the Curve; PK, pharmacokinetics; PD,  
3 pharmacodynamics; C<sub>max</sub> maximal concentration, TDM, Therapeutic Drug Monitoring.

4

## 5 **Article highlights**

- 6 • Inter- and intraindividual variability in the pharmacokinetics of antitubercular agents might  
7 be involved in explaining high variability of response, the likelihood of drugs'  
8 underexposure, the high prevalence of drug-related toxicity and the selection of multi-  
9 resistant strains.
- 10 • Actual rifampicin dose is suboptimal and trials investigating increased dose are ongoing.  
11 Potential effect of pyrazinamide in shortening treatment duration due to its great sterilizing  
12 activity is encouraging in designing new regimens after the failure of trials with  
13 fluoroquinolones.
- 14 • Pharmacogenetic studies observed an association between *SLCO1B1* genetic polymorphism  
15 (rs4149032) and reduced rifampicin concentrations. A *NAT2*-guided trial reported less  
16 isoniazid related liver injury and treatment failures.
- 17 • Drugs penetration in lesions and intracellular may contribute to treatment outcome for the  
18 relation with incidence of relapse or the development of phenotypic drug resistance.
- 19 • New regimens with new and optimized drugs are dramatically needed focusing on safety,  
20 efficacy and PK/PD characteristics of drugs; research on pharmacokinetics in special  
21 populations are warranted to better define individualized treatment approach.

22

23

## 24 **1. Introduction**

25 Tuberculosis (TB) with 9.6 million new cases is a worldwide leading infection and is responsible  
26 for approximately 1.5 million deaths in 2014[1].

1 The goal of reversing TB epidemic has been reached by 2015; currently, WHO has built up a  
2 strategy to end the global epidemic by 2035 with targets to reduce TB deaths by 95%, cut new cases  
3 by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic costs  
4 due to TB[2].

5 Combining several antitubercular drugs (ATDs) is a milestone in TB treatment[3].

6 This approach is due to the hypothesis of existing bacterial subpopulations with different drug  
7 susceptibility: a first subpopulation of extracellular and rapidly dividing mycobacteria early killed  
8 by therapy, a second subpopulation with an intermediate grade of replication residing in  
9 fagolysosomes and, possibly, a third subpopulation consisted of dormant and persister mycobacteria  
10 in monocyte-macrophagic cells and in caseum lesions[4]. Conversely, a second hypothesis  
11 considers this latter population having the same drug susceptibility as the others and being the cause  
12 of persistent disease, due to the fact that the mycobacteria are here sequestered in thick-walled  
13 granuloma where ATDs hardly penetrate.

14  
15 Therefore the activity of a multidrug regimen with specific characteristics of each component  
16 ensures a fast bactericidal effect followed by a sterilizing effect to prevent relapse and selection of  
17 drug resistance. Although the current TB regimen is effective with 95% of cure rate (in drug  
18 susceptible TB under optimal condition), there are still many undefined issues such as the high  
19 variability of response, the likelihood of drugs underexposure, the high prevalence of drug-related  
20 toxicity and the selection of multi-resistant strains. The lack of early biomarkers for predicting  
21 treatment efficacy, cure and identification of patients requiring prolonged treatment increased  
22 complexity to this challenging subject[5]. Moreover the current pipeline is insufficient to tackle the  
23 emergent issue of MDR/XDR TB (multidrug-resistant and extensively-drug resistant TB) issue[6].  
24 After 40 years of no ATDs development, bedaquiline and delamanid have received accelerated  
25 regulatory approval bringing some advance in treatment of resistant strains and some other  
26 compounds are under study.

1 Interindividual variability in the pharmacokinetics (PK) of ATDs might be involved in explaining  
2 such variability and has been identified as a key factor for the sterilizing effect and for the selection  
3 of phenotypic resistance. Low maximum plasma concentrations have been associated with treatment  
4 failure, relapse and acquired drug resistance regardless of HIV status; dose-adjustments after drug  
5 monitoring has been related to better clinical outcomes[7,8]. Pharmacogenetics (PG) is the study of  
6 interindividual variation in DNA sequences related to drug metabolic pathways. Inter-individual  
7 variability, tissue penetration and drug-to-drug interactions are partially explained by genetic  
8 variants in gene encoding for metabolizing or transporting proteins: knowing patients' genetic asset  
9 may pave the way to tailored treatment.

10 Repurposing existing drugs and exploring new regimens, different doses, dosing schedules and  
11 route of administration seem a productive tool to possibly shorten treatment in drug susceptible and  
12 improve outcome in MDR tuberculosis.[9] Preliminary studies and evidence in selected  
13 extrapulmonary disease point out that higher rifampicin (RIF) doses may be safe and increase  
14 treatment efficacy[10].

15 Aim of the following review is to provide an insight in clinical pharmacokinetics and  
16 pharmacogenetics of ATDs and to discuss warranted studies in this field.

17

18

## 19 **2.1 Methods**

20 Articles cited in this review were obtained through searches of the electronic database MEDLINE  
21 up to 15<sup>th</sup> December 2016, meeting abstract databases and reference lists from key reviews. Search  
22 terms included “tuberculosis”, “antitubercular”, “pharmacokinetics”, “pharmacogenetics” and  
23 “SNPs”. Priority was given to primary research publications. The search was limited to English, but  
24 was not restricted by date.

25

## **2.2 Combination of antitubercular treatment**

1

2 International guidelines recommend for drug-susceptible TB the association of RIF, isoniazid  
3 (INH), ethambutol (ETB) and pyrazinamide (PZA) for two months followed by four months of RIF  
4 and INH.

5 For MDR treatment anti-TB drugs are grouped according to efficacy and drug class. New  
6 regrouping has been published in the WHO's 2016 update . Group A are fluoroquinolones (FQ,  
7 levofloxacin, moxifloxacin and gatifloxacin) and group B are injectable drugs (amikacin,  
8 capreomycin, kanamycin). Other core second-line agents, in order of preference are  
9 ethionamide/prothionamide, cycloserine/terizidone, linezolid and clofazimine. Add-on agents were  
10 split in three different subgroups: D1 includes pyrazinamide, ethambutol and high-dose isoniazid  
11 (15-20 mg/kg); D2 consists of bedaquiline and delamanid; D3 is made up of p-aminosalicylic acid  
12 (PAS), imipenem-cilastatin, meropenem, clavulanate and thioacetazone[11].

13 Bedaquiline, delamanid and another new compound pretomanid (PA-824) are in clinical Phase 3  
14 and when the results will be available these new drugs will be re-evaluated to design the core MDR-  
15 TB regimen (STAND phase 3 trial testing the efficacy, safety and tolerability of moxifloxacin,  
16 pretomanid and PZA is presently on clinical hold)[12]. In patients with RIF-resistant or multidrug-  
17 resistant TB, a conventional regimen with at least five effective TB medicines during the intensive  
18 phase is recommended, including PZA and one drug chosen from group A, one from group B and at  
19 least two from group C (PZA+A<sub>1</sub>+B<sub>1</sub>+C<sub>2</sub>); if the minimum number of effective drugs is not  
20 reached an agent from group D2 and others from group D3 may be added to bring the total to five  
21 active agents. An intensive phase of 8 months is suggested for most patients and the total duration  
22 should be modified according to patients' response: new patients need to be treated for 20  
23 months.[13] A shorter MDR-TB regimen (9-12 months) may be used in patients previously  
24 untreated with second-line drugs without resistance to FQ and second line injectable agents:  
25 detailed information can be found in WHO treatment guidelines for drug-resistant tuberculosis,  
26 2016 update.[11]

### 1 2.3 Pharmacokinetics of ATDs and efficacy

2

3 Pharmacokinetic and pharmacodynamic (PD) properties of first, second-line and novel drugs are  
4 resumed in **Table 1, 2 and 3**. First-line anti tuberculars and FQ show concentration-dependent  
5 killing and have a long post antibiotic effect. AUC/MIC (where AUC is the area under the  
6 concentration-time curve of a drug) is the best PD parameter to predict the activity. For RIF,  
7 maximal concentration ( $C_{max}$ ) shows a good correlation with AUC and it is often used as a  
8 surrogate of the latter[14–16]. Gumbo *et al.* suggested that AUC/MIC is the PK/PD parameter most  
9 associated with bactericidal activity, while  $C_{max}$ /MIC is associated with the prevention of resistance  
10 selection[17].

