Perspective

Potential drug–drug interactions between antiretroviral therapy and treatment regimens for multi-drug resistant tuberculosis: Implications for HIV care of MDR-TB co-infected individuals

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ABSTRACT

HIV-positive TB co-infected patients are at increased risk of multidrug-resistant (MDR)-TB compared to HIV-negative patients. Co-treatment of MDR-TB and HIV is common particularly in Sub-Saharan Africa where the co-morbidity is endemic. We discuss potential cellular metabolic pathway–mediated drug–drug interactions and the possible effect on HIV treatment outcomes of commonly prescribed antiretroviral therapy.

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Background

According to the World Health Organization (WHO), tuberculosis (TB) is the leading cause of death attributed to a single microbial pathogen worldwide (Lange et al., 2018). Recent studies indicate that co-infected HIV-positive TB patients are at increased risk of multidrug-resistant (MDR)-TB compared to HIV-negative patients (Aliyu et al., 2018; Essomba et al., 2017). This could partly be because of more rapid disease progression in HIV-infected individuals. Furthermore, people living with HIV are also more likely to be exposed to MDR-TB patients, due to either increased hospitalizations in settings with poor infection control or association with peers including those that are more likely to have MDR-TB, such as prison settings (Mesfin et al., 2014). Other biopharmaceutical factors such as drug mal-absorption in HIV infected patients, especially rifampicin and isoniazid (Gurumurthy et al., 2004), may further explain the association between coinfection with HIV and MDR-TB. Possible drug–drug interactions between HIV antiretroviral therapy (ART) and drugs currently available to treat MDR-TB are of particular concern, especially in low-resource settings of Sub-Saharan Africa where co-morbidity is endemic (Tiberi et al., 2017). We discuss potential cellular metabolic pathway–mediated drug–drug interactions and possible effect on HIV treatment outcomes of commonly prescribed antiretroviral therapy.

Current recommended treatment guidelines for MDR-TB and HIV

The WHO guidelines recommend both diseases require immediate treatment upon diagnosis. Therefore, co-treatment is inevitable for all cases diagnosed with the co-morbidity. In most cases, TB is treatable and curable following approximately six month's treatment duration. MDR- TB is resistant to more than one anti-TB drug and at least isoniazid (INH) and rifampin (RIF). During the past 5 years, MDR-TB has increased by more than 20% annually (Lange et al., 2018). The currently recommended short course (9 month) treatment regimen for MDR-TB is preferred in most low-income countries (Harausz et al., 2018). Commonly prescribed "short-course" MDR-TB regimens include: Prothionamide (or ethionamide)/ high dose Isoniazid (defined as 16–20 mg/kg per day)/clofazimine/pyrazinamide/ethambutol and moxifloxacin in combination with either 1) kanamycin or 2) bedaquiline, including revised dosages of first line drugs in children (Horita

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et al., 2018). For both short and long term regimens Prothionamide/ clofazamine/ethambutol/pyrazinamide/high dose Isoniazid/kana-mycin (or bedaquiline) constitute, in part or solely, the intensive and continuous phase, respectively (Moodley et al., 2016).

In contrast, with no current cure on the immediate horizon, HIV requires life-long uninterrupted ART. Combined antiretroviral therapy (cART) of at least three antiretroviral drugs (ARVs) from different classes of drugs constitute the current HIV treatments (Moyle et al., 1998). Overall, six categories of antivirals are currently available: protease Inhibitors (PIs), nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs, NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), fusion inhibitors (FIs), integrase strand transfer inhibitors (INSTIs), and chemokine receptor antagonists (CRAs). LPV/r is the most-used PI in children today (Huang et al., 2015), and is the recommended antiretroviral (ARV) in first-line-ART for children less than three years old. For adults, the World Health Organization (WHO) recommended first-line regimens comprise two nucleoside reverse transcriptase inhibitors (NRTIs), such as tenofovir dis-oproxil fumarate (TDF) and lamivudine (3TC), and a nonnucleoside reverse transcriptase inhibitor (NNRTI), principally efavirenz/ nevirapine (World Health Organization, 2016) or the integrase; dolutegravir (WHO, 2015). Current recommended second-line regimens for adults include two NRTIs such as zidovudine with 3TC, and a boosted protease inhibitor (PI), with lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir preferred.

MDR-TB specific drug interactions with cellular metabolic pathways

MDR-TB agents exhibit overlapping enzyme inhibition and/or induction that might affect ART outcomes. At least five drugs constituting the recommended and commonly prescribed regimen for treatment of MDR-TB have been reported to inhibit the major metabolic pathways of ARVs including CYP3A4, CYP2B6, CYP2C9, and CYP219. Clofazimine a core MDR-TB drug and cytochrome P450 (CYP) enzyme inhibitor may cause significant CYP-enzyme mediated DDIs with ARVs. Its co-administration is associated with 2.69, 1.60, and 1.47 fold-increase in plasma concentrations of co-administered CYP3A4, CYP2C8, and CYP2D6 substrates respectively (Sangana et al., 2018). Based upon calculated area under the curve ratios (AUCR) of selected enzyme substrates: midazolam for CYP3A4, repaglinide for CYP2C8, and desipramine for CYP2D6, clofazimine is categorized as a moderate to strong inhibitor of CYP3A4 and weak CYP2C8 and CYP2D6 inhibitor. Co-administra-tion of drugs that are CYP3A4 substrates with the recommended 100 mg clofazimine daily dose resulted in a 2- to 6-fold increase in AUCs of such substrates (Sangana et al., 2018).

