

TMC125 in Combination With Medications Commonly Used in HIV Infection: Summary of Drug-Drug Interactions

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Introduction

- TMC125 is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) designed to have a high genetic barrier to the development of resistance^{1,2}; TMC125 also maintains activity despite common NNRTI mutations^{3,4}
- New formulation (F060; 200mg bid) with improved bioavailability provides comparable exposure to 800mg bid (TF035)
- $T_{1/2\text{term}}=30$ to 40 hours (distribution $t_{1/2}$ 3.9 to 5.4 hours)
- Exposure in bid dosing is approximately 4 times higher than after single dose
- Exposure is reduced by 50% when administered in a fasted state. TMC125 should be administered following a meal⁵
- In vitro*, TMC125 is a substrate and weak inducer of CYP3A4, a substrate and weak inhibitor of CYP2C9 and CYP2C19, and a weak inhibitor of P-glycoprotein ($IC_{50} = 10.5 \mu\text{g/mL}$ [$2.4 \mu\text{M}$])⁶
- Renal elimination of the administered dose is minimal (<1.2%)
- No drug interactions are anticipated with other drugs that are primarily renally excreted (eg, NRTIs and ribavirin)
- We summarize the pharmacokinetic (PK) interactions between TMC125 and other medications commonly used in HIV-infected patients

Methods

- Twenty-four clinical drug-drug interaction studies have been conducted to date
- No effect boundary (clinical equivalence limit) for TMC125 is 50-200%, based on TMC125-C223 PK/pharmacodynamic (PD) relationship⁷ (Figure 1)
- Steady-state PK studies include:
 - Two-way interaction studies with TMC125 and rifabutin, clarithromycin, didanosine (ddI), tenofovir (TDF), atazanavir (ATV), and ritonavir-boosted (r) PIs ATV, darunavir (DRV), lopinavir (LPV), and tipranavir (TPV)
 - One-way effect of omeprazole (OME) and ranitidine (RAN) on single-dose TMC125
 - One-way effect of TMC125 on (fos)amprenavir (FPV/r), LPV/saquinavir (SQV)/r, methadone, oral contraceptives (OC), single-dose sildenafil (SIL), and saquinavir (SQV)

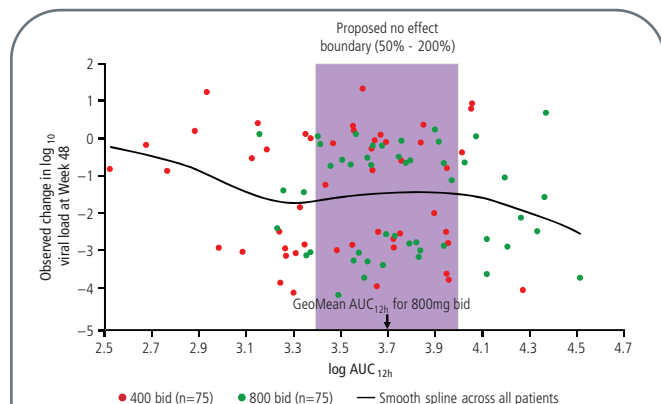


Figure 1. Relationship between TMC125 exposure (AUC) and change in viral load at Week 48.

Results

- TMC125 had no clinically relevant effect on most of the drugs studied (Table 1) – TMC125 increased exposure to FPV 69%, and decreased exposure to SIL 57%, N-desmethyl SIL 41%, and clarithromycin 39%
- No clinically relevant changes in TMC125 exposure were observed when TMC125 was combined with most of the drugs studied (Table 2) – TMC125 exposure decreased 76% with TPV/r
- TMC125 PK were comparable to historical controls when TMC125 was co-administered with LPV/SQV/r, SQV, methadone, OC, SIL or FPV/r
- Interactions of TMC125 with co-administered drugs are independent of formulation (Table 3)

Table 3. TMC125-C233: PK comparison with DRV/r and TDF between two TMC125 formulations