11 Studies have highlighted the importance of ATDs concentrations on the rate of kill of *M.*  
12 *tuberculosis* in hollow fiber systems[17], animal models[18] and patients[19].

13 Few clinical studies have prospectively shown the association between plasma drug concentrations  
14 and outcome and results are heterogeneous. Pasipanodya[20] found that the three best predictors of  
15 poor long term outcome were: PZA 24-hour  $AUC \leq 363$  mg\*h/L, RIF  $AUC \leq 13$  mg\*h/L, and INH  
16  $AUC \leq 52$  mg\*h/L. Moreover low RIF and INH  $C_{max}$  and AUC preceded all cases of acquired drug  
17 resistance. Burhan[21] investigated the relation between plasma concentrations of RIF, INH, PZA  
18 and culture results. Even if drug concentrations were below the reference values no relationship  
19 between post-dose concentration and culture conversion at 8 weeks was recorded. A post-hoc  
20 analysis showed that patients with low PZA levels and extensive lung lesions were at risk of one  
21 positive culture at week 4, 8 or 24/32. Similar result was obtained by Chideya[22] that found **that** a  
22 low PZA  $C_{max}$  was associated with worse outcomes in 255 TB patients from Botswana (where 69%  
23 were HIV coinfecting). A Danish small prospective study on 32 patients showed that 2h post-dose  
24 RIF and INH plasma concentrations were below the recommended ranges in the majority of  
25 patients and therapy failure occurred more frequently when RIF and INH concentrations were both  
26 below the normal ranges[23] A critical issue for predicting treatment outcome may be the number

1 of concomitantly underdosed drugs as reported in a few observations.<sup>20,23</sup> Conversely, a  
2 retrospective report on 17 Swiss patients[24], showed that despite low plasma concentrations the  
3 outcome was good in the whole small sample.

4 While the ATDS' synergistic effect is well known, an innovative study described the impact of PK  
5 on the sterilizing activity of the multidrug regimen[15]. The results showed that RIF  $C_{max} > 8.2$   
6 mg/L and PZA AUC/MIC  $> 11.3$  interacted positively on sterilizing activity (measured as Beta-  
7 slope of decline of bacillary burden in the sputum). In patients with RIF AUC  $< 35.4$  mg\*h/L an  
8 increase in PZA AUC/MIC and/or ETB  $C_{max}/MIC$  increased the beta-slope. On the other hand an  
9 increase in INH  $C_{max}$  decreased the sterilizing activity. This apparent antagonist effect of INH on  
10 activity of RIF is consistent with previous studies on hollow fiber system where short interval  
11 between administration of RIF and INH resulted in lower bactericidal and sterilizing effects[25].

12 Jindani[4], conversely, found that ETB had a sterilizing effect but it was judged to be antagonistic  
13 to RIF's one: a possible explanation could be that ETB may increase treatment sterilizing effect in  
14 patients with low RIF concentrations. At a higher RIF exposure, the effect of ETB is masked by the  
15 higher sterilizing effect of RIF, so that the overall effect is less than that of adding the effects of two  
16 drugs, manifesting as apparent antagonism.

17

18 A high inter- and inpatient variability in drug serum concentrations have been often observed and  
19 further complicate the interpretation of PK results.

20 Therapeutic drug monitoring (TDM) might be a useful tool and dose-optimization has proved to be  
21 beneficial in small non-controlled studies.

22 The proposed therapeutic ranges of plasma  $C_{max}$ , normally used as reference[26], are based on  
23 concentrations achieved by standard doses in healthy volunteers in controlled phase I studies and  
24 assumed to be effective in patients.

25 Data from real world report an improved outcome performing TDM in daily practice[7,8]. Low  
26 plasma concentrations seems related to drug-drug interactions (DDIs), use of fixed coformulations,



1 malnutrition, diabetes and coinfections[27–29].  
2 New methods for performing TDM are promising to implement sample collection in remote areas  
3 and to overcome technical issues (including the need for cold chain for storing samples).  
4 One of these methods is the use of dried blood and plasma spots (DBSs/DPSs). They require a  
5 smaller blood volume than conventional venous blood sampling. These devices can be shipped at  
6 room temperature[30].  
7 Regarding antitubercular drugs, limited data have been published. Assays with DPSs for RIF[31],  
8 RPT and several second line drugs have been developed.[32] To our knowledge, PZA and INH  
9 methods have been developed by Allanson *et al*: technical issues due to incomplete stability were  
10 reported for INH.[33]  
11 Although AUC/MIC is the most reliable PD parameter for ATDs, estimating AUC needs several  
12 samples and limited samples strategies (LSS) have been developed to determine what sampling  
13 time is most informative of the AUC. In the past, collection at 2 hours captured  $C_{max}$  and the 6-hour  
14 sample distinguished between delayed absorption and malabsorption[34]. Population  
15 pharmacokinetic models predicted AUC from 0 to 24 hours with optimal sampling at time points 1,  
16 3, 8 hours post-dose for RIF and 2, 6 (with also good estimation of  $C_{max}$ ) hours post-dose for  
17 levofloxacin and 1, 4 hours post-dose for amikacin and kanamycin, respectively[35–37].

18  
19

## 20 **2.4 First-line drugs characteristics and PK/PD relationships (see Table 1)**

21

### 22 **2.4.1 Rifampicin (RIF)**

23 RIF is a key sterilizing drug in the treatment of tuberculosis with relatively low early  
24 bactericidal activity usually administered at 8-12 mg/kg. RIF blocks the transcription  
25 inhibiting the bacterial DNA-dependent RNA polymerase. Mutations in the *rpoB* gene that

1 codes for the beta-subunit of the RNA polymerase are responsible for resistance to RIF. The  
2 MIC of RIF is 0.15-0.5  $\mu\text{g/mL}$ .

3 It is metabolized by a liver esterase (arylacetamide deacetylase) and is a potent inducer of  
4 PXR-mediated pathways, increasing its own and other compounds' clearance. Auto-  
5 induction has been reported to take about a week and full induction takes about three to four  
6 weeks[38]. This causes a decline in the AUC and terminal half-life over the first weeks of  
7 administration. The best size predictor for RIF clearance is fat-free mass instead of total  
8 body weight and it should be used to optimize dose. Antiacids do not affect the absorption  
9 of RIF. Simultaneous intake of high-fat food decreases RIF  $C_{\text{max}}$  by 36% (AUC is less  
10 affected) and increase  $T_{\text{max}}$  by 103%.[39] In most patients the target RIF  $C_{\text{max}}$  is 8 to 24  
11  $\mu\text{g/mL}$  after 600 mg of oral dose and an increased dose is recommended if  $C_{\text{max}}$  is less than 6  
12  $\mu\text{g/mL}$ .

13 Several evidences point out that RIF dose is at the lower limit of optimal efficacy and that  
14 the maximum effective dose has yet to be found[40]. The consensus among experts on the  
15 use of higher doses is increasing dramatically, as shown by growing data. A dose range trail  
16 from Boeree and colleagues showed safety of two weeks of RIF up to 35 mg/kg[41]. A  
17 higher dose (13 mg/kg intravenously) improved treatment outcome in Indonesian TB  
18 meningitis patients as reported by Ruslami[10], results from HIRIF trial with 3 study arms  
19 of 10, 15, 20 mg/kg are expected to be presented soon[42] ~~is ongoing~~. Last year, preliminary  
20 results of PanACEA MAMS-TB-01 trial were presented and two weeks high-dose (up to 35  
21 mg/kg) RIF in combination with INH, PZA and ETB showed a significant shortening of  
22 time to culture conversion over 12 weeks. Data about full study have still to be  
23 published[43].

24 Conversely, a study from Heemskerk and colleagues did not find a higher survival rate with  
25 “intensified” treatment for tuberculous meningitis (included 15 mg/Kg of RIF and 20 mg/kg

1 of levofloxacin) than that with standard treatment, but was argued that possibly the RIF dose  
2 was suboptimal[44,45].

