Tuberculosis and pharmacological interactions: A narrative review

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ABSTRACT

Keywords:  
Tuberculosis  
Drug-drug interactions  
Clinical use  
TB treatment

Even if major improvements in therapeutic regimens and treatment outcomes have been progressively achieved, tuberculosis (TB) remains the leading cause of death from a single infectious microorganism. To improve TB treatment success as well as patients' quality of life, drug-drug-interactions (DDIs) need to be wisely managed. Comprehensive knowledge of anti-TB drugs, pharmacokinetics and pharmacodynamic (PK/PD) parameters, potential patients' changes in absorption and distribution, possible side effects and interactions, is mandatory to built effective anti-TB regimens. Optimization of treatments and adherence to international guidelines can help bend the curve of TB-related mortality and, ultimately, decrease the likelihood of treatment failure and drop-out during anti-TB treatment. Aim of this paper is to describe the most relevant DDIs between anti-TB and other drugs used in daily clinical practice, providing an updated and “easy-to-use” guide to minimize adverse effects, drop-outs and, in the long run, increase treatment success.

1. Introduction

Even if major improvements in therapeutic regimens and treatment outcomes have been progressively achieved, tuberculosis (TB) remains the leading cause of death from a single infectious microorganism (World Health Organization, 2014, 2019). Since the introduction of rifampicin in the 70s’, an effective short-course regimen for drug-susceptible (DS) forms of TB has been saving millions of lives worldwide. A standardized regimen characterized by a 2-month intensive (bactericidal) phase with four drugs [isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z); 2HRZE] and a 4-month continuation (sterilizing) phase with HR is key to achieve microbiological and clinical cure, if taken correctly (World Health Organization, 2014, 2019). However, 10 million individuals are estimated to develop TB annually worldwide and treatment success is hampered by drug-resistant strains of Mycobacterium tuberculosis (Mtbc), comorbidities, scarce adherence to treatment, adverse events of anti-TB drugs, and drug-drug interactions (DDIs) (Villa et al., 2020; Riccardi et al., 2019; Bisson et al., 2020; Soanker et al., 2020). Optimization of treatments and adherence to international guidelines can help bend the curve of TB-related mortality, as well as decrease the likelihood of treatment failure and drop-out during anti-TB treatment (Nahid et al., 2019). New drugs have been added to the anti-TB armamentarium and new DDIs can occur (Berger et al., 2020; Dheda et al., 2019; Riccardi et al., 2018; Bigelow et al., 2020).

Aim of this paper is to describe the most relevant DDIs between anti-TB and other drugs used in daily clinical practice, providing an updated and “easy-to-use” guide to minimize adverse effects, drop-outs and, ultimately, increase treatment success.

2. Methods

For the first-line drugs HRZE and for every TB drugs enlisted in the World Health Organization guidelines for the management of DR-TB (WHO consolidated guidelines, 2019), the following information are described: i) pharmacokinetics and pharmacodynamic (PK/PD) parameters; ii) potential changes in absorption and distribution; ii) most prevalent DDIs; iv) therapeutic drug monitoring (TDM) when available.
2.1. Anti-TB drugs

2.1.1. Rifampicin

Rifampicin, which belongs to the ansamycins and was discovered in 1965 from the soil bacteria *Amycolatopsis rifamycinica* (Sensi, 1983), displays antibacterial activity against Gram-positive cocci and Gram-negative bacteria, as well as against mycobacteria (Rothstein, 2016). It can selectively inhibit the DNA-dependent RNA polymerase both by sterically blocking the path of the elongating RNA at the 5’ end and by decreasing the affinity of the RNA polymerase for short RNA transcripts (Campbell et al., 2001; Schulz and Zillig, 1981).

Rifampicin is an highly lipid-soluble drug with a PK profile that shares equal distribution in plasma and tissues, with a plasmatic half-life ranging between 2 and 5 h it strongly induces human P450 cytochrome oxidases, notably CYP3A4, CYP2A, CYP2B, CYP2C, and CYP3A, as well as the human P glycoprotein ABC transporter, thus leading to a number of remarkable DDIs (Riccardi et al., 2020a) (Table 1).

It is available both in oral (best adsorbed during fasting, avoiding food interactions) or intravenous formulations (Rothstein, 2016; Genbenacher and Kaufmann, 2012).

TDM of rifampicin should be ideally assessed 2 h post dose on empty stomach, with a desirable range of 8–15 mg/L, in order to ensure efficacy and avoid toxicity (Fernandes et al., 2017).

2.1.2. Isoniazid

Isoniazid, firstly discovered in 1920 and used as antimycobacterial compound in the 1950s, displays mycobactericidal action against replicating mycobacteria, whereas it is bacteriostatic against mycobacteria in the latent form (Harvey et al., 2006; Timmins and Deretic, 2006). Its efficacy relies on the destruction of the mycobacterial cell wall, acting as a produg activated by the mycobacterial enzyme KatG and generating reactive oxygen species (ROS) that interfere with the mycobacterial cell wall (Timmins and Deretic, 2006; Stehr et al., 2015).

