EVALUATION AND CLINICAL APPLICATION OF FOSTEMSAVIR CO-ADMINISTRATION WITH TUBERCULOSIS MEDICATIONS

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Introduction

- Fostemsavir (FTR) is a first-in-class attachment inhibitor approved in combination with other antiretrovirals (ARVs) for heavily treatment-experienced (HTE) adults living with multidrug-resistant human immunodeficiency virus-1 (HIV-1).
- FTR is a prodrug of temsavir (TMR), which binds to viral gp-120 and prevents viral attachment and entry into host CD4+ T-cells.
- TMR is primarily metabolised by esterases and cytochrome P450 (CYP) 3A4 as a secondary pathway representing 21.2% of TMR metabolism. TMR is a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate.
- TMR is not a CYP inhibitor up to 40 µM, and one of its metabolites is an inhibitor of CYP2C8 and CYP3A4. The risk was discharged with the clinical drug-drug interaction (DDI) study with maraviroc, a CYP3A4 substrate, and by regulatory guidance for both CYP2C8 and CYP3A4.
- TMR and its metabolites are inhibitors of BCRP and organic anion transporter protein 1B1/3 (OATP1B1/3).
- TMR and its metabolites are in vitro inhibitors of organic cation transporter (OCT1, OCT2) and multidrug and toxin extrusion (MATE) transporters; however, no DDI risk was predicted by FDA regulatory guidance (OCT1 potential risk by EMA guidance).
- There is a high prevalence of tuberculosis (TB) or multidrug-resistant tuberculosis (MDR-TB) and HIV co-infected patients in developing countries, thus consideration of DDI potential of co-administering FTR and TB regimen(s) is important.

Methods

- Clinical FTR DDI study results with rifampin (RIF) (Figure 1 and Table 1) and rifabutin ± ritonavir (RBT ± RTV; Figure 2 and Table 1), in vitro TMR enzyme and transporter profile, and review of 17 MDR-TB drugs based on victim or perpetrator enzyme and/or transporter profiles obtained via the University of Washington Drug Interaction Database (UWDIDB) were assessed to inform options for co-administration therapy.
- Recommendations were based on expected pharmacokinetic (PK) impact, DDI guidance, exposure-response relationships, and review of relevant treatment guidelines.

Results

Figure 1. Mean (+ SD) TMR Plasma Concentration-Time Profile Following Single-Dose Administration of FTR 1200 mg without and with RIF 600 mg[1]

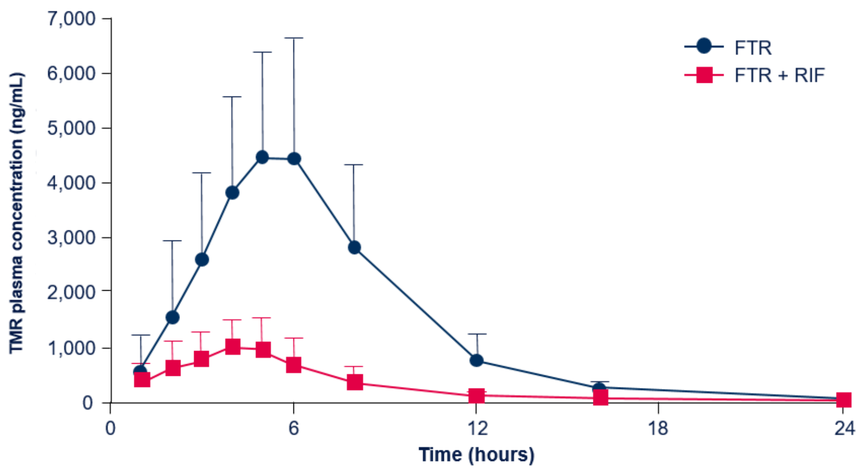

Figure 2. Mean (+ SD) TMR Plasma Concentration-Time Profile Following Repeat-Dose Administration of FTR 600 mg BID alone and with RBT 300 mg QD or with RBT 150 mg/RTV 100 mg QD[2]

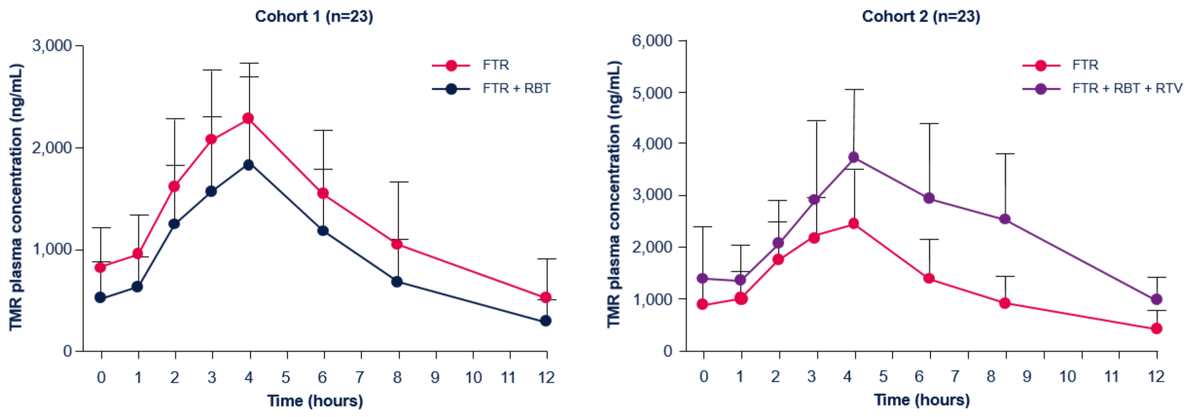

Table 1. Mean Ratio of TMR Pharmacokinetic Parameters (90% CI); No Effect = 1.00

Co-administered drug(s)	FTR dose	N	C_{max}	AUC_T or AUC_∞	C_T or C_{12}
RIF 600 mg QD[1]	1200 mg single dose	15	0.24 (0.21, 0.28)	0.18 (0.16, 0.2)	N/A
RBT 300 mg QD[2]	600 mg BID	19	0.73 (0.65, 0.83)	0.70 (0.64, 0.76)	0.594 (0.46, 0.77)
RBT ± RTV 150 mg QD/ 100 mg QD[2]	600 mg BID	16	1.50 (1.38, 1.64)	1.66 (1.52, 1.81)	2.58 (1.95, 3.42)