3 Some other clinical experiences have been conducted and TDM-based increased RIF dosage  
4 led to improved outcome[7,46,47].

5 Diacon and colleagues[48] found almost the double 2-day early bactericidal activity (EBA)  
6 and higher AUC (171 versus 100 ug\* h/ml) at 20 mg/kg comparing to 600 mg/die but  $C_{max}$   
7 did not differ in this study.

8 Moreover a non linear increase in exposure might be observed because of saturation of  
9 hepatic extraction, but a model-based evaluation showed saturation of RIF clearance already  
10 at doses of about  $\geq 450$  mg, confirming previous studies. This could explain the non  
11 linearity of RIF concentration with dose, underexposure of lower-weight patients and the  
12 correlation between faster RIF absorption and higher bioavailability[49]. RIF is a potent  
13 inducer of pregnane X receptor mediated expression of CYP3A4 in liver and in intestine and  
14 plasma concentration of several CYP3A4 substrates are reduced (e.g. HIV protease  
15 inhibitors, oral contraceptives, azoles, statins, methadone and quinidine). It induces several  
16 other CYPs (CYP1A2, CYP2D6), phase II enzymes and efflux transporters. It inhibits  
17 OATP1B1, an organic transporter protein expressed by epatocytes responsible for the uptake  
18 of many drugs into portal circulation.[50]

#### 20 **2.4.2 Rifabutin (RFB)**

21 RFB is derived from rifamycin S. It inhibits DNA-dependent RNA polymerase leading to  
22 suppression of RNA synthesis. It is mostly used in HIV co-infected patients because it has  
23 fewer drug interactions with antiretroviral agents (see section 2.8.2) [51]. It is a weaker  
24 CYP3A inducer than RIF (60% less) and is also metabolized by CYP3A4 giving the rise to  
25 bidirectional interactions. Standard dose is 300 mg/day, but dose adjustment is  
26 recommended with antiretroviral therapy. The  $C_{max}$  increases proportionally with increasing

1 the dose from 300 mg to 1200 mg/day. Concomitant intake of food decreases the rate of its  
2 absorption.

### 3 4 **2.4.3 Rifapentine (RPT)**

5 RPT is a cyclopentyl derivative of RIF with a longer half-life (14–15 hours). Its  
6 development held the hope that it would have allowed highly active once-weekly therapy; it  
7 is intermediate between RFB and RIF in activity as inducer of hepatic microsomal drug  
8 metabolizing P450 enzymes.

9 TBTC Study 22 compared once-weekly regimen of INH and RPT with twice weekly INH  
10 and RIF in the continuation phase of treatment for pulmonary tuberculosis in HIV-positive  
11 and HIV-negative patients. Acquired rifamycine monoresistance among HIV-positive  
12 patients arm led to the closure of HIV-seropositive arm of the study.[52]

13 The hypothesized reasons for the unexpected results were: the inadequate dose of RPT (600  
14 mg) and the inferior activity of INH due to the shorter half-life or the patients' acetylator  
15 status. A study by Weiner and colleagues in 2003 found that low INH plasma concentrations  
16 were associated with failure and relapse with once-weekly INH/RPT regimen[53].

17 Higher dosages of RPT were safely administered in following trials (RIFAQUIN study  
18 where RPT was used at 900 mg twice weekly and 1200 mg once weekly [54]and PREVENT  
19 TB study where RPT was used at 900 mg once weekly[55]). TBTC Study 29 compared RPT  
20 600 mg daily with RIF 600 mg daily administered without food and it was safe, well  
21 tolerated, and as effective as RIF. [56]

22 Population pharmacokinetic studies showed that increasing the dose of RPT led to a minor  
23 bioavailability of the drug and less-than-dose-proportional pharmacokinetics but no plateau in  
24 exposures from 450 mg to 1800 mg was observed. [57] Studies to assess the safety, activity  
25 and pharmacokinetics of higher daily RPT doses in patients with active TB are needed.[58]

1 Currently, RPT is only available in US and, according to CDC guidelines[59], its use is  
2 recommended for the treatment of latent TB infection at the dose of 1200 mg with INH  
3 given once weekly for 12 weeks. It is also an option in the continuation phase of treatment  
4 for multi-sensitive TB in selected patients (HIV-negative patients without cavitory lesions  
5 and negative culture at 2 months of treatment[60]) at the dose of 600 mg with INH 900 mg  
6 once weekly in uncommon situations where more than once-weekly DOT is difficult to  
7 achieve. In 2010, European Commission assigned to RPT orphan drug status for TB  
8 treatment.

#### 9 10 **2.4.4 Isoniazid (INH)**

11 INH is a prodrug, converted by mycobacterial enzyme *katG* to its active form. The  
12 mechanism of action is to inhibit the mycolic acid synthesis, disrupting the bacterial cell  
13 wall.[61] Mutations in *katG* and *inhA* genes are responsible for main mechanisms of INH  
14 resistance.[62]

15 INH has the highest early bactericidal activity (EBA) and acts against replicant extracellular  
16 mycobacteria. Its effect rapidly decreases after first days and its activity is associated with  
17 AUC and acetylator status. MIC ranges from 0.01 to 0.25 µg/mL. Studies investigating EBA  
18 activity have shown that maximum achievable EBA with clinically tolerable doses[63] was  
19 ~~with~~ at plasma concentrations of 2-3 µg/mL. It is recommended to give INH on empty  
20 stomach because food and antacids reduce INH  $C_{max}$  (high-fat meal causes a drop of 51% of  
21  $C_{max}$ ).

#### 22 23 **2.4.5 Pyrazinamide (PZA)**

24 Pyrazinamide's mechanism of action is still not well defined and the drug appears to act, at  
25 least partially, by acidifying the cytoplasm of the cell. It is a prodrug that requires  
26 conversion to pyrazinoic acide (POA) by an amidase encoded by *pncA*. Mutation of this

1 gene is the more common cause of PZA resistance. A study in mice found that systemic  
2 delivery of POA was not sufficient to reduce bacillary burden, even if POA concentration in  
3 plasma, ELF (epithelial lining fluid) and lung lesion were similar to those produced by  
4 effective doses of PZA. New technics exploring delivering of POA at the site of  
5 infection[64] (into macrophages or intrapulmonary with adjunct inhalation therapy[65]) are  
6 ongoing. PZA has the potential effect of shortening treatment duration due to its great  
7 sterilizing activity. A trial exploring a regimen containing PZA, pretomanid and  
8 moxifloxacin showed efficacy at week 8, even in MDR-TB strains[66]. Recommended  
9 therapeutic range is 20-60 ug/mL.[26] Coadministration of allopurinol with PZA decreases  
10 pyrazinic acid clearance and causes acid uric accumulation due to inhibition of acid uric  
11 excretion[67].

12 Recent hollow fiber PK/PD study demonstrated that PZA's sterilizing effect was best  
13 explained by the AUC/MIC ratio, whereas resistance suppression was linked to T>MIC.  
14 Monte Carlo simulations revealed that doses higher than the currently recommended 2 g/day  
15 would have a better likelihood of achieving the AUC/MIC ratio associated with 90% of  
16 maximal effect, but safety concerns arise. PZA serum clearance has been shown to increase  
17 with increases in body weight[14].

