

Pharmacokinetic Interaction Between Rifabutin (RFB) and Fosamprenavir (FPV)/ Ritonavir (RTV) in Healthy Subjects

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Introduction

FPV (Lexiva, Telzir), the phosphate ester pro-drug of the HIV-1 protease inhibitor (PI) amprenavir (APV), is approved for the treatment of HIV infection in adults. The approved dosing of FPV is both with and without RTV, a potent CYP3A4 inhibitor.

RFB is commonly used for the prophylaxis of Mycobacterium avium complex (MAC) infection or the treatment of tuberculosis in HIV-infected patients with advanced disease. As a CYP3A4 substrate, plasma RFB exposure is substantially increased by several CYP3A4 inhibitors, including HIV PIs. Concomitant administration of APV 1200mg BID and RFB 300mg QD for 10 days increased RFB AUC(0-24) and Cmax 2.93 and 2.19-fold, respectively, compared to RFB 300mg QD (3). Concomitant administration of LPV/r 400mg/100mg BID and RFB 150mg QD, a 50% dose reduction, for 10 days increased RFB AUC(0-24) and Cmax 3.03-fold and 4.90-fold, respectively, compared to RFB 300mg QD (2).

25-O-desacetyl-rifabutin (dAc-RFB) is an active metabolite of RFB that is equipotent to RFB on a molar basis (1). Plasma dAc-RFB exposure is approximately 10% that of RFB, and, therefore, contributes to 10% of the total antimycobacterial activity of RFB. Concomitant administration of APV 1200mg BID and RFB 300mg QD for 10 days increased plasma dAc-RFB AUC, Cmax and Cmin 13.35-, 7.39-, and 32.9-fold, respectively, relative to RFB 300mg QD alone (3). Concomitant administration of LPV/r 400mg/100mg BID and RFB 150mg QD increased dAc-RFB AUC, Cmax and Cmin 47.5-, 23.6- and 94.9-fold, respectively, and total antimycobacterial AUC was increased 5.73-fold (2). A reduction in RFB dose of at least 75% is recommended when co-administered with LPV/r (2).

This study was designed to compare steady-state plasma RFB, dAc-RFB, and total antimycobacterial pharmacokinetics (PK) following coadministration of 75% dose-reduced RFB (RFB 150mg every other day) with FPV/r 700/100mg BID and RFB 300mg QD. Plasma APV pharmacokinetic parameters were compared to historical control.

Methods

Scheme 1. Study Design

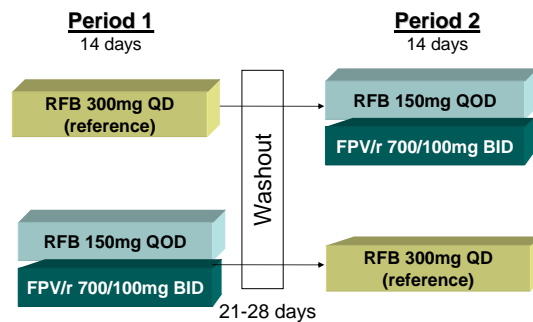


Table 1. Pharmacokinetic Sampling Schedule

Treatment	Day	Analyte	Time Relative to Morning Dose (Hour)
RFB 300mg QD	9 11	RFB dAc-RFB	0
RFB 300mg QD	13	RFB dAc-RFB	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24
RFB 150mg QOD + FPV/r 700/100mg BID	9 11	APV RFB dAc-RFB	0
RFB 150mg QOD + FPV/r 700/100mg BID	13	APV	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12
RFB 150mg QOD + FPV/r 700/100mg BID	13	RFB dAc-RFB	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48

- Plasma APV, RFB and its active metabolite 25-O-desacetyl-rifabutin (dAc-RFB) concentrations were measured by LC/MS/MS.
- Total antimycobacterial concentrations were determined by summing RFB and dAc-RFB concentrations in uM units
- PK parameters were determined by WinNonlin Pro v4.1 non-compartmental analysis.
- ANOVA was used to determine geometric least squares (GLS) mean ratios comparing plasma RFB, 25-O-desacetyl-rifabutin and total antimycobacterial PK parameters following FPV/RTV+RFB to those following RFB alone.
- APV PK parameters were compared to historical data.