Isoniazid can be administered orally, intramuscularly, or intravenously; it is promptly absorbed after oral administration and reaches the peak of serum concentrations after 0.5–2 h (Timmins and Deretic, 2006).

Isoniazid inhibits the cytochrome P450 system and i acts as a mild monoamine oxidase inhibitor (MAO-I) (Stehr et al., 2015) (Table 2).

TDM should be assessed 2 h post dose on empty stomach, with a desirable range of 3–6 mg/L (Fernandes et al., 2017).

2.1.3. Pyrazinamide

Pyrazinamide is a nicotinamide analog included in the anti-TB regimen in 1970 and characterized by sterilizing activity and efficacy against semi-dormant MTB strains. Moreover, it displays synergistic activity when added to rifampicin-containing regimens (Gopal et al., 2019; Jimenez del Cerro and Rivera Hernandez, 1992). In fact, it penetrates necrotic caseous tissue, where it is converted to the active form pyrazinoyl acid, killing non-growing, drug-tolerant tubercle bacilli through the inhibition of the coenzyme A biosynthesis (Jimenez del Cerro and Rivera Hernandez, 1992).

Pyrazinamide displays excellent oral absorption, without any food interferences (Jimenez del Cerro and Rivera Hernandez, 1992). It can increase blood ureic acid level, leading to acute gout. Liver is probably involved in its katabolism.

Concomitant administration of pyrazinamide with isoniazid and/or rifampicin is associated with an increased risk of hepatotoxicity due to an additive effect. Careful assessment is needed when it is prescribed with potentially hepatotoxic agents (e.g., pexidartinib, pretomanid, mipomersen).

A unique case of cyclosporine plasmatic level reduction after pyrazinamide association was reported (Peets et al., 1965).

TDM should be ideally assessed 2 h post dose on empty stomach, with a desirable range of 20–60 mg/L (Fernandes et al., 2017).

2.1.4. Ethambutol

Ethambutol, which was discovered in 1961, is a bacteriostatic against actively growing mycobacterial bacilli: it inhibits the enzymes arabinosyltransferases involved in the synthesis of mycobacterial cell wall (Lee and Nguyen, 2020).

Ethambutol can be administered orally or intravenously and is promptly absorbed after oral administration, reaching the peak of serum concentrations after 2 h (Lee and Nguyen, 2020); it undergoes partial hepatic metabolism.

Coadministration with aluminium salts should be avoided because it delays and reduces the absorption of ethambutol (Riccardi et al., 2020b). Other drugs potentially causing optic neuritis should be avoided (Riccardi et al., 2020b).

TDM should be ideally assessed between 2 and 6 h post dose on full or empty stomach, with a desirable range of 20–60 mg/L (Fernandes et al., 2017).

2.1.5. Linezolid

Linezolid is a synthetic oxazolidinone with bacteriostatic activity against mycobacteria and Gram-positive bacteria (Dryden, 2011). It binds to the 50S subunit of the prokaryotic ribosome, preventing formation of the initiation complex and inhibiting protein synthesis (Quinn and Stern, 2009). Linezolid, which is available both intravenously and orally with excellent bioavailability (fatty food can decrease its absorption) (Dryden, 2011), is metabolized to two inactive metabolites, an aminooxyacetic acid (metabolite A) and a hydroxethyl glycine (metabolite B), with a plasmatic elimination half-life of 3.4–7.4 h (Quinn and Stern, 2009). It is a reversible inhibitor of monoamine oxidases A and B and serotonin agonists should be carefully prescribed to avoid the occurrence of the serotonin syndrome (Ziganshina et al., 2013) (Table 3).

TDM of linezolid should be ideally assessed immediately before the administration, with a desirable range of 2–7 mg/L (Fernandes et al., 2017).

2.1.6. Fluoroquinolones (Levofoxacin and Moxifloxacin)

Fluoroquinolones, which can inhibit the DNA gyrase responsible for supercoiling of nucleic acid, show a broad-spectrum antimicrobial activity (Reynolds et al., 1996). Levofoxacin and moxifloxacin are recommended by the WHO for the treatment of multi-drug resistant (MDR)-TB (WHO consolidated guidelines, 2019). Moxifloxacin is available both orally and intravenously, whereas moxifloxacin can be administered only orally. Their prescription with or without other drugs was associated with the risk of cardiac arrhythmias, fungal or bacterial infections, psychosis, and convulsions (Gler et al., 2012) (Table 4).

TDM should be ideally assessed 2 h after their administration on full or empty stomach, with a desirable range of 8–12 mg/L and 3–5 mg/L for levofoxacin and moxifloxacin, respectively (Fernandes et al., 2017).