In the context of MDR-TB, a higher isoniazid dose may be needed to overcome resistance and elevated minimal inhibition concentrations (MICs). In a randomized controlled trial of MDR-TB patients in India, the use of isoniazid at 16–18 mg/kg/day when compared with low dose (5 mg/kg) or placebo was associated with better 6 month culture conversion rates and shorter time to culture conversion (Katiyar et al., 2008). Isoniazid has been reported to play a determinant role in clinical success of short-term MDR-TB treatment regimens (Van Deun et al., 2010). Most studies however have used an isoniazid dose closer to 10 mg/kg, which is at the lower end of what is usually referred to as a "high-dose" range. As a result, WHO recommends that in both children and adults, high-dose isoniazid for use in shorter and longer MDR-TB regimens is defined as 10–15 mg/kg per day, with dosing >15 mg/kg per day applicable in populations in which the faster drug acetylator phenotype is common. Notably, isoniazid exhibits pronounced and dose-dependent inhibition of CYP3A4 and CYP2C19 at its therapeutic level (Desta et al., 2001). Additionally, isoniazid co-administration produced a 1.5 fold increase in *AUC* of triazolam (a substrate of CYP3A4) following a single oral dose ((26.5–38.6 ng h/ mL) (Shimokawa et al., 2015; Ochs et al., 1983).

Orally administered ethionamide and prothionamide also inhibit the same CYP reactions. The [I]max/Ki values of ethion-amide on CYP1A2, CYP2B6, CYP2C19, CYP3A4 (M), and CYP3A4 (T) were ≤ 0.77, and those of prothionamide on CYP1A2, CYP2C9, CYP3A4 (M), and CYP3A4 (T) were ≤0.52. The highest [I]max/Ki value for ethionamide was 1.4 on CYP2C8, and the highest [I]max/ Ki values for prothionamide were 2.2, 1.8, and 1.3 on CYP2B6, CYP2C19, and CYP2C8, respectively, while thioacetazone exhibited mild CYP3A4 enzyme inhibition with a [I]max/K_i value of only 0.14 (Shimokawa et al., 2015). CYP2B6 (the major metabolic pathway for efavirenz) is also induced by ethionamide.

Clofazimine is a strong inhibitor of the drug transporters P-gp, BCRP and MRP1 (Te Brake et al., 2016) for which ARVs, particularly PIs, are known substrates (Marquez and Van Bambeke, 2011). These membrane transporters have an intrinsic efflux role, and may regulate intracellular concentrations of drugs and other xenobiotics. Their inhibition may therefore result in toxic plasma concentration of such substrates.

ART drug interactions with cellular metabolic pathways

Five Cytochrome P-450 (CYP) sub-families and uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes (Dickinson et al., 2010) constitute the major metabolic pathways for which antiretroviral drugs are substrates (Table 1). CYP3A4, which is known to exhibit overlapping substrate specificity with CYP3A5 (Huang et al., 2004) constitutes the major metabolic pathway for about 85% of commonly used ARVs, including all NNRTs and PIs that form the backbone for first and second cART regimens. CYP2B6 constitutes the major metabolic pathway for efavirenz and an alternative pathway for nevirapine, while CYP2C9 and CYP2C19 and CYP2D6 constitute alternative pathways for nevirapine and etravrine and ritonavir. UGT on the other hand, mediates the major

Table 1
Major metabolic pathways of commonly used antiretroviral drugs.

Enzyme	Antiretroviral drug			
	NNRTIs	PIs	CCR5 Coreceptor Inhibitors	Intergrase Inhibitors
CYP3A4/5	Nevirapine, Efavirenz, Etravirine, Rilpirine, Emtricitabine	Retonavir, lopinavir, saquinavir, Fosamprenavir, Atazanavir, duranvir	Maraviroc	Elvitegravir Dolutegravir
CYP2B6	Efavirenz, Nevirapine			
CYPC9	Etravrine, Nevirapine,			
CYPC19	Etravrine			
CYP2D6	Nevirapine	Retonavir		
UGT	Etravrine, Rilpivirine, abacavir			Raltegravir, elvitegravir, Dolutegravir

metabolic pathway for integrase inhibitors: raltegravir, elvitegravir and dolutegravir as highlighted in Table 1.

CYP3A4 is the main metabolic pathway for commonly used PIs, including lopinavir and atazanavir and for the NNRTIs nevirapine and emitricibine. It also constitutes a key alternative pathway for efavirenz. Although the cumulative inhibitory effect and subsequent effect on plasma concentrations of co–administered antiretroviral PIs and NNRTIs is not well defined, it is plausible to postulate that an additive or augmented effect might result in ART-associated toxicity.

