Supplementary table S1

Antituberculosis drugs used for MDR-TB and lopinavir/ritonavir: a summary of evidence for drug-drug interactions

Disposition of antituberculosis drugs (*WHO classification*)	**Potential for drug-drug interactions (DDIs) with lopinavir and ritonavir**
Ofloxacin, levofloxacin *(fluoroquinolones, group A)* • Protein binding is concentration-independent and roughly 25%(1, 2). • Primarily excreted unchanged in the urine, with <5% metabolized in the liver(3).	***Ofloxacin, levofloxacin*** No studies in adults or children; DDIs unlikely
Moxifloxacin *(fluoroquinolones, group A)* • Protein binding 25-50%(1, 4). • Multiple routes of elimination; 50% undergoing glucuronide and sulphate conjugation in the liver, 25% excreted unchanged in the faeces, and 20-25% excreted unchanged in the urine(5–8). • Moxifloxacin is not metabolized by the cytochrome P450 system and is not known to inhibit CYP450 enzymes(6). • Moxifloxacin is subject to p-glycoprotein-mediated active transport(9).	***Moxifloxacin*** Possible – through p-glycoprotein mediated active transport. Inhibition and induction of p-glycoprotein have been reported as possible causes of DDIs in general(10, 11). Lopinavir and ritonavir are substrates of p-glycoprotein and both can inhibit p-glycoprotein(12, 13). No studies in adults or children.

Disposition of antituberculosis drugs (*WHO classification*)	**Potential for drug-drug interactions (DDIs) with lopinavir and ritonavir**
Aminoglycoside: amikacin and capreomycin *(core second-line agent, group B)* • >99% of aminoglycosides are excreted unchanged by the kidney, with age-related changes in renal clearance being important in pediatric pharmacokinetics(14).	***Aminoglycoside: amikacin and capreomycin*** No studies in adults and children; DDIs unlikely
Ethionamide *(core second-line agent, group C)* • Protein binding is approximately 30%(15). • A very small proportion of the drug is excreted unchanged, and the first step in thioamide metabolism in the liver is transformation to the active sulfoxide metabolites by monooxygenases. These monooxygenases have many properties in common with the cytochrome P450 system (CYP P450) and often have overlapping substrate specificities(16).	***Ethionamide*** Possible – through CYP450 involvement No studies have been conducted in adults or children.
Terizidone *(core second-line agent, group C)* • Primarily excreted unchanged in urine(17). Data is limited regarding the pharmacokinetics of terizidone/cycloserine.	***Terizidone*** Interactions are unpredictable

Disposition of antituberculosis drugs (*WHO classification*)	**Potential for drug-drug interactions (DDIs) with lopinavir and ritonavir**
Clofazimine *(core second-line agent, group C)* • Multiple metabolites have been identified(18, 19). The drug is mainly eliminated in the faeces, and after cessation of treatment the drug is slowly released from tissue into serum and then eliminated(20). • Clofazimine is a weak inhibitor of CYP3A4(21).	***Clofazimine*** Possible – through CYP3A4 inhibition. No studies have been conducted in adults or children.
Linezolid *(core second-line agent, group C)* • Protein binding is reported to be 31%. • Linezolid has a complex metabolism with two primary and multiple minor metabolites, mediated by a non-enzymatic chemical oxidation mechanism. The primary route of elimination is non-renal, accounting for roughly 65%(22, 23). • Linezolid does not appear to be metabolized via cytochrome P-450, nor is it an inducer or inhibitor of this enzyme system(23, 24). • It is a substrate of p-glycoprotein(25, 26). • Linezolid is also a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents(27).	***Linezolid*** Possible – through p-glycoprotein mediated active transport. Inhibition and induction of P-glycoprotein have been reported as possible causes of drug–drug interactions in general(10, 11). Ritonavir and lopinavir are substrates of p-glycoprotein and both can inhibit p-glycoprotein(12, 13). No studies have been performed in adults or children.

Disposition of antituberculosis drugs (*WHO classification*)	**Potential for drug-drug interactions (DDIs) with lopinavir and ritonavir**
High-dose Isoniazid *(add on agent, group D)* • Low protein binding(28, 29). • Isoniazid is predominantly metabolized (50-90%) in the liver and intestines, via N-acetylation of its hydrazine functionality by arylamine N-acetyltransferase 2 (NAT2) to N-acetyl-isoniazid(28). • Isoniazid potentially inhibits CYP2C19 and CYP3A4 in a concentration dependent manner(30).	***High-dose Isoniazid*** Possible – Isoniazid can potentially inhibit CYP2C19 and CYP3A4, which might decrease lopinavir metabolism and increase lopinavir concentrations. Lopinavir being a substrate of CYP3A4. Isoniazid preventive therapy, given at 5 mg/kg, increased the median lopinavir area under the time-concentration curve (AUC) at steady state by 5% (122.9 vs. 141.1 h·mg/L,) in a study of 16 adults, but this was not statistically significant (p=0.41)(31).No studies have been performed in children, specifically for high-dose isoniazid.

Disposition of antituberculosis drugs (*WHO classification*)	**Potential for drug-drug interactions (DDIs) with lopinavir and ritonavir**
Para-amino salisylic acid (PAS) *(add on agent, group D)* • Approximately 50-70% protein bound(32). • Roughly 70% of absorbed PAS is acetylated to N-acetyl-p-aminosalicylate (APAS) by N-acetyltransferase-1 (NAT-1), with 25% conjugated with glycine to form p-aminosalicyluric acid (PAA)(33). There is considerable metabolism in the gut and liver resulting in a large first pass effect(34).	***Para-amino salisylic acid (PAS)*** No studies have been performed in adults and children but DDIs are unlikely

Disposition includes absorption, distribution and elimination (metabolism and excretion) and was specified as applicable to drug-drug interactions potential; MDR-TB, multi-drug resistant tuberculosis

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