2.1.7. Delamanid

Delamanid is a dihydro-nitroimidazooxazole with early bactericidal activity for patients aged ≥3 years (WHO consolidated guidelines, 2019; Gupta et al., 2016; Gupta et al., 2015; Matsumoto et al., 2006). It was recently approved for the treatment of MDR-TB.

The pro-drug is activated by a deazaflavin dependent nitro-reductase into a metabolite which blocks the cell wall synthesis of methoxymycolic and ketomycolic acids, two components of mycobacterial (European Medicines Agency, 2014).

Delamanid administered orally has a three-fold increased bioavailability intake a high-fat meal (Diacon et al., 2011). Its maximum plasmatic concentration is reached 4–5 h after oral administration, its half-life lasts 38 h, with a steady-state achieved after 10–14 days (Paccaly et al., 2012).

Being a CYP3A4 substrate, its level is strongly reduced in case of co-administration with strong CYP3A4 enzyme inducers (e.g., rifampicin).
## Table 1

Most common rifampicin DDIs.

| Class of drug | Drug | Mediated protein or mechanism | Rifampicin PL | Drug PL | Other effects | References |
|---------------|------|--------------------------------|---------------|---------|---------------|------------|
| Analgesics    | Methadone | CYP3A4; CYP2B6; CYP2C9; CYP2C19; CYP2C9 | ↓ | | overdose if inducer discontinuation | Kreek et al. (1976) |
|               | Morphine   | CYP3A4; hepatic metabolism induction | | | | Fromm et al. (1997) |
|               | Oxycodone, fentanyl, codeine | CYP3A4 | | | | |
| Anesthetics   | Alfentanil | CYP3A4 | ↓ | | hepatotoxicity, hepatic encephalopathy | Most and Markle (1974) |
|               | Halothane  | | | | | |
| Antacids      | Aluminum hydroxy/magnesium hydroxide | | | | increased gastric pH; chelation | |
| Anti-arrhythmics | Amiodarone | CYP3A4 | ↓ | | severe coagulation disorders | Zarembski et al. (1999) |
|               | Disopyramide | – | | | | Aitio et al. (1981) |
|               | Propafenone | CYP3A4 | | | | |
| Antibiotics   | Quinidine  | CYP3A4 | ↑ | | | |
|               | Clarithromycin | CYP3A4 | ↓ | | | |
|               | Clindamycin | CYP3A4 | ↓ | | | |
|               | Cefazolin, other cephalosporins | | | | hepatic metabolism induction | |
|               | Chloramphenicol | CYP3A4 | ↓ | | | |
|               | Dapsone    | CYP3A4; CYP2C9; CYP2C19; P glycoprotein | ↓ | | | |
|               | Doxycycline | CYP3A4; CYP2E1 | | | | |
|               | Linezolid  | P glycoprotein | | | | |
|               | Moxifloxacin | | | | glucuronidation; sulphation; P glycoprotein | |
| Anticoagulants | Warfarin   | CYP3A4 | ↓ | | | Cann (1996) |
|               | Dabigatran | P glycoprotein | | | | Product Information. Pradaxa (dabigatran). |
|               | Apixaban   | CYP3A4; P glycoprotein | | | | Product Information. Eliquis (apixaban) |
|               | Rivaroxaban | CYP3A4 | | | | Product Information. Xarelto (rivaroxaban) |
|               | Edoxaban   | P glycoprotein | | | | Product Information. Savaysa (edoxaban) |
| Anticonvulsants | Phenytoin  | CYP2C9; CYP2C19 | ↑ | | | |
|               | Lamotrigine | glucuronidation | | | | |
| Antidepressants | Nortriptyline, amitriptyline | CYP450 | | | | Bechchuk and Stewart (1991) |
| Anti-diabetics | Chlorpropamide | CYP450 | | | | |
|               | Rosiglitazone | CYP2C8 | | | | Niemi et al. (2004) |
| Antiepileptics | Ondansetron | CYP3A4; CYP1A2 | | | | Villikka et al. (1999) |
| Antifungals   | Caspofungin | – | | | | |
|               | Fluconazole | CYP450 | | | | |
|               | Itraconazole, ketoconazole | CYP3A4 | ↑ | | | |
|               | Posaconazole | CYP3A4; P glycoprotein; UGT1A1 | ↑ | | | |
| Anthelmintics | Praziquantel | CYP450 | | | | Banerji et al. (2019); Ebert et al. (2000) |
| Antimalarials | Atovaquone | rifampicin enzyme-induction | | | | |
|               | Quinine    | CYP3A4 | ↓ | | | |
| Antipsychotics | Haloperidol | CYP3A4 | ↓ | | | |
| Antituberculars | Isoniazid | additive hepatotoxicity | | | | Aocella et al. (1972) |
|               | Pyrazinamide | effect | | | | MeNeill et al. (2005); CDC (2001) |
|               | Delamanid  | CYP3A4 | ↑ | | | |
| Antivirals HCV | Daclatasvir, simeprevir, sofosbuvir, ledipasvir | CYP3A4; P glycoprotein | ↓ | | | |
| Anxiolytics/hypnotics | Zolpidem | CYP3A4; CYP1A2 | | | | |
|               | Dizepam, triazolam | hepatic metabolism induction | | | | |
| Bronchodilators | Theophylline | CYP3A4; CYP1A2 | ↓ | | | |
| Cancer therapies | Cyclophosphamide | | | | | |

