Fostemsavir and QT Prolongation: Clinical Applications for Co-administration With Other Agents

P030

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Key Takeaways

- **Guideline recommendations, the University of Liverpool HIV Drug Interactions database, and data from phase 2b/3 fostemsavir (FTR) clinical studies were used to assess corrected QT interval (QTc) prolongation risk with FTR and other co-administered agents**
- **FTR should be used with caution in patients with a history of QT interval prolongation when co-administered with a drug that has a known risk of Torsades de Pointes (TdP) or in patients with relevant pre-existing cardiac disease**

Introduction

- FTR, a prodrug of temsavir (TMR), is a first-in-class gp120-directed attachment inhibitor approved in the United States, Europe, and elsewhere at a dose of 600 mg twice daily (BID) in combination with other ARVs for adults with multidrug-resistant HIV-1 who are otherwise unable to construct a suppressive ARV regimen due to resistance, prior intolerance, or safety concerns[1,2]
- In preclinical studies in dogs, FTR and TMR minimally prolonged the QT interval (~8 to 18 msec) at maximum observed TMR concentrations ≥3600 ng/mL[2,3]
  - Mean peak plasma TMR concentration with FTR 600 mg BID in heavily treatment-experienced participants in the phase 3 BRIGHTE study was 1770 ng/mL[3]
- A thorough QT/QTc interval study in healthy volunteers demonstrated that a supratherapeutic dose of FTR 2400 mg BID was associated with a mean (upper 90% CI) Fridericia-corrected QT (QTcF) prolongation of 11.2 (13.3) msec, above the clinically important threshold of 10 msec[3]
  - No clinically meaningful effect on QTc interval was observed with FTR 1200 mg once daily (QD), with a maximum (upper 90% CI) QTcF prolongation of 4.3 (6.3) msec
  - With FTR 600 mg BID, model-derived upper 90% CIs of QTcF prolongation at maximum TMR concentration were ≤3.2 and ≤5.0 msec for administration alone or with cobicistat 150 mg QD, respectively, suggesting that QT interval effects ≥10 msec are unlikely to occur with the therapeutic FTR dose
- Because QTc prolongation is primarily a concentration-dependent effect and FTR is partially metabolized by cytochrome P450 3A4, we examined potential drug-drug interactions (DDIs) between FTR, pharmacokinetic enhancers, and other agents commonly used in HIV associated with QTc prolongation or TdP risk

Methods

- QTc prolongation risk with FTR co-administered with medications commonly used in HIV or other ARVs was assessed using US FDA guideline recommendations,[4] the University of Liverpool HIV Drug Interactions database,[5] and data from phase 2b and phase 3 FTR clinical studies
- **Phase 2b 205889 study (NCT01384734):** Treatment-experienced participants were randomized to receive 1 of 4 FTR doses (400 mg BID, 800 mg BID, 600 mg QD, or 1200 mg QD) or ATV/r (300 mg/100 mg QD) with RAL 400 mg BID + TDF 300 mg QD
  - Withdrawal criteria included QTcF value >500 msec or confirmed second- or third-degree atrioventricular block
- **Phase 3 BRIGHTE study (NCT02362503):** Heavily treatment-experienced participants failing their current ARV regimen with limited treatment options received FTR 600 mg BID + optimized background therapy
  - Withdrawal criteria included confirmed QT value >500 msec; confirmed QTcF value >470 msec for women and >450 msec for men or confirmed increase >60 msec over baseline; confirmed PR interval >260 msec; or confirmed second- or third-degree atrioventricular block
  - Participants remained on study if QTcF prolongation (>470 msec for women, >450 msec for men, or >60-msec increase over baseline) was believed secondary to a reversible cause, which could be readily acted upon and allowed for the timely return of the QTcF interval to below the discontinuation threshold

Results

QTc Prolongation in FTR Clinical Studies

- A plasma TMR concentration of 7500 ng/mL intersects with the clinically important QTc prolongation threshold of 10 msec (upper bound of the 90% CI), which is ~4-fold greater than the mean peak plasma TMR concentration with FTR 600 mg BID in the phase 3 BRIGHTE study (1770 ng/mL)[3]
- Through 96 weeks with FTR 600 mg BID in the BRIGHTE study, 7/371 (2%) participants discontinued for protocol-defined QTcF prolongation >450 msec; all were non-serious events
  - Although discontinued from the study, 6 participants remained on FTR through the named patient program (NPP 207214); none experienced a symptomatic cardiovascular event or documented ventricular tachyarrhythmia
- Through 96 weeks in a phase 2b study of FTR 400 mg BID, 800 mg BID, 600 mg QD, or 1200 mg QD (N=200), no participants discontinued for protocol-defined QTcF prolongation >500 msec

Guidance for Monitoring QTc Prolongation With FTR Co-administration

- A systematic evaluation of the University of Liverpool HIV Drug Interactions database showed no significant or reported high potential for QTc prolongation when FTR is co-administered with medications commonly used in HIV (Table 1) or other ARVs (Table 2)
  - No interaction was expected with and no guidance for monitoring QTc prolongation was specified for co-administration of FTR with INSTIs, NRTIs, or doravirine
- The combinations of greatest concern with FTR co-administration include several antiarrhythmics due to potential additive QTc prolongation risk and are not recommended when FTR + boosted PIs or FTR + RPV are used