Table 2. Potential Enzyme-Mediated DDI of FTR and MDR-TB Drugs

DDI Risk Assessment	Potential DDI Risk
FTR/TMR as Perpetrator Interactions	
CYP450 Inhibition • Bedaquiline: CYP3A4 substrate	**Low Risk**
CYP450 Induction • Bedaquiline: CYP3A4 substrate	**N/A**
UGT (& other non-CYP enzymes) inhibition • Moxifloxacin: UGT1A1, 1A9, SULT2A1 substrate • Pyrazinamide: AO and XO substrate • Thioacetazone: FMOs substrate	**Low Risk** *DDI by SULT/AO/ XO/FMO unknown*
FTR/TMR as Victim Interactions	
CYP450 Substrate • Clofazimine: In vitro CYP3A4 inhibitor, weak CYP3A4 inducer • Isoniazid: In vitro CYP3A4 inactivator • Prothionamide, Ethionamide, Linezolid, Ethambutol, p-Aminosalicylic Acid (PAS), Meropenem, Thioacetazone: In vitro CYP3A4 inhibitors with no clinical DDI reported	**Potential TMR increase via CYP3A4 inhibition** *for TMR/clofazimine, TMR/isoniazid*
UGT (& other non-CYP enzymes) substrate	**N/A**

UGT=uridine 5”-diphosphoglucuronosyltransferase; AO=aldehyde oxidase; XO=xanthine oxidase; FMO=flavin monooxygenase; SULT2A=hydroxysteroid sulfotransferase.

Table 3. Potential Transporter-Mediated DDI of FTR and MDR-TB Drugs

DDI Risk Assessment	Potential DDI Risk
FTR/TMR as Perpetrator Interactions	
ABC Transporters (P-gp, BCRP, MRP2) • Most MDR-TB agents are P-gp substrates	**Low Risk**
Hepatic SLC Transporters (OATP1B1, OATP1B3, OATP2B1, & OCT1) • PAS: OATP1B1, OCT1 substrate	**Potential PAS increase via OATP1B1 inhibition**
Kidney SLC Transporters (OCT2, OATs, MATEs) • Ethambutol: OCT1, OCT2, OCT3, MATE1, and MATE2K substrate • PAS: OCT2, OAT1/3 substrate • Levofloxacin: OCTs substrate	**Low Risk**
FTR/TMR as Victim Interactions	
ABC Transporters (P-gp, BCRP, MRP2) • Levofloxacin: In vitro P-gp inhibitor • Clofazimine: In vitro P-gp and BCRP inhibitors • Ethionamide: In vitro BCRP inhibitor	
Hepatic SLC Transporters (OATP1B1, OATP1B3, OATP2B1, & OCT1) • Kanamycin: In vitro OATP2B1 inhibitor • Clofazimine: In vitro OATP1B1, 1B3, and 2B1 inhibitor • Ethionamide: Weak OATP1B1 inhibitor • Isoniazid: Moderate in vitro OATP1B1 and 1B3 inhibitors	**Low Risk** *no clinical DDI data recorded to date for these TB drugs as transporter inhibitors*
Kidney SLC Transporters (OCT2, OATs, MATEs) • Levofloxacin: In vivo OCT1/2 inhibitor • Moxifloxacin: In vitro OCTs inhibitor • Clofazimine, Linezolid: In vitro OAT1/OAT3 inhibitor • Pyrazinamide: In vitro OCT1 inhibitor	

P-gp=P-glycoprotein; BCRP=breast cancer resistance protein; OATP=organic anion transporter protein; OCT=organic cation transporter; OAT=organic anion transporter; MATE=multidrug and toxin extrusion.

Discussion

- Prior data on clofazimine and isoniazid (CYP3A4 inhibitors) suggest up to 50% increase in TMR concentration predicted by DDI regulatory guidance (Table 2).
- TMR and its metabolites inhibit OATP1B1/3 and a DDI study with rosuvastatin (OATP1B and BCRP substrate) showed ~70% increase in rosuvastatin AUC[3]; therefore, TMR may increase P-aminosalicylic acid (PAS; OATP1B1/OCT1 substrate) concentrations (Table 3).
- Bedaquiline, moxifloxacin, pyrazinamide, prothionamide, thioacetazone, ethambutol, levofloxacin, ethionamide, kanamycin, and linezolid have low PK DDI risk with TMR (Tables 2 and 3).
- Because certain medications used to treat TB may prolong the QT interval,[4] caution is advised with FTR co-administration since an increase in QTcF interval of 10 msec was observed at approximately 4-fold higher dose.[3,5]

Conclusions

Co-administration of FTR and drugs commonly used to treat TB are not expected to result in clinically meaningful interactions, except for RIF, which is contraindicated due to the potential loss of therapeutic effect of TMR.

Please join us on Thursday, 8th October, for one of the two live Meet the Experts Q&A sessions with our senior medical experts around our most recent data presented at HIV Glasgow 2020.

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