(continued on next page)
Lopinavir/ritonavir increase plasmatic levels of delamanid and, then, the risk of toxicity (Riccardi et al., 2020c). It was recommended caution when prescribed with clofazimine (Yadav et al., 2016).

The risk of QTc prolongation is increased when administered with fluoroquinolones and in hypoalbuminemic patients. Currently, no standardized TDM range has been proposed.

2.1.8. Clofazimine

Clofazimine is a hydrophobic riminophenazine which presumably interferes with the mycobacterial respiratory chain and ion transporters (Riccardi et al., 2020c).

It is prescribed for non-tuberculous mycobacteria-related diseases, TB, and leprosy; its oral bioavailability is ~70%, improved by food for an

Table 1 (continued)

| Class of drug | Drug | Mediated protein or mechanism | Rifampicin PL | Drug PL | Other effects | References |
|---------------|------|-------------------------------|--------------|--------|--------------|------------|
| Lipid lowering drugs | | | | | | |
| Isoniazid | | | | | | |
| Antidepressants | Desipramine | | | | | |
| Anticonvulsants | Valproate | | | | | |
| Antidiabetics | Glimepiride | | | | | |
| Antituberculars | Rifampicin | | | | | |
| Recreational drugs | Theophylline | | | | | |
| | Alcohol antagonists | Dusion | dopamine metabolism inhibition | CYP3A4; CYP2B6; CYP2C9 | | | |
| | Acetaminophen | Acetaminophen | CYP2E1 | | | |
| | Anticonvulsants | Valproate | CYP3A4 | | | |
| | Antidiabetics | Glimepiride | | | | |
| | Antituberculars | Rifampicin | | | | |
| | Alcohol | Theophylline | CYP3A4; CYP1A2 | | | |

Abbreviations: DDI, drug-drug interactions; PL, plasmatic level; SOT, solid organ transplantation; NNRTI, Non-nucleoside reverse transcriptase inhibitors; PI, Protease inhibitors.

Lopinavir/ritonavir increase plasmatic levels of delamanid and, then, the risk of toxicity (Riccardi et al., 2020c). It was recommended caution when prescribed with clofazimine (Yadav et al., 2016).

The risk of QTc prolongation is increased when administered with fluoroquinolones and in hypoalbuminemic patients. Currently, no standardized TDM range has been proposed.

Table 2

| Class of drug | Drug | Mediated protein or mechanism | Isoniazid PL | Drug PL | Other effects | References |
|---------------|------|-------------------------------|--------------|--------|--------------|------------|
| Alcohol antagonists | Dusion | dopamine metabolism inhibition | CYP3A4; CYP2B6; CYP2C9 | | | |
| Acetaminophen | Acetaminophen | CYP2E1 | | | | |
| Anticonvulsants | Valproate | CYP3A4 | | | | |
| Antidiabetics | Glimepiride | | | | | |
| Antituberculars | Rifampicin | | | | | |
| Alcohol | Theophylline | | | | | |

Abbreviations: DDI, drug-drug interactions; PL, plasmatic level; NNRTI, Non-nucleoside reverse transcriptase inhibitors; PI, Protease inhibitors.
### Table 3

**Most common linezolid DDIs.**

| Class of drug | Drug | Mediated protein or mechanism | Linezolid PL | Drug PL | Other effects | References |
|---------------|------|--------------------------------|--------------|---------|---------------|------------|
| Adrenergic agents | Pseudoephedrine | ↑ sympathomimetic effect | systolic hypertension | Hendershot PE, 2001 |
| northern agents | Phenylpropanolamine |  |  |  |  |  |
| Antibiotics/ antituberculars | Rifampin | P glycoprotein | ↓ | Trittler R, 2005; Egle H, 2005; Gebhart BC, 2007; Gandelman K, 2011 |
| Anticoagulants | Warfarin | MAO inhibitor | low grade ↓ INR seratonin syndrome | Saka Y, 2015; Boyer EW, 2005 |
| SSRI | Paroxetine |  |  |  |  |  |
| SSRI | Fluvoxamine |  |  |  |  |  |
| SSRI | Fluoxetine |  |  |  |  |  |
| SSRI | Citalopram |  |  |  |  |  |
| SSRI | Fluoxetine |  |  |  |  |  |
| SSRI | Sertraline |  |  |  |  |  |
| SSRI | Escitalopram |  |  |  |  |  |
| SSRI | Vilazodone |  |  |  |  |  |
| SNRI | Venlafaxine, desvelafaxina |  |  |  |  |  |
| SNRI Anti-Parkinson | Duloxetine | MAO inhibitor | serotonin syndrome | Boyer EW, 2005; FDA Drug Safety Communication, 2011 |
| Morphine derivatives | Dextromethorphan | ↑ sympathomimetic effect | serotonin syndrome | Hendershot PE, 2001 |
| Opioid analgesics | Meperidine |  |  |  |  |  |
| Fentanyl |  |  |  |  |  |  |