Dose regimen of coadministered drug	Dose regimen of TMC125 (formulation)	LS mean ratios of AUC (95% CI)	
		TMC125	Coadministered drug
DRV/r 600/100mg bid for 8 days	100mg bid for 16 days (F060)	0.63 (0.54–0.73)	1.06 (1.00–1.13)
DRV/r 600/100mg bid for 8 days	800mg bid for 16 days (TF035)	0.67 (0.52–0.86)	1.23 (1.16–1.31)
TDF 300mg qd for 8 days	200mg bid for 16 days (F060)	0.81 (0.75–0.88)	1.15 (1.09–1.21)
TDF 300mg qd for 8 days	800mg bid for 16 days (TF035)	0.68 (0.54–0.86)	1.16 (1.09–1.23)

Conclusions

- Drug interactions of TMC125 with medications commonly used in HIV therapy are well-characterized and manageable
- TMC125 can be combined with most of the drugs studied without dose adjustment:
 - Efavirenz, nevirapine, TPV/r, full-dose ritonavir and unboosted PIs are not recommended in combination with TMC125
 - FPV and sildenafil may require dose adjustment
 - Co-administration with clarithromycin is not recommended for treatment of *Mycobacterium avium* complex
- TMC125 200mg bid (F060 formulation) is the dose used in phase III trials:
 - Drug interactions are independent of formulation

References

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Table 1. PK parameters of co-administered drugs in the presence of TMC125

Dose regimen of co-administered drug	Dose regimen of TMC125 (formulation)	N	HIV status	PK	Mean ratio* of PK parameters for co-administered drug (90% CI)			Reference
					C _{max}	AUC _{8, 12, 24h or last}	C _{min}	
No dose adjustment necessary when co-administered								
ATV/r 300/100mg qd for 7 days	800mg bid for 14 days (TF035)	13	–	↓	0.97 (0.89–1.05)	0.86 (0.79–0.93)	0.62 (0.55–0.71)	HIV8 2006, abstract P278
DRV/r 600/100mg bid for 8 days	100mg bid for 16 days (F060)	13	–	↔	1.03 (0.98–1.09)	1.06 (1.00–1.13)	1.02 (0.89–1.17)	IAC 2006, abstract TuPe0086
ddl 400mg qd for 8 days	800mg bid for 16 days (TF035)	14	–	↔	0.91 (0.58–1.42)	0.99 (0.79–1.25)	NA	IAS 2005, abstract WePe3.3C16
Ethinylestradiol 0.035mg qd for 3 cycles	200mg bid for 15 days during 3rd cycle (F060)	16	–	↑	1.33 (1.21–1.46)	1.22 (1.13–1.31)	1.09 (1.01–1.18)	HIV8 2006, abstract P277
Norethindrone 1mg qd for 3 cycles			–	↔	1.05 (0.98–1.12)	0.95 (0.90–0.99)	0.78 (0.68–0.90)	HIV8 2006, abstract P277
LPV/r 400/100mg bid for 13 days and a single dose on Day 14	1,600mg bid for 13 days and a single dose on Day 14 (TF035)	13	–	↔	0.85 (0.62–1.05)	0.80 (0.49–1.07)	0.92 (0.15–1.68)	ICAAC 2002, abstract A-1824
LPV 400mg bid	800mg bid for 14 days (TF035)	15	+	↓	0.84 (0.74–0.95)	0.82 (0.70–0.96)	0.76 (0.54–1.08)	CROI 2006, abstract 575b
SQV 800–1,000mg bid			+	↔	0.85 (0.61–1.19)	0.87 (0.62–1.21)	0.87 (0.60–1.28)	CROI 2006, abstract 575b
RTV 100mg bid ongoing regimen			+	↔	0.89 (0.69–1.15)	0.87 (0.67–1.12)	0.88 (0.57–1.37)	CROI 2006, abstract 575b
R-methadone ongoing regimen	100mg bid for 14 days (F060)	16	–	↔	1.02 (0.96–1.09)	1.06 (0.99–1.13)	1.10 (1.02–1.19)	IAC 2006, abstract TuPe0084
S-methadone ongoing regimen			–	↔	0.89 (0.82–0.96)	0.89 (0.82–0.96)	0.89 (0.81–0.98)	IAC 2006, abstract TuPe0084
Rifabutin 300mg qd for 14 days	800mg bid for 21 days (TF035)	12	–	↓	0.90 (0.78–1.03)	0.83 (0.75–0.94)	0.76 (0.66–0.87)	IDSA 2006, abstract 1059
TDF 300mg qd for 8 days	200mg bid for 16 days (F060)	19	–	↑	1.15 (1.04–1.27)	1.15 (1.09–1.21)	1.19 (1.13–1.26)	ICAAC 2006, abstract A-371