#### 18 **2.4.6 Ethambutol (ETB)**

19 ETB is a semisynthetic antibiotic which is bacteriostatic against *Mycobacterium*  
20 *tuberculosis*. ETB acts by inhibiting arabinosyl transferase enzyme, thus blocking the  
21 synthesis of arabinogalactan, which forms the mycobacterial cell wall.[68]

22 Mutations in *embB* gene that code for arabinosyl transferase enzyme are related with ETB  
23 resistance (MIC above 5 µg/mL). Resistance to ETB is higher in INH-resistant strain due  
24 to the correlation with mutation at *katG* Ser315 and *iniA*, which encodes an efflux pump  
25 transporter.  
26

1 Concentrations measured in lung tissue, ascitis and pleural fluids are far higher than ones  
2 reached in plasma. ETB does not penetrate intact meninges, but in patients with TB  
3 meningitis the penetration increases by 10-50%. Aluminium-containing antiacids decreases  
4 the C<sub>max</sub> by 28% and AUC by 10%. Although mechanisms of sex-related differences in  
5 drug concentration are poorly understood lower ETB concentrations were found in female  
6 patients. In the same study albumin levels were inversely correlated with concentrations and  
7 the reason for this is unclear but is possibly related to altered pharmacokinetics in more  
8 severe diseases or malnutrition[28]. Recommended plasma concentrations are between 2 and  
9 6 µg/mL. Some reports suggest that increasing the dose to 25 mg/kg/daily would be the  
10 preferred regimen for most patients, monitoring for toxic effects.[69]

#### 11 12 **2.4.7. Streptomycin (S)**

13 Streptomycin, discovered almost 70 years ago, was the first agent of the aminoglycosides  
14 class to be used for TB treatment, promptly replaced by INH. Its use is limited by relatively  
15 high rates of resistance (particularly in high incidence countries); current guidelines  
16 recommend its administration as fourth drug in multisensitive TB treatment (as alternative to  
17 ETB).

18 Aminoglycosides act mostly as protein synthesis inhibitors both as 30S-subunit ribosome  
19 blockers and interference with proofreading process. They also disrupt the integrity of  
20 bacterial cell membrane.

21 While S is not usually included with second-line drugs it can be used as the injectable agent  
22 of the core MDR-TB regimen if none of the three other agents (amikacin, capreomycin and  
23 kanamycin) can be used and if the strain can be reliably shown to be sensitive. However S  
24 resistance does not play a part in the definition of XDR-TB and that DST (Drug  
25 Susceptibility Testing) results are not considered accurate[70].

1 Streptomycin resistance has been ascribed to mutational changes in *rpsL* and 16-S ribosomal  
2 RNA genes involving ribosomal binding protein or the ribosomal binding site. Isolates  
3 resistant to S are not cross-resistant to amikacin, kanamycin, or capreomycin. The members  
4 of the aminoglycoside family share the potential for nephrotoxicity, ototoxicity and rarely  
5 neuromuscular blockade. Intramuscular injection of 1 g yields peak plasma concentration of  
6 35-45 µg/mL and it is virtually excluded from SNC. Recommended dosage in younger  
7 adults with normal renal function is 15 mg/kg/day IM. The drug can be safely given IV  
8 when needed, although is not approved for such use[71]. In patients with reduced renal  
9 function is recommended a dose of 15 mg/kg twice/thrice-a-week.

## 11 **2.5 Second-line drugs characteristics and PK/PD relationships (Table 2-3)**

### 13 **2.5.1 Fluoroquinolones**

14 Fluoroquinolones act by inhibiting two bacterial enzymes, DNA gyrase and topoisomerase  
15 IV involved in DNA replication. They exhibit concentration-dependent killing and a post-  
16 antibiotic effect.[72] Limited data from human studies are available for evaluating the PD  
17 thresholds necessary for maximizing therapeutic success. The two most commonly FQ used  
18 for the treatment of MDR-TB are levofloxacin and moxifloxacin due to their high  $C_{max}/MIC$   
19 profile. Recently, three major international multicentre phase III trials demonstrated that  
20 four different 4-month regimens did not provide as good a standard of care as the 6-month  
21 regimen[54,73,74]. DDIs (drug-drug interactions) between RIF and moxifloxacin have been  
22 reported. Moxifloxacin AUC is reduced by 27%, and the half-life decreased by 36%,  
23 although no change in the peak concentration in serum was identified. This effect seems to  
24 be mediated by increased activity of the sulfate conjugation pathway of moxifloxacin  
25 metabolism, because coadministration of RIF resulted in marked increases in levels of the



1 M-1 metabolite. Some authors suggest to increase moxifloxacin dose to 600 mg/day when  
2 coadministered with RIF.[75][76]

3 A hollow fiber study determined that moxifloxacin was able to suppress the development of  
4 resistance with freeAUC<sub>0-24h</sub>/MIC of 53 µg\*hour/ml. In clinical trial simulations  
5 moxifloxacin 400 mg/day had a target attainment rate of only 59%, improved to 90% with a  
6 dose of 800 mg; this was further confirmed in murine models but safety in humans has not  
7 yet been established[14]. Resistance to FQ depends on substitution in the GyrA and/or GyrB  
8 and is defined by the WHO as resistance to at least 2 µg/ml of ofloxacin. Sterilizing activity  
9 of moxifloxacin decreases gradually against strains with increasing levels of resistance  
10 (from low to high). Therefore among strains resistant to 2 mg/L ofloxacin identification of  
11 moxifloxacin level of resistance is required[77].

### 12 13 **2.5.3 Capreomycin, amikacin and kanamycin**

14 Capreomycin, amikacin and kanamycin, according to new WHO classification, are  
15 considered as a group (group B) because they are all administered by intramuscular or  
16 intravenous injection, have similar pharmacokinetics and toxicity and are excreted by renal  
17 route. Capreomycin is a polypeptide active against *M. tuberculosis*, including most MDR-  
18 TB strains. MIC ranges from 1 to 50 µg/mL. The dose is 500 mg-1 g IM 5 times/week. If an  
19 isolate is resistant to both S and kanamycin capreomycin should be used.

20 Amikacin is the most active *in vitro* aminoglycoside against *M. tuberculosis* as well as in  
21 animal models. Limited data are available in human tuberculosis because of its cost and  
22 relatively greater toxicity (as compared to S and capreomycin, in the US it replaced  
23 kanamycin). The dose is 7-10 mg/kg five times/week and TDM is available in laboratories.

24 Amikacin and kanamycin are considered to be very similar and have a high frequency of  
25 cross-resistance. Kanamycin is an aminoglycoside active against most S-resistant strains. It

1 has no clear advantage over amikacin, except for lower cost; the dose is 15 mg/kg IM,  
2 limited to 500 mg/day due to a certain risk of ototoxicity.

#### 3 4 **2.5.4 Other second-line drugs**

5 Few data are available about PK/PD parameters of other second line drugs and data we have  
6 are mostly desumed from non-TB models[16].

7 Linezolid (LZD) is an oxazolidinone agent. It is active against gram-positive bacteria,  
8 including resistant strains. It is used in the treatment of nosocomial pneumonia, skin and soft  
9 tissues infections caused by gram-positive bacteria. As second-line agent it can be used in  
10 the treatment of MDR TB and belongs, according to last WHO update to C group. It acts by  
11 binding to the 50S subunit of bacterial/mycobacterial ribosome producing an early inhibition  
12 of protein synthesis.[78] LZD for other human pathogens is time and concentration  
13 dependent. In a study on TB patients the correlation between plasma concentrations and  
14 activity is linear at values AUC/MIC less than 120 but disappears once  $T > MIC$  reaches  
15 100% (where T/MIC is the cumulative percentage of the dosing interval that the drug  
16 concentration exceeds the MIC under steady-state condition)[79].

17 Gebhart and colleagues found that RIF, inducing P-gp expression, leads to increased  
18 clearance of LZD (reduction in LZD serum concentration up to 30%) supporting the  
19 hypothesis that P-gp expression plays a role in the potential interaction between the two  
20 drugs[80], but several reports confirmed the efficacy on this combination[81].

21  
22 Bedaquiline is a novel diarylquinoline that acts by inhibiting the *M. tuberculosis* adenosine  
23 triphosphate (ATP) synthase. It was approved by US FDA in 2012 and by EMA (European  
24 Medicine Agency) in 2013. It is metabolized by CYP3A4 to M2 as main metabolite and a  
25 significant reduction in exposure results if coadministered with RIF or RPT.[82] MIC  
26 ranges from 0.03 to 0.12 ug/mL. Its activity against both susceptible and MDR strains seems

1 to be promising to shorten treatment duration. Food increases the bioavailability by  
2 twofolds. It has an extensive tissue distribution and steady state is reached after 7 days with  
3 a time-dependent bactericidal activity[83]. The dose is 400 mg/day for 14 days followed by  
4 200 mg thrice-a-week. It has a synergic activity with PZA.[84] Its PK characteristics are  
5 compatible with once a week administration.[85] There are concerns on safety because of  
6 the cardiovascular toxicity and QT prolongation (see section 2.6). Animal reproduction  
7 studies have failed to demonstrate a risk to the fetus, but no data on pregnant women are  
8 available (for FDA pregnancy category B).