Abbreviations: DDI, drug-drug interactions; PL, plasmatic level; SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin and Norepinephrine Reuptake Inhibitor; MAOi, monoamine oxidase inhibitor.

### Table 4

**Most common antitubercular fluoroquinolones DDIs.**

| Class of drug | Drug | Mediated protein or mechanism | Levo/moxi PL | Drug PL | Other effects | References |
|---------------|------|--------------------------------|--------------|---------|---------------|------------|
| Antacids | Aluminum/magnesium/ calcium salts | chelation | ↓ |  |  | (Nix et al., 1990) |
| | Sucrallate |  |  |  |  |  | (Lehto et al., 1994) |
| Anti-arrhythmics | Quinidine, procainamide (IA class) | ↑ QT interval | rare: arrhythmias, torsade de pointes | (Owens, 2001) |
| | Amiodarone, sotalole (III class) |  | rare: arrhythmias, torsade de pointes | (Owens, 2001) |
| Antibiotics/ antituberculars | Rifampin | glucuronidation; sulphation ↓ moxifloxacin | ↑ INR | (Nijland et al., 2007) |
| Anticoagulants | Warfarin | metabolism inhibition; vitamin K-producing intestinal bacteria inhibition | ↑ | Jones CB, 2002 |
| Anti-diabetes | Insulin | ATP-sensitive K channels | ↑ glycemia | Gajjar DA, 2000 |
| | Oral hypoglycemics |  | ↑ glycemia | Gajjar DA, 2000 |
| Bronchodilators | Theophylline | GABA? | SNC toxicity | Segev S, 1988 |
| | Bepridil | ↑ QT interval | rare: arrhythmias, torsade de pointes | Segev S, 1988 |
| Calcium channel blockers | Osimertinib | ↑ QT interval | rare: arrhythmias, torsade de pointes | Bian S, 2020 |
| Cancer therapies |  |  |  |  |  |  |
| Immunosuppressants | Cyclosporine | low grade ↓ hepatic metabolism | ↑ | Federico S, 2006 |
| | Tacrolimus |  |  |  |  | Federico S, 2006 |
| | Diclofenac, others | GABA? | ↑ | CNS toxicity | Seguev S, 1988 |
| NSAIDs | Fenbufen |  | ↑ | CNS toxicity | Seguev S, 1988 |
| Retrovirals | Didanosine | chelation (AI or Mg-containing formulations) | ↓ | Sahai J, 1993 |
| Supplements | Calcium supplements | chelation | ↓ |  |  |  |
| | Iron supplements |  |  |  |  |  |
| | Zinc supplements |  |  |  |  |  |
| Others | Cimetidine | low grade ↓ tubular secretion | ↑ |  |  |  |
| | Probenecid |  |  |  |  |  |
| | Vegetable charcoal | oral moxifloxacin ↓ absorption | ↓ |  |  |  |

Abbreviations: DDI, drug-drug interactions; PL, plasmatic level; Levo, levo moxifloxacin; Moxi, moxifloxacin; NSAIDs, Nonsteroidal anti-inflammatory drugs; SOT, solid organ transplantation; CNS, central nervous system; GABA, gamma-aminobutyric acid receptors.
increased absorption (Riccardi et al., 2020c).

Clofazimine can inhibit CYP3A4 in vitro, but also can weakly induce CYP3A4 (Riccardi et al., 2020c). It can prolong QTc interval and impair the liver function (Riccardi et al., 2020c).

TDM should be assessed 2 h after its administration on full or empty stomach, with a desirable range of 0.5–4 mg/L (Fernandes et al., 2017).

2.1.9. Bedaquiline

Bedaquiline is an oral diarylquinoline, approved for pulmonary MDR-TB in adults (Yadav et al., 2016; Andries et al., 2014). It blocks the proton pump (specifically, subunit c) for mycobacterial ATP synthase, critically reducing ATP level and, then, causing cell death (Hartkoorn et al., 2014). Synthesis of subunit c is encoded by the atpE gene and its mutation in Mycobacterium tuberculosis is directly associated to poor drug susceptibility (Centers for Disease Control). Furthermore, mutations of the drug genome sequencing (WGS) for bedaquiline should be performed to assess the susceptibility of the collected strains (Alffaenar et al., 2015). DDIs have been observed between bedaquiline and CYP3A4 inducers and inhibitors (Table 5). Bedaquiline can cause QT prolongation, leading to cardiac arrhythmia and/or death. Hence, patients should be monitored for symptoms of cardiac toxicity and by electrocardiogram during the follow-up. It should be interrupted in case of clinically significant ventricular arrhythmia or QTc >500 ms (Nguyen et al., 2018). Ongoing studies are evaluating the most accurate TDM values (Nguyen et al., 2018; Bolhuis et al., 2016).

