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

Abstract

Introduction

WHO global strategy is to end TB epidemic by 2035. Pharmacokinetic and pharmacogenetic studies are widely spreading and might confirm their potential role in optimizing treatment outcome in specific settings. Insufficient drug exposure seems to be a relevant factor for tuberculosis outcome and for the risk of emergence of phenotipic resistance.

Areas Covered

This review will report available pharmacokinetic and pharmacogenetic data of first and second-line antituberculars relating to efficacy and toxicity. Pharmacodinamic implications of optimized drugs are discussed. A specific session describes innovative investigations on drug penetration in lesions.

Expert Opinion

The optimal use of available antitubercular drugs is paramount for tuberculosis control and eradication. Waiting for the results of ongoing trials higher RIF doses should be reserved to those with tubercular meningitis. TDM using limiting sampling strategies, is suggested in patients at risk of failure and in those subjects with slow response to treatment. Further studies are needed in order to provide definitive recommendations of pharmacogenetic-based individualization: however lower INH doses in *NAT2* slow acetilators and higher RIF doses in those presenting *SLCO1B1* loss of function genes are promising strategies. Data on tissue drug penetration are needed as well as pharmacological modelling in order to inform tailored strategies.

Keywords: Tuberculosis, *SLCO1B1*, high-dose rifampicin, lesion penetration, therapeutic drug monitoring, acetylator status.

Abbreviations: RIF, rifampicin, RFB, rifabutin; RPT, rifapentine; INH, isoniazid; ETB, ethambutol; PZA, pyrazinamide; AUC Area Under the Curve; PK, pharmacokinetics; PD, pharmacodinamics; C_{max} maximal concentration, TDM, Therapeutic Drug Monitoring.

Article highlights

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

1. Introduction

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

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

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

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

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

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

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

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

2.1 Methods

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

2.2 Combination of antitubercular treatment

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

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

Bedaquiline, delamanid and another new compound pretomanid (PA-824) are in clinical Phase 3 and when the results will be available these new drugs will be re-evaluated to design the core MDR-TB regimen (STAND phase 3 trial testing the efficacy, safety and tolerability of moxifloxacin, pretomanid and PZA is presently on clinical hold)[12]. In patients with RIF-resistant or mutidrug-resistant TB, a conventional regimen with at least five effective TB medicines during the intensive phase is recommended, including PZA and one drug chosen from group A, one from group B and at least two from group C ($PZA+A_1+B_1+C_2$); if the minimum number of effective drugs is not reached an agent from group D2 and others from group D3 may be added to bring the total to five active agents. An intensive phase of 8 months is suggested for most patients and the total duration should be modified according to patients' response: new patients need to be treated for 20 months.[13] A shorter MDR-TB regimen (9-12 months) may be used in patients previously untreated with second-line drugs without resistance to FQ and second line injectable agents: detailed information can be found in WHO treatment guidelines for drug-resistant tuberculosis, 2016 update.[11]

2.3 Pharmacokinetics of ATDs and efficacy

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

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

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

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

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

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

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

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

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

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

malnutrition, diabetes and coinfections[27–29].

New methods for performing TDM are promising to implement sample collection in remote areas and to overcome technical issues (including the need for cold chain for storing samples).

One of these methods is the use of dried blood and plasma spots (DBSs/DPSs). They require a smaller blood volume than conventional venous blood sampling. These devices can be shipped at room temperature[30].

Regarding antitubercular drugs, limited data have been published. Assays with DPSs for RIF[31], RPT and several second line drugs have been developed.[32] To our knowledge, PZA and INH methods have been developed by Allanson *et al*: technical issues due to incomplete stability were reported for INH.[33]

Although AUC/MIC is the most reliable PD paramether for ATDs, estimating AUC needs several samples and limited samples strategies (LSS) have been developed to determine what sampling time is most informative of the AUC. In the past, collection at 2 hours captured C_{max} and the 6-hour sample distinguished between delayed absorption and malabsorption[34]. Population pharmacokinetic models predicted AUC from 0 to 24 hours with optimal sampling at time points 1, 3, 8 hours post-dose for RIF and 2, 6 (with also good estimation of C_{max}) hours post-dose for levofloxacin and 1, 4 hours post-dose for amikacin and kanamycin, respectively[35–37].

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

2.4.1 Rifampicin (RIF)

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

codes for the beta-subunit of the RNA plymerase are responsible for resistance to RIF. The MIC of RIF is 0.15-0.5 μg/mL.

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

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

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

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

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

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

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

2.4.2 Rifabutin (RFB)

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

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

2.4.3 Rifapentine (RPT)

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

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

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

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

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

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

2.4.4 Isoniazid (INH)

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

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

2.4.5 Pyrazinamide (PZA)

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

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

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

2.4.6 Ethambutol (ETB)

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

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

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

2.4.7. Streptomycin (S)

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

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

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

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

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

2.5.1 Fluoroquinolones

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

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

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

2.5.3 Capreomycin, amikacin and kanamycin

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

Amikacin is the most active in *vitro* amynoglicoside against *M. tuberculosis* as well as in animal models. Limited data are available in human tuberculosis because of its cost and relatively greater toxicity (as compared to S and capreomycin, in the US it replaced kanamycin). The dose is 7-10 mg/kg five times/week and TDM is available in laboratories. Amikacin and kanamycin are considered to be very similar and have a high frequency of cross-resistance. Kanamycin is an amynoglicoside active against most S-resistant strains. It