Dose adjustments of co-administered drug may be necessary

Clarithromycin [†] 500mg bid for 5 days	200mg bid for 8 days (F060)	15	–	↓	0.66 (0.57–0.77)	0.61 (0.53–0.69)	0.47 (0.38–0.57)	IDSA 2006, abstract 1351
14-OH clarithromycin			–	↑	1.33 (1.13–1.56)	1.21 (1.05–1.39)	1.05 (0.90–1.22)	IDSA 2006, abstract 1351
FPV/r 700/100mg bid ongoing regimen	800mg bid for 14 days (TF035)	8	+	↑	1.62 (1.47–1.79)	1.69 (1.53–1.86)	1.77 (1.39–2.25)	ICAAC 2006, abstract A-370
Sildenafil 50mg single dose	800mg bid for 13 days and a single dose on Day 14 (TF035)	15	–	↓	0.55 (0.40–0.75)	0.43 (0.36–0.51)	NA	IWCPT 2006, abstract 45
N-desmethyl sildenafil			–	↓	0.75 (0.59–0.96)	0.59 (0.51–0.68)	NA	IWCPT 2006, abstract 45

Co-administration with TMC125 is not recommended

ATV 400mg qd for 7 days	800mg bid for 14 days (TF035)	14	–	↓	0.97 (0.73–1.29)	0.83 (0.63–1.09)	0.53 (0.38–0.73)	HIV8 2006, abstract P278
IDV 800mg tid for 6 days	1,600mg bid for 14 days (TF034)	10	–	↓	0.72 (0.58–0.89)	0.54 (0.46–0.62)	0.24 (0.18–0.34) [‡]	ICAAC 2002, abstract A-1827
SQV 1,200mg single dose	900mg bid 14 days (TF002)	12	–	↓	0.54 (0.34–0.86)	0.48 (0.29–0.80)	NA	ICAAC 2002, abstract A-1827
TPV/r 500/200mg bid for 8 days	800mg bid for 16 days (TF035)	19	–	↑	1.14 (1.02–1.27)	1.18 (1.03–1.36)	1.24 (0.96–1.59)	CROI 2006, abstract 583

[†]In combination with TMC125 versus alone; no effect = 1.00; [‡]14-OH clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC) and therefore the overall activity against this pathogen may be altered. An alternative antibacterial (ie, azithromycin) is recommended for treatment of MAC when TMC125 is administered; [‡]C_{trough}; NA = not available