2.1.10. Cycloserine/Terizidone

Cycloserine, which is similar to the amino acid D-alanine, can interrupt the inclusion of the D-alanine into the peptidoglycan of the cell wall (Cycloserine, 2008; http://www.tbdrugmonograph). It has an oral bioavailability when not administered with a high fat meal (http://www.tbdrugmonograph). It can show central nervous system (CNS) toxicity (careful administration in case of alcohol exposure, history of seizure, depression, suicidal behaviours, and mood instability) and can interfere with the absorption of isoniazid (http://www.tbdrugmonograph). Cycloserine should be used with extreme caution in patients with renal impairment and avoided when creatinine clearance of <50 ml/min (http://www.tbdrugmonograph). Terizidone, which is composed by two molecules of cycloserine, shares the same pharmacological features of cycloserine, but it can be administered in patients with a creatinine clearance <50 ml/min and in patients in dialysis with an appropriate dose adjustment (http://www.tbdrugmonograph). Terizidone also penetrates less in CNS being therefore more tolerable.

2.1.11. Meropenem/imipenem-cilastatin

Meropenem and imipenem-cilastatin are broad-spectrum carbapenems used with clavulanic acid in the treatment of MDR-TB. Meropenem with clavulanic acid has bactericidal activity and can sterile cultures within 2 weeks inhibiting the BiaC beta-lactamase (De Lorenzo et al., 2013). They are administered intravenously and may have neuro-toxicity (caution in patients with TB meningitis and when coadministered with ganciclovir and valproic acid). Renal function should be periodically checked due to their renal excretion (De Lorenzo et al., 2013).

TDM of meropenem has a desirable range of 8–12 mg/L (Fernandes et al., 2017).

2.1.12. Amikacin

The aminoglycoside amikacin can inhibit mycobacteria, Gram-negative bacteria, Nocardia spp., and Staphylococcus aureus, by blocking the 30S ribosomal subunit with the modification of the conformation of the A site, reducing proofreading capabilities of the ribosome and thus increasing mistranslation (Ramirez and Tolmasky, 2017).

It is mainly administered intravenously, intramuscularly, through nebulization, but it can be administered intrathecally or intraventricularly (Ramirez and Tolmasky, 2017). It shows a renal excretion, and can increase the risk of ototoxicity and nephrotoxicity, especially in case of long-term exposure. TDM can reduce the risk of adverse events (Ramirez and Tolmasky, 2017). DDIs can be relevant with other drugs associated with oto- and nephron-toxicity (e.g., diuretics, cephalosporins, ciclosporin, colistimethate sodium, and tacrolimus). There is increased risk of hypocalcaemia when prescribed with bisphosphonates.

TDM should be < 5 mg/L (trough, immediately before infusion) and 25–35 mg/L (peak, 1 h after intravenous administration) (http://www.tbdrugmonograph).

2.1.13. Ethionamide/Prothionamide

Ethionamide, which was discovered in 1959, is a prodrug undergoing hepatic metabolism. Its efficacy was proved for M. tuberculosis, M. bovis, M. Laepre, M. Avium, and M. smegmatis (Ethionamide, 2008; http://www.tbdrugmonograph). It disrupts the mycobacterial cell wall through the inhibition of the inhA gene product enoyl-ACP reductase. Ethionamide is available orally and can be administered both with and without food (Ethionamide, 2008). Neurotoxicity is linked to increased blood level of ethionamide. Alcohol exposure can favour psychotropic reactions. Prothionamide is a thioamide interchangeable with ethionamide (http://www.tbdrugmonograph).

It should be administered with caution in patients with liver failure. Moreover, it is structurally similar to methimazole and, then, thyroid function should be routinely checked to avoid the occurrence of hypothyroidism (http://www.tbdrugmonograph). In diabetic patients glucose blood level should be monitored for the risk of hypoglycaemia (http://www.tbdrugmonograph).

2.1.14. P-aminosalicylic acid (PAS)

PAS, discovered in 1944, is available in an oral formulation; it should be administered with acid food to increase its absorption (Abulfathi et al., 2020).

DDIs with dichlorphenamide may lead to increased levels of PAS by unknown mechanism. PAS may decrease blood level of rifampicin. Moreover, PAS decreases effects of benazepril by pharmacodynamic antagonism and increases adverse events of dapsone.