9 Delamanid is a nitroimidazole and inhibits mycolic acid synthesis. It has been approved in  
10 2014 by EMA. It has a good oral bioavailability, enhanced with food and has a  
11 concentration dependent bactericidal effect. The dose is 100 mg twice-a-day. MIC ranges  
12 from 0.006 to 0.024 ug/mL in both susceptible and resistance strains. It is thought to be  
13 primarily metabolized by albumin, with secondary contributions from P450 enzymes,  
14 primarily CYP3A4. Delamanid resulted teratogenic in reproductive toxicity studies in  
15 animals, but no data in humans.[86]

16 The use of the more recently approved drugs is currently recommended in adult patients  
17 with pulmonary MDR-TB for 24 weeks when an effective treatment containing four  
18 second-line drugs in addition to PZA cannot be designed and/or when there is documented  
19 evidence of resistance (or intolerance) to any FQ or second-line injectable drug (the latter  
20 specifically for delamanid). Additional indication for delamanid is the presence of risk  
21 factors of poor outcome such as: advanced/extended disease, HIV coinfection, high sputum  
22 bacillary load, low BMI, and comorbidities (e.g. diabetes mellitus). The concomitant use of  
23 bedaquiline and delamanid is not allowed by manufacturers and is not recommended by  
24 WHO (nevertheless a sequential use is permitted)[87]. Two case reports of co-administration  
25 were published[88,89] and it may be considered in selected patients and in presence of  
26 appropriate monitoring conditions.

1 Pretomanid (PA-824), another nitroimidazole, is in Phase II studies. It is a prodrug that  
2 needs to be activated by mycobacterial glucose-6-phosphate dehydrogenase. Surprisingly, it  
3 exhibits a time-dependent bactericidal activity[90]. MIC ranges from 0.015 to 0.25 ug/mL  
4 against susceptible and resistant strains. Concomitant intake of foods increase the absorption  
5 and it exhibits a high tissue penetration. Promising results have been observed in EBA  
6 studies with combination of pretomanid/bedaquiline/ pyrazinamide[91] and  
7 pretomanid,/moxifloxacin/pyrazinamide (at 2[92] and 8 weeks[66]).  
8

## 9 **2.6 Pharmacokinetics and toxicity**

10 Combination antitubercular treatment is associated with a significant incidence of ~~drug-associated~~  
11 side effects: preventing toxicity might be beneficial also in terms of treatment interruption  
12 (estimated approximately at 5%), failures and selection of resistance[93]. Clinically relevant  
13 adverse effects include nausea, rash and occasional hepatotoxicity.

14 Concentration-dependant toxicity has been observed for ETB (optical neuritis) and PZA  
15 (hepatotoxicity), whereas for INH and RIF it is still uncertain[94,95].  
16

17 RIF-induced hepatitis occurs in up to 2.5% and it does not seem to be dose related even with higher  
18 doses[96]. Intermittent regimens with higher RIF doses (1200 mg or more) seem to be rather related  
19 with higher risk of flulike syndrome[97].[98]:[99].

20 RFB can cause neutropenia and anterior uveitis and the risk appears to increase as RFB and 25-  
21 desacetyl-RFB exceeds 1 µg/mL.[9]

22 Periphery neuropathy, through the increase of the excretion of pyridoxine, is a rare INH dose-  
23 dependent adverse event. Patients at increased risk are those with HIV infection, diabetes, renal  
24 failure, alcoholism, malnutrition and pregnant/lactating women. Supplemental pyridoxine (vitamin  
25 B<sub>6</sub>) is recommended at the dose of 150 mg 3 times per week. In lactating women taking INH,

1 supplementation of pyridoxine has to be administered to newborns as well for the passage through  
2 breast-feeding.

3

4 Regarding second-line drugs few data are available about toxicity related with plasma  
5 concentrations.

6 The primary concerns with aminoglycosides are auditory, vestibular and renal toxicity[100] and  
7 seem related to higher cumulative dose and older age.

8 Higher doses of moxifloxacin (600-800 mg) are being studied but dose escalation needs particular  
9 attention due to the risk of QT prolongation.

10 Data on LZD are mainly derived from gram-positive bacterial infections, its use is limited by its  
11 long-term adverse effects, including myelosuppression, lactic acidosis, ocular and peripheral  
12 neuropathy. The mechanism through toxicity occurs is not perfectly understood and the dose for  
13 mycobacteria has not yet clearly been established, even if 600 mg daily seems to be generally  
14 accepted. Maintenance of a serum LZD  $C_{min}$  between 2 and 7  $\mu\text{g/mL}$  has been suggested as a step  
15 for improving safety outcomes while retaining appropriate efficacy.

16 Bedaquiline prolongs QT and this effect extends for weeks after drug discontinuation. A study on  
17 healthy volunteers did not observe effect of a single incremented dose of 800 mg on QT and **no**  
18 association were found between QT and bedaquiline or M2 (major metabolite) plasma  
19 concentrations[101].

20 Delamanid may affect the length of QT interval as well: this appears to be dose-related and  
21 increasing over the initial 6–10 weeks of treatment. The effect has been linked to delamanid's major  
22 metabolite DM-6705. Both CYP3A4 inducers and inhibitors may increase levels of DM-6705,  
23 necessitating more intensive cardiac monitoring in such settings[86].

24

25 **2.7 Pharmacogenetics**

1 The interindividual differences genetically determined play a relevant role in designing a tailored  
2 treatment approach. Historically metabolizing phenotypes (later discovered to be associated with  
3 *NAT-2* genetic variants) have been associated with INH metabolism and toxicity; recently several  
4 pieces of evidence have been published on the effect of single nucleotide polymorphisms (SNPs) in  
5 genes encoding for proteins involved in drug disposition.

6

### 7 **2.7.1 Rifampicin and PG**

8 RIF is a substrate of P-glycoprotein and OATP1B1; the latter is an influx transporter mainly  
9 expressed in basolateral membrane of hepatocytes and that facilitates RIF uptake into  
10 hepatocytes. Genetic variants in *SLCO1B1* (encoding for OATP1B1) have been shown to  
11 affect the protein expression and activity.

12 In particular, Chigutsa and colleagues[102] undertook a study in South African patients with  
13 tuberculosis and found that *SLCO1B1* genetic polymorphism rs4149032 (which occurs at a  
14 high frequency in the black African population) is associated with reduced RIF  
15 concentrations. Patients heterozygous and homozygous for this polymorphism had  
16 reductions in the bioavailability (and, thus, AUC) of RIF of 18% and 28%, respectively.  
17 This study suggests that an increase in RIF dose would be desirable for carriers of the  
18 *SLCO1B1* polymorphism and a simulation showed that increasing the daily RIF dose by 150  
19 mg in patients with the polymorphism would result in plasma concentrations similar to those  
20 of wild-type individuals and would reduce the percentage of patients with  $C_{max}$  below 8  
21 mg/L (from 63% to 31%). Two other common non-synonymous *SLCO1B1* variants have  
22 been studied: rs2306283 (previously referred to as 388A>G) and rs4149056 (commonly  
23 referred to as 521T>C). These two variants are in partial linkage disequilibrium.  
24 Consequently, there are four important haplotypes: *SLCO1B1*\*1A, containing neither  
25 variant, *SLCO1B1*\*1B (rs2306238), *SLCO1B1*\*5 (rs4149056) and *SLCO1B1*\*15 (both). The  
26 *SLCO1B1*\*15 haplotype have been found to be associated with rifampin-induced liver injury

1 in a Chinese population and may have a role in cholestatic/mixed injury although other  
2 studies in similar ethnic groups did not confirm such observation.[103,104]

3 Weiner and colleagues[105] studied the effect of genetic polymorphisms of *ABCB1*  
4 (encoding for P-glycoprotein), *SLCO1B1* and *SLCO1B3* in patients with TB from different  
5 regions (North America, Spain, Africa) and in healthy subjects. The results showed that  
6 patients with *SLCO1B1* 463C>A variants (rs11045819) had a 36% lower RIF AUC  
7 compared to CC genotypes.