Table 2. PK parameters of TMC125 in the presence of co-administered drugs

Dose regimen of co-administered drug	Dose regimen of TMC125 (formulation)	N	HIV status	PK	Mean ratio* of TMC125 PK parameters (90% CI)			
					C _{max}	AUC _{12h or last}	C _{min}	Reference
No dose adjustment necessary when co-administered								
ATV/r 300/100mg qd for 7 days	800mg bid for 14 days (TF035)	14	–	↑	1.30 (1.17–1.44)	1.30 (1.18–1.44)	1.26 (1.12–1.42)	HIV8 2006, abstract P278
DRV/r 600/100mg bid for 8 days	100mg bid for 16 days (F060)	14	–	↓	0.68 (0.57–0.82)	0.63 (0.54–0.73)	0.51 (0.44–0.61)	IAC 2006, abstract TuPe0086
ddl 400mg qd for 8 days	800mg bid for 16 days (TF035)	15	–	↔	1.16 (1.02–1.32)	1.11 (0.99–1.25)	1.05 (0.93–1.18)	IAS 2005, abstract WePe3.3C16
LPV/r 400/100mg bid for 13 days and a single dose on Day 14	1,600mg bid for 13 days and a single dose on Day 14 (TF035)	13	–	↑	1.15 (0.94–1.41)	1.17 (0.96–1.43)	1.23 (0.98–1.53)	ICAAC 2002, abstract A-1824
Omeprazole 40mg qd for 8 days [†]	100mg single dose (F060)	18	–	↑	1.17 (0.96–1.43)	1.41 (1.22–1.62)	NA	IAC 2006, abstract TuPe0082
Ranitidine 150mg bid for 8 days [†]	100mg single dose (F060)	18	–	↓	0.94 (0.75–1.14)	0.86 (0.76–0.97)	NA	IAC 2006, abstract TuPe0082
Rifabutin 300mg qd for 14 days	800mg bid for 21 days (TF035)	12	–	↓	0.63 (0.53–0.74)	0.63 (0.54–0.74)	0.65 (0.56–0.74)	IDSA 2006, abstract 1059
TDF 300mg qd for 8 days	200mg bid for 16 days (F060)	23	–	↓	0.81 (0.75–0.88)	0.81 (0.75–0.88)	0.82 (0.73–0.91)	ICAAC 2006, abstract A-371
Clarithromycin [†] 500mg bid for 5 days	200mg bid for 13 days (F060)	15	–	↑	1.46 (1.38–1.56)	1.42 (1.34–1.50)	1.46 (1.36–1.58)	IDSA 2006, abstract 1351

Co-administration with TMC125 is not recommended

ATV 400mg qd for 7 days	800mg bid for 14 days (TF035)	14	–	↑	1.47 (1.36–1.59)	1.50 (1.41–1.59)	1.58 (1.46–1.70)	HIV8 2006, abstract p278
EFV 600mg qd for 14 days	900mg single dose (TF002)	12	–	↓	0.83 (0.73–0.93)	0.59 (0.52–0.68)	NA	ICAAC 2002, abstract A-1827
IDV 800mg tid for 6 days	1,600mg bid for 14 days (TF034)	10	–	↑	1.51 (1.16–1.97)	1.51 (1.20–1.90)	1.52 (1.20–1.91)	ICAAC 2002, abstract A-1827
NVP 200mg bid for 14 days	900mg single dose (TF002)	5	–	↓	0.64 [‡]	0.45 [‡]	NA	ICAAC 2002, abstract A-1827
RTV 600mg bid for 7 days	400mg single dose (TF002)	11	–	↓	0.68 (0.55–0.85)	0.54 (0.41–0.73)	NA	ICAAC 2002, abstract A-1827
TPV/r 500/200mg bid for 8 days	800mg bid for 16 days (TF035)	19	–	↓	0.29 (0.22–0.40)	0.24 (0.18–0.33)	0.18 (0.13–0.25)	CROI 2006, abstract 583

[†]In combination with co-administered drug versus alone; no effect = 1.00; [‡]Ranitidine and omeprazole were tested in the same volunteers but administered separately; [‡]CI not available due to limited sample size; [‡]14-OH clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC) and therefore the overall activity against this pathogen may be altered. An alternative antibacterial (ie, azithromycin) is recommended for treatment of MAC when TMC125 is administered. Abbreviations: EFV = efavirenz; IDV = indinavir; NA = not available; NVP = nevirapine; RTV = ritonavir