3. Discussion

The ambitious WHO goal of TB elimination can be achieved if a comprehensive strategy is implemented. The WHO TB Strategy, approved by the World Health Assembly in 2014, is built on three pillars (World Health Organization, 2014).

One of them, which can be found in the previous WHO strategy, is based on the improvement of the clinical management of individuals infected by Mycobacterium tuberculosis strains (World Health Organization, 2014).

The mismanagement of patients with TB disease can be associated to a poor prognosis, increased risk of transmission of Mtb to susceptible individuals, and emergence (and spread) of drug-resistant strains (Bisson et al., 2020; Nahid et al., 2019; Dheda et al., 2019).

The successful outcome of the TB patients depends on patient- and healthcare-related factors. The appropriate prescription of effective and safe drugs is the outcome of several variables: adherence to scientifically sound treatment guidelines, availability of quality-assured drugs, accurate assessment of the drug susceptibility testing for the collected Mtb isolates, and adequate follow-up (which depends on the efficiency of the national and regional healthcare infrastructure and of the national TB program).

However, patient's adherence to the prescribed regimens is key, especially for individuals infected by MDR MTB strains, where the duration of the therapy is longer (~24 months) and characterized by a high risk of drug-related adverse events (the currently available
| Class of drug  | Drug                                   | Mediated protein or mechanism | Bedaquiline PL | Other drug PL | Other effects | References |
|---------------|----------------------------------------|------------------------------|----------------|---------------|---------------|------------|
| Antidepressant| citalopram                             | QTc prolongation             |                |               |               |            |
|               | escitalopram                           |                              |                |               |               |            |
| Antibiotic    | clarithromycin                         | QTc prolongation             |                |               |               |            |
|               | azithromycin                           |                              |                |               |               |            |
|               | levofloxacin                           |                              |                |               |               |            |
|               | moxifloxacin                           |                              |                |               |               |            |
|               | lefamulin                              |                              |                |               |               |            |
| Antiparasitic | fexinidazole                           |QTc prolongation             |                |               |               |            |
|               | piperazine                             |                              |                |               |               |            |
|               | chloroquine                            |                              |                |               |               |            |
|               | halofantrine                           |                              |                |               |               |            |
|               | pentamidine                            |                              |                |               |               |            |
| Antifungal    | posaconazole                           |QTc prolongation, inhibition of CYP3A4↑ |                |               |               |            |
|               | voriconazole                           |QTc prolongation, inhibition of CYP3A4↑ |                |               |               |            |
|               | fluconazole                            |QTc prolongation, inhibition of CYP3A4↑ |                |               |               |            |
|               | itraconazole                           | inhibition of CYP3A4↑         |                |               |               |            |
| Antipsychotic | thioridazine                           |QTc prolongation             |                |               |               |            |
|               | flupentixol                             |                              |                |               |               |            |
|               | pimozide                               |                              |                |               |               |            |
|               | amitriptyline                           |                              |                |               |               |            |
|               | clomipramide                           |                              |                |               |               |            |
|               | alopauridine                           |                              |                |               |               |            |
|               | droperidol                             |                              |                |               |               |            |
|               | olanzapine                             |                              |                |               |               |            |
|               | risperidone                            |QTc prolongation             |                |               |               |            |
| Cancer drugs  | nilotinib                              |QTc prolongation             |                |               |               |            |
|               | entrectinib                            |                              |                |               |               |            |
|               | ribociclib                             |                              |                |               |               |            |
|               | vemurafenib                            |                              |                |               |               |            |
|               | dacarboxil                              |                              |                |               |               |            |
|               | encorafenib                            |                              |                |               |               |            |
|               | enzalutamid                             |                              |                |               |               |            |
|               | gilteritinib                            |                              |                |               |               |            |
|               | midostaurin                             |                              |                |               |               |            |
|               | mitotane                               |                              |                |               |               |            |
|               | osimertinib                             |QTc prolongation, induction of CYP3A4↓ |                |               |               |            |
|               | toremilene                             | induction of CYP3A4↓          |                |               |               |            |
|               | dabrafenib                             |QTc prolongation, induction of CYP3A4↓ |                |               |               |            |
|               | lorlatinib                             | induction of CYP3A4↓          |                |               |               |            |
|               | pexidartinib                           |QTc prolongation             |                |               |               |            |
| Procyntetic/antiemetic | domperidon                           |QTc prolongation             |                |               |               |            |
|               | ondansetron                             |                              |                |               |               |            |
| Anti-hyperlipidemic | probucol                           |QTc prolongation             |                |               |               |            |
| Anti-arrhythmics | amiodarone                             |QTc prolongation             |                |               |               |            |
|               | dronedarone                            |                              |                |               |               |            |
|               | flecainide                             |                              |                |               |               |            |
|               | pilsicainide                           |                              |                |               |               |            |
|               | propafenone                            |                              |                |               |               |            |
|               | dofetilide                             |                              |                |               |               |            |
|               | sotalol                                |QTc prolongation             |                |               |               |            |
| Antihistamine | astemizole                             |QTc prolongation             |                |               |               |            |
| Antituberculars | clofazimine                            |QTc prolongation             |                |               |               |            |
|               | demetalid                              |                              |                |               |               |            |
|               | rifampicin                             |induction of CYP3A4↓         |                |               |               | Svensson 2015 |
|               | rifabutine                             |induction of CYP3A4↓         |                |               |               |            |
|               | rifapentine                            |induction of CYP3A4↓         |                |               |               |            |
| Antihypertensive | lofexidine                            |QTc prolongation             |                |               |               |            |
| Antiretroviral | lopinavir                              |QTc prolongation             |                |               |               |            |
|               | atazanavir                             |QTc prolongation             |                |               |               |            |
|               | darunavir                              |QTc prolongation             |                |               |               |            |
|               | cobicistat                             |QTc prolongation             |                |               |               |            |
|               | ritonavir                              |QTc prolongation             |                |               |               |            |
|               | efavirenz                              |QTc prolongation             |                |               |               |            |
|               | etravirien                             |QTc prolongation             |                |               |               | (Pandie et al., 2016) |
| Analgesic | methadone                              |QTc prolongation             |                |               |               |            |
| Pulmonary hypertension drug | bosentan                              |induction of CYP3A4↓         |                |               |               |            |
| Antiepileptic | cenobamate                            |induction of CYP3A4↓         |                |               |               |            |
|               | carbamazepine                          |induction of CYP3A4↓         |                |               |               |            |
|               | phenobarbital                          |induction of CYP3A4↓         |                |               |               |            |
|               | phenytoin                              |induction of CYP3A4↓         |                |               |               |            |
| Antivirals anti-HCV | ombitasvir                            |inhibition of CYP3A4↑         |                |               |               |            |
|               | paritaprevir                           |inhibition of CYP3A4↑         |                |               |               |            |
|               | dasabuvir                              |inhibition of CYP3A4↑         |                |               |               |            |