8 Another investigated gene was the carboxylesterase 2 (*CES2*) because have been shown to  
9 significantly affect the plasma concentrations of RIF. *CES2* is thought to be responsible for  
10 the formation of the main metabolite of RIF by deacetylation[106].

11 Moreover mixed results have been published on the effect of *ABCB1* SNPs on RIF  
12 exposure. *ABCB1* encodes for P-gp that is both a substrate of RIF and could be induced by  
13 RIF. More studies are needed to investigate the potential to influence drugs transport and  
14 intracellular accumulation[107].

### 16 **2.7.2 Isoniazid and PG**

17 INH is primarily metabolized by acetylation via N-acetyl transferase 2 (NAT2). The rate of  
18 elimination of INH depends on NAT2 metabolic activity and the activity is controlled by  
19 active alleles. According to *NAT2* genotype patients can be characterized as slow (without  
20 any active alleles), intermediate (heterozygous for *NAT2\*4*) and rapid acetylators  
21 (homozygous for *NAT2\*4*, wild type). Rapid acetylators are at higher risk of treatment  
22 failure whereas slow acetylators may develop hepatotoxicity. Gene frequency for the slow  
23 allele varies in different ethnic groups and geographical areas being 10% in Japanese and  
24 Eskimos, 60% in Caucasians and subjects of African Ancestors and 90% in subjects from  
25 the Middle-East.

1 A genotype-guided randomized and controlled trial investigated the rate of treatment failure  
2 and INH related liver injury (INH-DILI) in 172 Japanese patients with pulmonary TB[108].  
3 Patients in the PGx-arm (pharmacogenetic guided arm) received 2.5 mg/kg, 5 and 7.5 mg/kg  
4 INH according to their slow, intermediate or rapid acetylator status, respectively while those  
5 in the standard dose arm received approximately 5 mg/kg. INH-DILI occurred in 78% of the  
6 slow acetylators in the standard-treatment (STD), while none of the slow acetylators in the  
7 PGx-treatment experienced either INH-DILI or early treatment failure. Among the rapid  
8 acetylators, early treatment failure was observed with a significantly lower incidence rate in  
9 the PGx-treatment than in the STD-treatment (15% vs. 38%).

### 11 **2.7.3 Ethambutol and PG**

12 A recent pharmacogenetic study from our group found an association between SNPs in  
13 *ABCB1*, *CYP24A1*, Vitamin D Receptor (*VDR*) gene and plasma/intracellular ETB  
14 concentrations. Further researches are needed to understand the clinical relevance of these  
15 findings[109].

### 17 **2.7.4 Second-line drugs and PG**

18 The influence of SNPs in genes encoding for transporters on FQ plasma concentrations has  
19 been investigated for moxifloxacin. Weiner and colleagues found that SNP 3435C>T  
20 (rs1045642) in *ABCB1* gene coding for P-gp have not influence on moxifloxacin PK levels.

21 Therefore P-gp does not seem to be a major determinant of moxifloxacin disposition.[75]

22 So far no study was published about PG of aminoglycosides, except for one report of oral  
23 tobramycin absorption influenced by P-gp inhibitors.

24 The only published data regarding LZD and PG is the reported interaction between RIF and  
25 LZD that may be dependant on P-gp and therefore, potentially, on SNPs affecting P-gp  
26 activity.[80]



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**2.7.4 Hepatotoxicity and PG**

The incidence of hepatotoxicity during antitubercular treatment varies from 2% to 28%[110]. The exact mechanism is unknown but toxic metabolites have a role in the development of it.

Investigations of genetic polymorphisms relating to drug induced hepatitis have been conducted and *CYP2E1* and *GST* genes resulted to influence the incidence of it.

*CYP2E1* activity depends on INH blood concentrations. INH or its metabolite could both induce and inhibit *CYP2E1*. The variant *CYP2E1* genotype is more susceptible to the inhibition than the common genotype. The enhanced activity causes increased production of hepatotoxins and consequently increased risk of hepatotoxicity[111].

Furthermore *CYP2E1* polymorphisms were found to be related with the severity of antitubercular drug-induced hepatotoxicity[112].

*GSTs* enzymes are involved in detoxification of drugs and other chemical substances. Of the five encoding loci *GSTM1* and *GSTT1* were reported to be associated with hepatotoxicity in Western Indian population. Homozygous deletion at *GSTM1* and *GSTT1* loci could influence susceptibility to INH-induced liver toxicity[113].

**2.8 Pharmacokinetics in special populations**

Three groups of patients may be at higher risk of failure and/or side effects and therefore might benefit from personalization of ATD dosage: pediatrics, HIV-positive and diabetic subjects.

**2.8.1 Pediatrics**

1 Approximately 1 million of TB cases occur in children every year: interpatient variability in  
2 enhanced in children and the risk of under-dosing is consistent. In 2010, WHO recommended  
3 increased pediatric dosages for RIF (10–20 mg/kg), INH (7–15 mg/kg), PZA (30– 40 mg/kg),  
4 and ETB (15–25 mg/kg), which are higher than the adult recommended dose. To date, few  
5 studies have evaluated the PK of the WHO revised dosages in children[114]. A study on 127  
6 Indian children showed increased concentration of INH, PZA and RIF with revised dosages,  
7 though the change was not significant for RIF. In this study no effect on outcome or due to  
8 malnutrition was observed. The effect of malnutrition, heavily affecting some settings, on  
9 pharmacokinetics of ATDs in children is not well known[115].

10 From these and other data much additional work is needed to characterize the PK and PD of the  
11 four first-line anti-TB drugs in pediatric patients.

12 The use of bedaquiline under 18 years old is off label. A PK and safety study is planned. So far  
13 no pediatric formulation is available. The dose is 6 mg/kg as loading dose followed by dose of 3  
14 mg/kg.

15 Delamanid, through compassionate use, can be administered to children older than 6 years old or  
16 above 20 kg. Good PK data and safety have been shown in this population. Pediatric formulation  
17 is being developed. The dose is: 100 mg twice daily if >35 Kg; 50 mg twice daily if 20-35 Kg. A  
18 case series has been published (children between 8 and 17 years old) with good results.[116]

### 20 **2.8.2 HIV-positive patients**

21 TB is the most frequent infection in people living with HIV accounting for one third of deaths. In  
22 Sub-Saharan Africa most of the people with TB are HIV positive and death rate by TB infection  
23 are higher in this population[1]. Treatment for HIV infected patients do not require any  
24 adjustment in doses except that intermittent regimens are no longer recommended, as stated by  
25 international guidelines, due to the increased risk of relapse, failure and acquired RIF  
26 resistance[117,118].

1 The effect of HIV co-infection on the pharmacokinetics of the four first-line anti-TB drugs (and  
2 treatment outcome) seems to be largely dependent on the patient's clinical status and on the  
3 concurrent medications the patient is receiving. In some of the earlier studies[119], patients with  
4 advanced HIV/AIDS showed a significant decrease in plasma levels of the first-line anti-TB  
5 drugs; recent data did not confirm these observations.[120]

6 Clinically relevant DDIs have been reported between ATDs and antiretroviral drugs (ARVs).  
7 Rifamycins are potent inducers of phase I (e.g. CYP450) and phase II (e.g. UGT) liver enzymes  
8 and may reduce plasma concentrations of concomitant drugs metabolized by these enzymes.  
9 Guidelines recommend the use of RIF with efavirenz (at standard dose, 600 mg), raltegravir  
10 (exposure to standard dose of 400 mg twice-a-day seems to ensure adequate raltegravir  
11 concentrations, but more data are needed[121]) and dolutegravir (doubling the dose, 50 mg  
12 twice-a-day). The extent and direction of effect of RIF on efavirenz seems to be dependant on  
13 *CYP2B6* genotype: the presence of *CYP2B6*\*6/\*6 genotype is associated with slow efavirenz  
14 metabolism, and other alternative metabolic pathways gain importance (*CYP1A2*, *CYP2A6*,  
15 *CYP3A4/5*). Higher efavirenz concentration has been found in patients harbouring haplotype  
16 *CYP2B6*\*1/\*6 and especially *CYP2B6*\*6/\*6. This increase in EFV plasma exposure under TB  
17 regimen it can be partially explained also by an inhibitory effect of isoniazid (usually in the TB  
18 regimen) on alternative metabolic pathways.[122] RIF is contraindicated with protease inhibitors  
19 (PI) because causes relevant (50-80%) decreases in PI concentration: higher dose of  
20 lopinavir/ritonavir (400/400 mg twice daily) may be necessary but higher incidence of liver and  
21 gastro-intestinal toxicity was reported. Population pharmacokinetic models suggested that  
22 darunavir/ritonavir (1600/200 mg once daily, 800/100 mg twice daily and 1200/150 mg twice  
23 daily) could potentially overcome reduced darunavir concentrations with RIF.[123] This is a  
24 significant problem in patients on second-line ARV regimens (often receiving PIs) since RIF is  
25 expensive and often unavailable.