Table 1. FTR Co-administration With Medications Commonly Used in HIV[a]

Guidance for monitoring QTc prolongation risk[5]	Anti-arrhythmics	Anti-depressants	Anti-psychotics	Anti-microbials	Other medications
• QTc prolongation unlikely to occur during co-administration with FTR • Given the known QT prolongation risk associated with these drugs, ECG monitoring is recommended	Amiodarone Bepridil Disopyramide Dofetilide Flecainide Quinidine	Citalopram Escitalopram	Donepezil Haloperidol Ziprasidone	Macrolides: • Azithromycin • Clarithromycin • Erythromycin Quinolones: • Ciprofloxacin • Levofloxacin • Moxifloxacin Fluconazole Pentamidine	Cocaine Methadone[b] Ondansetron Oxaliplatin
• Use FTR with caution when co-administered with drugs with a known TdP risk • These drugs have a possible or conditional risk of QTc prolongation and/or TdP		Nortriptyline Venlafaxine	Aripiprazole Paliperidone	Itraconazole Ketoconazole	Levetiracetam
• No QTc prolongation guidance specified • No clinically significant interaction expected	Digoxin Lidocaine (lignocaine) Mexiletine Propafenone	Amitriptyline Fluoxetine Paroxetine Sertraline Trazodone	Olanzapine Quetiapine Risperidone	Metronidazole Piperacillin Tazobactam Sulfameth-oxazole/ Trimethoprim	Diazepam Sumatriptan

[a]No guideline recommendation available for co-administration with FTR or other medications, except where noted for methadone.[4] [b]↔ Total methadone, R(-) methadone (active metabolite), S(+) methadone; *no dose adjustment needed*.[4]

Table 2. FTR Co-administration With ARVs[a]

ARV	Data and guideline recommendation[4]	Guidance for monitoring QTc prolongation risk[5]
NNRTIs		
RPV	↔ TMR expected; *no dose adjustment needed*	• QTc prolongation is unlikely to occur with FTR + RPV • Use FTR and RPV with caution when co-administered with drugs with a known TdP risk
EFV	↓ TMR possible; ↔ EFV expected; *no dose adjustment needed*	• Use FTR with caution when co-administered with drugs with a known TdP risk • EFV has a possible risk of QTc prolongation and/or TdP
ETR	TMR AUC ↓ 50%; ↔ ETR; *no dose adjustment needed*	No guidance specified
PIs		
ATV/r	TMR Cmax and AUC ↑ 54%-58%; ↔ ATV, RTV; *no dose adjustment needed*	• QTC prolongation is unlikely to occur with FTR + ATV/r or FTR + ATV/c • Increase in TMR exposure is not considered clinically significant
ATV/c	↑ TMR possible; ↔ ATV expected; *no dose adjustment needed*	
LPV/r	↑ TMR possible; ↔ LPV expected; *no dose adjustment needed*	• Use FTR with caution when co-administered with drugs with a known TdP risk • LPV has a possible risk of QTc prolongation and/or TdP
DRV/r	TMR Cmax and AUC ↑ 52%-63%; ↔ DRV, RTV; *no dose adjustment needed*	No guidance specified
DRV/c	TMR Cmax and AUC ↑ 79%-97%; ↔ DRV, COBI expected; *no dose adjustment needed*	No guidance specified
CCR5 antagonist		
MVC	↔ TMR; MVC AUC ↑ 25%; *no dose adjustment needed*	No guidance specified

[a]ARVs with a potential interaction specified in US HIV treatment guidelines[4] and recommendation for monitoring QTc prolongation risk specified in the University of Liverpool HIV Drug Interactions database[5] were included. INSTIs (BIC, CAB, DTG, EVG/c, and RAL), NRTIs (TDF, TAF, FTC, 3TC, and ABC), and doravirine had no interaction expected and no guidance for monitoring QTc prolongation specified.

Conclusions

- When combined with other ARVs, FTR does not require dose adjustment and QTc prolongation is unlikely to occur
- Clinically significant interactions may occur with agents with known TdP risk, and any such agents should be used with caution when co-administered with FTR + boosted PIs or FTR + RPV
- Evaluation of FTR-containing ARV regimens, pre-existing cardiac disease, and age must be considered when co-administering FTR with agents with known TdP risk

References: 1. Rukobia [US prescribing information]. ViiV Healthcare; 2022. **2.** Rukobia [EU summary of product characteristics]. ViiV Healthcare; 2022. **3.** Lagishetty et al. *Clin Transl Sci*. 2020;13:769-776. **4.** Panel on Antiretroviral Guidelines for Adults and Adolescents. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed September 9, 2022. **5.** University of Liverpool HIV Drug Interactions. https://www.hiv-druginteractions.org/. Accessed September 19, 2022.

Acknowledgments: This study was funded by ViiV Healthcare. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

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