Dolutegravir, an alternative drug to efavirenz or nevirapine in adult first-line ART, although primarily metabolized by UGT, is partially metabolized by CYP3A4/5 (Moss et al., 2015). Although the impact of clofazimine on UTG is not well established, a DTG area under the AUC ratio AUCR (AUCinhibitor/AUCcontrol) of 3.0 was reported, comparable to those reported with lopinavir and other strongly inhibited antiviral agents during co-administration with clofazimine (Sangana et al., 2018). Similarly AUCRs of 2.25, 2.93 and 5.59 were reported for the anti-TB drugs bedaquiline, clarithromycin and delamanid, respectively (Ochs et al., 1983). Therefore, the inductive effect of MDR-TB agents may affect other drugs, including other anti-TB agents.

Potential effects of TB and HIV co-treatment related drug–drug interactions

Although there are no clinically demonstrated enzyme-inhibitory effect(s) of isoniazid during intermittent TB prevention or with TB treatment among ART recipients, its coadministration in the absence of rifampicin (a strong enzyme inducer) may elevate concentrations of NNRTIs and PIs and contribute to related toxicities. High dose rifampicin has been proposed for drug sensitive TB (Boeree et al., 2017). Due to enzyme induction, rifampicin affects dolutegravir concentrations requiring a double dose of DTG during HIV–drug sensitive TB co-treatment. The interaction could worsen with increasing rifampin doses. However, its co-administration with high INH dose and other strong enzyme inhibitors that constitute MDR-TB treatment might have clinical benefits, but this needs to be further investigated. Although there is limited data, rifampicin is reported to enhance clofazimine activity against *Mycobacterium tuberculosis* (Zhang et al., 2017). Co-administration of the two drugs during MDR-TB/ HIV treatment might enhance both the efficacy and safety. Overall, concomitant use of MDR-TB agents and ARVs with overlapping enzyme inhibitory effects may potentiate inhibition of these enzymes. Third, anti-TB drug inhibitory effect(s) on multiple ARV drug metabolic pathways (singularly or in combination) might cause multiple ARV drug toxicities, a combination of which could result in significant clinical consequences. Fourth, anti-TB drug-related enzyme inhibition leading to ARV supra-therapeutic concentrations could result in subsequent ARV regimen drug–drug interactions as well as ARV–non-ARV drug interactions that otherwise would not occur. Lastly, considering that HIV patients often receive multiple treatments for HIV co-morbidities, including malaria and fungal infections, and non-infection related diseases (including diabetes and AIDS defining cancers), the enzyme inhibitory effect(s) of MDR-TB drug regimens could have a broader impact on the overall care of HIV-infected individuals and ART outcome. Notably, concomitant use of newly proposed resistant TB drugs such as delamanid, pretomanid and linezolid with cART is also faced with limitations including: possible cellular metabolic pathway–mediated drug–drug interactions, poor tolerability because of toxicities and uncertainties over efficacy. Based on a number of research results, delamanid was approved in the European Union, Japan, and the Republic of Korea in 2014 for the treatment of pulmonary MDR-TB. However its use is still marred by

safety concerns including QT prolongation especially in patients with hypoalbuminemia (<2.8 mg/dL) and efficacy concerns in the elderly, children, adolescents under 18 years, pregnant women, breast-feeding women, and patients with extra pulmonary TB. Although delamanid (100 μM) had little potential for mechanism-based inactivation on key CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), its metabolites have been reported to inhibit key CYPs. Similarly, while linezolid neither inhibits human cytochrome P450s, CYPIA2, 2C9, 2C19, 2D6, 2E1 or 3A4 nor induces hepatic microsomal CYP1A, CYP3A and, CYP4A, it has been associated with a 1.5-fold increase in levels of CYPP2B and CYP2E in rats. Indeed, on the basis of these and other potential DDI, it is recommended that caution needs to be exercised during treatment of MDR-TB / HIV co-morbidity (HIV Drug Interactions, 2019). Linezolid prolonged use in MDR-TB patients is particularly limited by its cumulative dose-related toxicity. Pretomanid on the other hand is still under study and has not gained entry into the WHO categorization of second-line anti-tuberculosis drugs recommended for the treatment of rifampicin-resistant and multidrug-resistant tuberculosis.

In conclusion, there are reasonable chances of clinically important DDIs between MDR-TB and ARVs that may account for poor HIV treatment outcomes. Thus MDR-TB and HIV treatment requires proper guidance due to significant drug–drug interactions. Therefore pharmacokinetic (PK) and pharmacodynamic (PD) studies to evaluate the extent of these drug interactions and their impact on treatment outcomes including safety and efficacy are imperative. Analyses at the sub-populations level is essential, since ethnic-driven genetic polymorphisms in ARV metabolic pathways could play a role in both PK and PD. In particular, the use of rifampicin as part of MDR-TB treatment regimens might have significant clinical consequences regarding efficacy and safety of MDR-TB / HIV co-treatment, and this should be further evaluated.

Conflict of interest

Authors have got no conflict of interest to declare.

Ethical approval

Not applicable.

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