1 RFB is a less potent inducer than RIF and RFP; however its main metabolite (25-desacetyl-RFB)  
2 is a CYP3A4 substrate. Co-administration of RFB with potent CYP3A4 inhibitors (such as  
3 ritonavir and cobicistat), may increase the risk of adverse effects such as anterior uveitis.  
4 Consequently, current guidelines recommend modifying RFB doses when administered with  
5 PI/r, although there is a lack of international consensus as to the optimal dose: 150 mg every  
6 other day has been associated with treatment failure and selection of RIF-resistant strains.[124]  
7 Evidences favor the administration of RFB 150 mg every day although 150 mg thrice-a-week is  
8 recommended with atazanavir/ritonavir (for the increase in RFB and 25-desacetyl-RFB  $C_{max}$  and  
9 AUC). [51] A dose-increase to 450 mg is suggested when RFB is co-administered with  
10 efavirenz: no other dose-adjustment is currently suggested. Coadministration of rilpivirine is  
11 contraindicated. [125]

12 Regarding bedaquiline no major interactions are expected with the use of integrase inhibitors: on  
13 the contrary administration of CYP3A4 inducers and inhibitors should be avoided.[82][126]  
14 Little effects were seen with delamanid (lopinavir/ritonavir was associated with a 20% increase  
15 in delamanid exposure and a 30% increase in delamanid's metabolite DM-6705). South african  
16 cohort observed good clinical outcomes in a cohort of HIV-positive patients largely treated with  
17 lopinavir/ritonavir.[86]

### 19 **2.8.3 Diabetic patients**

20 Type 2 diabetes mellitus (DM) is a strong risk factor for TB infection and is associated with a  
21 slower response to treatment and with higher mortality rates. Some diabetic patients experience  
22 delayed or reduced drug absorption: the results of several observations on ATDs plasma  
23 concentrations are however heterogeneous. In some studies, DM was associated with decreased  
24 plasma levels of RIF and INH[27,127], whereas in others, there was no clear relationship  
25 between plasma concentrations of first-line ATDs and DM[128,129]. Consequently the

1 relationship between low plasma concentrations and poor outcomes need to be further studied in  
2 diabetic patients in order to identify other potential predictors and tailor antiTB treatment.

### 4 **2.9 Intralesion, intracellular and intrabacterial pharmacokinetics**

5  
6 The sites of action of ATDs in pulmonary tuberculosis are the tissue compartments with pulmonary  
7 lesions and specifically drugs have to be in adequate concentrations in the ELF, in alveolar  
8 macrophages and inside mycobacteria. Despite the efficacy of antitubercular regimen little is know  
9 about the penetration of drugs and if this aspect plays a role in the long needed combination  
10 therapy. Considering that drug concentrations are associated to treatment outcome lesion  
11 penetration may contribute to it for the relation with incidence of relapse or the development of  
12 phenotypic drug resistance. Determination in venous plasma may not correctly predict real exposure  
13 of drugs to organs and to different components of a lesion.

14 Moreover inoculum effect (the variation of MIC according to the number of bacterial population)  
15 and phenotypic tolerance (variation of MIC according to metabolic state of subpopulations) at the  
16 site of infection may have a relevant role in determining the efficacy of regimen and the selection of  
17 resistance.

18 Kjellsson and colleagues[130] found in a rabbit model that RIF, PZA and INH (RIF>PZA>INH)  
19 reached lower lesion concentrations in comparison to plasma ones, although RIF seems to  
20 accumulate in uninvolved lung tissue. In contrast moxifloxacin displayed the highest distribution in  
21 lesions, using tissue homogenate.

22 MALDI-MSI technology was applied by Prideaux and colleagues[131] to observe that, within the  
23 granuloma, moxifloxacin reached very low levels in the caseum (where typically reside persister  
24 mycobacteria) in comparison to the cellular granuloma regions. We may speculate that this is the  
25 reason why FQ-using shortening trails failed. PZA seems to be the only agent with good diffusion  
26 into caseum and be active against persister mycobacteria. Prideaux and colleagues[132] described

1 in human lung lesions, using very refined methods, the distribution of these drugs, confirming  
2 previous results. Besides, lipophilic drugs (RIF, RPT, bedaquiline, pretomanid and clofazimine)  
3 seems to be more active than hydrophilic agents (INH, PZA, ETB, amikacin, moxifloxacin) against  
4 dormant mycobacteria in hypoxic condition as within cellular granuloma, whereas in the necrotic  
5 centre the pH ranges between 7.2 and 7.4.[133]

6 Haartkoorn et al[134] investigated INH, ETB and RIF activity inside infected macrophages. RIF is  
7 a drug with excellent activity against intracellular bacilli, concentrating from 2 to 5-fold in  
8 macrophages, however higher concentrations were required to kill intracellular mycobacteria. INH  
9 modulated the growth of mycobacteria at similar concentrations inside and outside the cell. Dhillon  
10 found, in animal model, that PZA and ETB expresses bacteriostatic activity in macrophages with a  
11 MIC equivalent to extracellular one.[135]

12 From previous studies aminoglycosides have intracellular/extracellular (I/E) ratio that is lower than  
13 1, INH has an I/E ratio of around 1, RIF has an I/E ratio of between 2 and 5, and ETB and the  
14 macrolides have I/E ratios ranging from 10 to >20[136,137].

15 Some experience have been made measuring drug concentrations inside PBMCs (peripheral blood  
16 mononuclear cells) for being easily and readily collectable, and possibly a good surrogate of  
17 alveolar macrophages, partially confirming previous results of I/E ratio[138,139].[140]. Reduced  
18 permeability of *M. tuberculosis* to drugs further contributes to the inferior susceptibility of the  
19 quiescent bacterial population to the therapy. Interestingly, studies have reported that intrabacterial  
20 penetration of FQ is reduced in non replicating mycobacteria and is only partially explained by  
21 efflux. Moreover polyamine (organic compounds present both in eukaryotic and prokaryotic cells)  
22 inhibit uptake of fluoroquinolones and accumulate with inflammation contributing to the  
23 development of dormancy for their tuberculostatic effect[141].

24

### 25 **3. Conclusion**

26

1 Pharmacokinetic variability of ATDs is driven by multiple factors and reported data point the way  
2 toward individualized dosing. Maximizing efficacy of existing drugs and minimizing toxicity on a  
3 large scale with TDM and pharmacogenetics will likely show benefit. More data are needed  
4 especially for second-line drugs and new released drugs.  
5 Efficacy, safety, tolerability and potential sterilizing effect of increased rifampin dosing need to be  
6 further explored because promising results from EBA studies are limited to bactericidal activity.  
7 *NAT2* influence on pharmacokinetics offers an example of how dosing can be adjusted for different  
8 patient genotype and could be extended to *SLCOB1* polymorphisms.

#### 10 **4. Expert opinion**

11 Ending the tuberculosis epidemic is one of the key goals of the WHO post-2015 strategy. It will be  
12 achievable with the widespread and well-tolerated treatment administered to all precociously  
13 diagnosed patients with tuberculosis and with the optimized therapy for patients harbouring  
14 resistant strains. The best use of currently available drugs is critical in delivering efficacious and  
15 safe treatment and to implement shorter combinations: the failure of fluoroquinolones shortening  
16 trials tells us that we need to better understand the tissue penetration of antibiotics. ATDs' plasma  
17 concentrations are associated with treatment efficacy but clear cut off have not being defined and  
18 the majority of patients are cured despite very low plasma levels; yet significant variability and  
19 underexposure of ATDs are common features and the relationship with concentrations at the site of  
20 action (intra-macrophage and intra-lesional) are poorly understood.