Abbreviations: DDI, drug-drug interactions; PL, plasmatic level.
therapeutic armamentarium is less effective, less safe, and more expensive if compared with that adopted for drug-susceptible TB (Nahid et al., 2019; Dheda et al., 2019).

The poor adherence and the risk of adverse events depend on the anti-TB drugs themselves and on their pharmacological interactions with other concomitant therapeutics.

Then, the clinical success inevitably passes through the prevention of DDIs and drug-adverse events to improve TB treatment adherence and, ultimately, the WHO outcome treatment success. Careful evaluation of possible DDIs before creating an anti-TB regimen is a key moment to ensure efficacy, safety, and ameliorate patients’ quality of life (19,57).

Up-to-date knowledge of anti-TB drugs PK/PD parameters coupled with TDM are helpful tools to guide physicians to tailored and effective treatments.

The aim of the present article was to give a concise summary that can aid physicians in their daily clinical practice.

However, several potential interactions are unknown because of some of them occurred in countries where an effective pharma-co-vigilance system is not in place. The low TB incidence countries characterized by a lower treatment prescription rate cannot assess some interactions which can occur where more TB patients are treated.

Furthermore, the evolving drug market has a marginal impact in low income countries where TB incidence is high. The combination of those epidemiological conditions does not help identifying the full pharmacological profile of the anti-TB drugs.

More information can be retrieved from the HIV/AIDS-related evidence: major efforts have been performed since the 90’s to better describe the characteristics of the anti-HIV drugs (Bisson et al., 2020).

The high incidence of TB/HIV co-infection has favoured the study of DDIs occurrence of DDIs-related adverse events should be kept into careful strength and the efficacy of the health-care system. In theory, those DDIs and drug-adverse events to improve TB treatment adherence and, ultimately, the WHO outcome treatment success. Careful evaluation of anti-TB drugs PK/PD parameters coupled with TDM are helpful tools to guide physicians to tailored and effective treatments.

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CRediT authorship contribution statement

Niccolò Riccardi: Conceptualization, Validation, Writing - original draft, Writing - review & editing. Diana Canetti: Data curation, Methodology, Validation, Writing - original draft, Writing - review & editing. Paolo Rodari: Data curation, Methodology, Validation, Writing - original draft, Writing - review & editing. Giorgio Besozzi: Validation, Writing - review & editing. Laura Saderi: Data curation, Methodology, Validation, Writing - review & editing. Marco Dettori: Validation, Writing - original draft, Writing - review & editing. Luigi R. Codecasa: Supervision, Validation, Writing - review & editing. Giovanni Sotgiu: Conceptualization, Project administration, Supervision, Validation, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supervision, Validation, Writing - review & editing. Giovanni Sotgiu: Conceptualization, Project administration, Supervision, Validation, Writing - review & editing.

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