

Sonia Patel,¹ Vilma Vega,¹ Alftan Dyson,¹ Rakesh Guduru,² Golkoo Morcos,^{1*} Mónica Calderón,¹ Andrew Mannebach,² Bruce Gilliam,¹ Andrew Clark,³ Allan Tenorio,¹ Katy Moore^{1*}

¹ViiV Healthcare, Durham, NC, USA; ²GSK, Durham, NC, USA; ³ViiV Healthcare, Brentford, UK

*Employee of ViiV Healthcare at the time of the study.



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 BRIGHTHE study was 1770 ng/mL³
- 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 msec³
 - 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 BRIGHTHE 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 BRIGHTHE study (1770 ng/mL)³
- Through 96 weeks with FTR 600 mg BID in the BRIGHTHE 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
<ul style="list-style-type: none"> 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	Citalopram	Donepezil	Macrolides:	Cocaine
	Bepidil	Escitalopram	Haloperidol	• Azithromycin	Methadone ^b
<ul style="list-style-type: none"> 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 	Disopyramide		Ziprasidone	• Clarithromycin	Ondansetron
	Dofetilide			• Erythromycin	Oxaliplatin
<ul style="list-style-type: none"> No QTc prolongation guidance specified No clinically significant interaction expected 	Flecainide			Quinolones:	
	Quinidine			• Ciprofloxacin	
				• Levofloxacin	
				• Moxifloxacin	
				Fluconazole	
				Pentamidine	
		Nortriptyline	Aripiprazole	Itraconazole	Levetiracetam
		Venlafaxine	Paliperidone	Ketoconazole	
	Digoxin	Amitriptyline	Olanzapine	Metronidazole	Diazepam
	Lidocaine	Fluoxetine	Quetiapine	Piperacillin	Sumatriptan
	(lignocaine)	Paroxetine	Risperidone	Tazobactam	
	Mexiletine	Sertraline		Sulfamethoxazole/	
	Propafenone	Trazodone		Trimethoprim	

^aNo 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; <i>no dose adjustment needed</i>	<ul style="list-style-type: none"> 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; <i>no dose adjustment needed</i>	<ul style="list-style-type: none"> 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; <i>no dose adjustment needed</i>	No guidance specified
PIs		
ATV/r	TMR Cmax and AUC ↑ 54%-58%; ↔ ATV, RTV; <i>no dose adjustment needed</i>	<ul style="list-style-type: none"> QTc prolongation is unlikely to occur with FTR + ATV/r or FTR + ATV/c
ATV/c	↑ TMR possible; ↔ ATV expected; <i>no dose adjustment needed</i>	<ul style="list-style-type: none"> Increase in TMR exposure is not considered clinically significant
LPV/r	↑ TMR possible; ↔ LPV expected; <i>no dose adjustment needed</i>	<ul style="list-style-type: none"> 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; <i>no dose adjustment needed</i>	No guidance specified
DRV/c	TMR Cmax and AUC ↑ 79%-97%; ↔ DRV, COBI expected; <i>no dose adjustment needed</i>	No guidance specified
CCR5 antagonist		
MVC	↔ TMR; MVC AUC ↑ 25%; <i>no dose adjustment needed</i>	No guidance specified

^aARVs with a potential interaction specified in US HIV treatment guidelines⁴ and recommendation for monitoring QTc prolongation risk specified in the University of Liverpool HIV Drug Interactions database⁵ 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.

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