21 Therapeutic drug monitoring may be suggested in groups at risk of failure, toxicity or lower  
22 exposure such as children and adolescents, HIV-positive individuals, diabetics, patients with renal  
23 or liver impairment or subjects taking potentially interacting drugs. Its use in those with delayed  
24 response to treatment has been tested and we strongly recommend its application. Underexposure,  
25 especially if involving more than one compound, requires adequate dose adjustments and further  
26 controls. The lack of PK laboratories (performing HPLC/UPLC or GC techniques) calls for

1 capacity building in centralized facilities and for the use of dried blood/plasma spots for safe and  
2 cheap samples delivery. Sequential samples or application of Limited Samples Strategy (LSS) to  
3 calculate AUC are preferred rather than a 2-hour post-dose sample to correctly estimate drugs' peak  
4 concentrations.

5 Furthermore the optimization of currently available first-line drugs involves their tailored per  
6 kilogram dose, their once-daily administration, the correct relationship to food intake (fasted RIF,  
7 INH and fed ETB and PZA) and the avoidance of potentially interacting drugs.

8 The individualization of ATDs' dose according to subjects' genetic variants require more  
9 prospective data as well as controlled trials. In the meanwhile we collect, after patients' signing  
10 written informed consents, *NAT2*, *SLCO1B1* and *PXR* genotypes. We are currently reducing INH  
11 dose in *NAT2* slow metabolizers (4 mg/kg) and increasing RIF dose (to 15 mg/kg) in subjects with  
12 loss of function in *SLCO1B1*.

13 Presumably an increased RIF dose will be soon recommend for all patients independently from  
14 disease localization, if safety concerns will not be arisen from ongoing studies. In the meanwhile we  
15 also use a 15 mg/kg RIF dose in patients with TB meningitis and in those with low RIF  $C_{max}$   
16 concentrations (<8 µg/mL).

17 Insufficient knowledge on treatment in pediatric population worths research investments in  
18 selecting the appropriate dose: *in vivo* to *in vitro* extrapolation modelling might be a promising  
19 option to study the PK in fragile and rapidly changing patients.

20 Finally cellular and tissue pharmacology need to be assessed and new formulations explored (such  
21 the promising nanoformulations allowing for slow and/or targeted release of drugs) in order to tailor  
22 antitubercular treatment dose and duration to patients' and disease characteristics. We believe this  
23 may be the future of antiTB pharmacology: the goal would be to have an imaging technique  
24 allowing us to estimate drug penetration *in vivo*. Positron emission tomographies may allow to  
25 identify zone in which tracer-associated drugs are insufficiently penetrating: this may inform  
26 clinical decisions such as dose increase, use of second-line drugs and even referral for surgical



1 removal of lesions. An integration of drugs' plasma information with tissue specific PK/PD  
2 parameters could lead to optimization of existing drugs: physiologically based pharmacokinetic  
3 modelling is a promising field that may help designing informative trials.

4 One of the challenging areas in understading PK/PD relationships of ATDs is the lack of early  
5 biomarkers for defining drug efficacy. While EBA is expensive and not related to sterilizing  
6 activity other markers are under investigation such as sputum and urine molecular studies and  
7 whole blood bactericidal activity (WBA), but the description of this topic is beyond the scope of  
8 this review. We envisage significant efforts in identifying cheap and sensitive early biomarkers of  
9 antymycobacterial activity and treatment response.

10 Tuberculosis is a challenging infection for the long needed treatment, multidrug regimen and  
11 potential toxicities and drug interactions. Only with global initiative and collaborations between  
12 researchers the open issues may be resolved: in the future we will be able to administer to all  
13 affected subjects the right drug at the right dose for the righ patient.

14

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16 (•=of importance, ••= of considerable importance)

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2

	Rif	Rfb	<u>Rpt</u>	Inh	Etb	Pza	S
Dose	600 mg	300 mg	600 mg	300 mg	25 mg/kg	25-35 mg/kg	15 mg/kg
Binding protein [%]	88.6	71-85	98	10-15	10-30	10-40	34
Metabolism	Hepatic deacetylation, Autoinduction	Hepatic <u>deacetylation</u> , CYP3A	Hepatic <u>deacetylation</u>	Acetylation by NAT2	<u>10-15% hepatic, 50-55% eliminated</u>	Hepatic, 3% excreted unchanged	Eliminated 29-89% unchanged
Plasma half life [hours]	3-4	25-36	15	1.5 fast acetylators 4 slow acetylators	2-4	10	3
Parameter best predictive of activity[16]	AUC/MIC C <sub>max</sub> /MIC	AUC/MIC C <sub>max</sub> /MIC	AUC/MIC C <sub>max</sub> /MIC	AUC/MIC > C <sub>max</sub> /MIC	AUC/MIC	AUC/MIC	AUC/MIC
Therapeutic range µg/ml[26]	8-24	0.3-0.9	8-30	3-6	2-6	20-60	35-45
Threshold associated with poor outcome[20]	AUC≤13 mg*h/l	AUC≤13 mg*h/l	N/A	AUC≤52 mg*h/l	N/A	AUC≤363 mg*h/l	N/A
I/P	2-5	N/A	N/A	1	10-20	<1[138]	<1

ratio[136]

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1

2 **Table 1**

3 **Pharmacokinetic and pharmacodynamic properties of currently recommended antitubercular**  
4 **drugs.**

5 (Rif, rifampicin; Rfb, rifabutin; **Rpt**, rifapentine; Inh, isoniazid; Etb, ethambutol; Pza,

6 pyrazinamide; S, streptomycin; AUC, Area Under the Curve; N/A, not assessed)

7



	Lfx	Mfx	Cs	PAS	Eto	Cfz	Lzd
Dose	500-1000 mg qd	400 mg	10-15 mg/kg	4 gr bid	15-20 mg/kg	100 mg	600 mg
Binding protein [%]	24-38	30-50	<20%	50-60	30	No data	31
Metabolism	Minimally hepatic	52% (N-sulfate and acyl glucuronide conjugates)	<b>65% excreted unchanged. 35% hepatic</b>	Hepatic via acetylation	Prodrug; Hepatic	<b>Hydrolytic dehalogenation, deamination, hydration and glucuronidation</b> [142]	Minimally hepatic via oxidation
Plasma half life	9 hrs	7 hrs	7-10 hrs	0.75-1	2-9 hrs	Up to 70 days	5-6 hrs
Parameter best predictive of activity[16]	AUC/MIC better than C <sub>max</sub> /MI C	AUC/MIC better than C <sub>max</sub> /MIC	N/A	N/A	N/A	N/A	T/MIC
Therapeutic range µg/ml	8-12[26]	3-5[26]	20-35[26]	20-60[26]	1-5[26]	0.5-4[26]	2-7

1

2 **Table 2**

3 **Pharmacokinetic and pharmacodynamic properties of principal second-line antitubercular**  
4 **drugs.**

5 (Lfx, levofloxacin; Mfx, moxifloxacin; Cs, cycloserine; PAS, para-aminosalicylic acid; Eto,

6 ethionamide; Cfz, clofazimine; Lzd, linezolid; AUC, Area Under the Curve; N/A, not assessed)

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2

	Bdq	Dlm	PA-824	
Dose	400 mg for 2 w then 200 mg 3x/w	100 mg bid	100 mg/200 mg	
Binding protein [%]	99	99	95	6 7
Metabolism	Hepatic, via CYP3A4	Hepatic	Prodrug; hepatic	
Plasma half life [hours]	24-30	30-38	16-20	9 10
Parameter best predictive of activity[16]	T/MIC	AUC/MC	T/MIC	
Therapeutic range µg/ml	N/A	N/A	N/A	14 15 16

17

18 **Table 3**

19 **Pharmacokinetic and pharmacodynamic properties of novel agents.**

20 (Bdq, bedaquiline; Dlm, delamanid; PA-824, pretomanid; AUC, Area Under the Curve; N/A, not  
21 assessed)