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

2.5.4 Other second-line drugs

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

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

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

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

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

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

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

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

2.6 Pharmacokinetics and toxicity

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

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

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

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

Periphery neuropathy, through the increase of the excretion of pyridoxine, is a rare INH dose-dependent adverse event. Patients at increased risk are those with HIV infection, diabetes, renal failure, alcoholism, malnutrition and pregnant/lactating women. Supplemental pyridoxine (vitamin B_6) is recommended at the dose of 150 mg 3 times per week. In lactating women taking INH,

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

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

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

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

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

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

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

2.7 Pharmacogenetics

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

2.7.1 Rifampicin and PG

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

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

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

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

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

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

2.7.2 Isoniazid and PG

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

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

2.7.3 Ethambutol and PG

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

2.7.4 Second-line drugs and PG

The influence of SNPs in genes encoding for transporters on FQ plasma concentrations has been investigated for moxifloxacin. Weiner and colleagues found that SNP 3435C>T (rs1045642) in *ABCB1* gene coding for P-gp have not influence on moxifloxacin PK levels. Therefore P-gp does not seem to be a major determinant of moxifloxacin disposition.[75]

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

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

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 polimorphisms 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

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

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

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

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

2.8.2 HIV-positive patients

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

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

Clinically relevant DDIs have been reported between ATDs and antiretroviral drugs (ARVs). Rifamycins are potent inducers of phase I (e.g. CYP450) and phase II (e.g. UGT) liver enzymes and may reduce plasma concentrations of concomitant drugs metabolized by these enzymes. Guidelines recommend the use of RIF with efavirenz (at standard dose, 600 mg), raltegravir (exposure to standard dose of 400 mg twice-a-day seems to ensure adequate raltegravir concentrations, but more data are needed[121]) and dolutegravir (doubling the dose, 50 mg twice-a-day). The extent and direction of effect of RIF on efavirenz seems to be dependant on *CYP2B6* genotype: the presence of *CYP2B6*6/*6* genotype is associated with slow efavirenz metabolism, and other alternative metabolic pathways gain importance (CYP1A2, CYP2 A6, CYP3A4/5). Higher efavirenz concentration has been found in patients harbouring haplotype *CYP2B6*1/*6* and expecially *CYP2B6*6/*6*. This increase in EFV plasma exposure under TB regimen it can be partially explained also by an inhibitory effect of isoniazid (usually in the TB regimen) on alternative metabolic pathways.[122] RIF is contraindicated with protease inhibitors (PI) because causes relevant (50-80%) decreases in PI concentration: higher dose of lopinavir/ritonavir (400/400 mg twice daily) may be necessary but higher incidence of liver and gastro-intestinal toxicity was reported. Population pharmacokinetic models suggested that darunavir/ritonavir (1600/200 mg once daily, 800/100 mg twice daily and 1200/150 mg twice daily) could potentially overcome reduced darunavir concentrations with RIF.[123] This is a significant problem in patients on second-line ARV regimens (often receiving PIs) since RFB is expensive and often unavailable.

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

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

2.8.3 Diabetic patients

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

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

2.9 Intralesion, intracellular and intrabacterial pharmacokinetics

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

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

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

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

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

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

From previous studies aminoglycosides have intracellular/extracellular (I/E) ratio that is lower than 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 macrolides have I/E ratios ranging from 10 to >20[136,137].

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

3. Conclusion

Pharmacokinetic variability of ATDs is driven by multiple factors and reported data point the way toward individualized dosing. Maximizing efficacy of existing drugs and minimizing toxicity on a large scale with TDM and pharmacogenetics will likely show benefit. More data are needed especially for second-line drugs and new released drugs.

Efficacy, safety, tolerability and potential sterilizing effect of increased rifampin dosing need to be further explored because promising results from EBA studies are limited to bactericidal activity.

NAT2 influence on pharmacokinetics offers an example of how dosing can be adjusted for different patient genotype and could be extended to *SLCOB1* polymorphisms.

4. Expert opinion

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

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

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

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

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

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

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

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

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

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

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

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

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2

	Rif	Rfb	**Rpt**	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 **deacetylation,** CYP3A	Hepatic **deacetylation**	Acetylation by NAT2	**10-15% hepatic, 50-55% eliminated unchanged**	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_{max}/MIC	AUC/MIC C_{max}/MIC	AUC/MIC C_{max}/MIC	AUC/MIC > C_{max}/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]	

Table 1

Pharmacokinetic and pharmacodinamic properties of currently recommended antitubercular drugs.

(Rif, rifampicin; Rfb, rifabutin; **Rpt**, rifapentine; Inh, isoniazid; Etb, ethambutol; Pza, pyrazinamide; S, streptomycin; AUC, Area Under the Curve; N/A, not assessed)

	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)	**65% excreted unchanged. 35% hepatic**	Hepatic via acetylation	Prodrug; Hepatic	**Hydrolytic dehalogenation, deamination, hydration and glucuronidation**[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_{max}/MIC	AUC/MIC better than C_{max}/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

Table 2

Pharmacokinetic and pharmacodinamic properties of principal second-line antitubercular drugs.

(Lfx, levofloxacin; Mfx, moxifloxacin; Cs, cycloserine; PAS, para-aminosalicylic acid; Eto, ethionamide; Cfz, clofazimine; Lzd, linezolid; AUC, Area Under the Curve; N/A, not assessed)

	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
Metabolism	Hepatic, via CYP3A4	Hepatic	Prodrug; hepatic
Plasma half life [hours]	24-30	30-38	16-20
Parameter best predictive of activity[16]	T/MIC	AUC/MC	T/MIC
Therapeutic range μg/ml	N/A	N/A	N/A

Table 3

Pharmacokinetic and pharmacodinamic properties of novel agents.

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