Results

Table 2. Subject Disposition and Demography

Number of Subjects:	RFB 300mg QD	RFB 150mg QOD + FPV/r 700/100mg BID
Dosed n	17	22
Completed n	17	15
Total Number Subjects Withdrawn n (%)	0	7 (32%)
Withdrawn due to Adverse Events n (%)	0	5 (23%)*
Withdrawn for Other Reasons n (%)	0	2 (9%)
Demographics	Total	
n	22	
Females: Males	4 : 18	
Mean Age in Years (SD)	35.3 (9.5)	
Mean Weight in Kg (SD)	82.4 (12.4)	
Race: (Caucasian : African American)	18 : 4	

* 3 subjects withdrew for rash, 1 for nausea, and 1 for myalgia/fever/increased WBC

Figure 1. RFB and dAc-RFB Pharmacokinetic Profiles

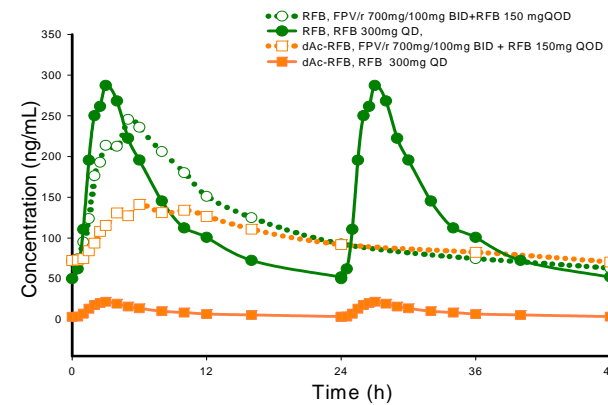


Table 3. RFB, dAc-RFB and Total Antimycobacterial PK Parameters and Treatment Comparisons

Parameter	RFB 300mg QD ¹	RFB 150mg QOD + FPV/r 700/100mg BID ¹	Treatment Comparison ²
Rifabutin			
AUC (0-48) µg.h/mL	6.11 ³ (5.33-7.01)	5.81 (5.04-6.68)	0.951 (0.843-1.07)
Cmax µg/mL	0.313 (0.267-0.366)	0.268 (0.227-0.316)	0.861 (0.716-1.04)
Cavg ⁴ µg/mL	0.127 (0.111-0.146)	0.121 (0.105-0.139)	0.951 (0.843-1.07)
25-O-desacetyl-RFB			
AUC (0-48) µg.h/mL	0.411 ³ (0.343-0.493)	4.60 (4.17-5.06)	11.2 (9.65-13.0)
Cmax µg/mL	0.024 (0.019-0.030)	0.139 (0.124-0.156)	5.79 (4.79-6.98)
Cavg ⁴ µg/mL	0.009 (0.007-0.010)	0.096 (0.087-0.106)	11.2 (9.65-13.0)
Total antimycobacterial			
AUC (0-48) µM.h	7.74 ³ (6.77-8.86)	12.7 (11.5-14.0)	1.64 (1.46-1.84)

- Parameters shown as geometric mean (95% CI)
- Treatment comparisons shown as geometric least squares mean ratios (90%CI)
- RFB AUC(0-48) following RFB 300mg QD determined by doubling AUC(0-24)
- Cavg was determined by AUC(0-t)/t

Table 4. APV PK Parameters and Treatment Comparisons

Parameter	FPV/r 700/100mg BID (Historical control) ¹	RFB 150mg QOD + FPV/r 700/100mg BID ¹	Treatment Comparison ²
APV			
AUC (0-t) µg.h/mL	34.8 (32.64-37.18)	47.1 (40.2-55.1)	1.35 (1.17-1.56)
Cmax µg/mL	5.38 (5.06- 5.735)	7.29 (6.43-8.27)	1.36 (1.18-1.55)
Ct µg/mL	1.97 (1.83-2.13)	2.32 (1.98-2.72)	1.17 (0.995-1.39)

- Parameters shown as geometric mean (95% CI)
- Treatment comparisons shown as geometric least squares mean ratios (90% CI)

Table 5. Drug Related AEs by System

Adverse Event	RFB 300mg QD Treatment A N=17	RFB 150mg QOD + FPV/r 700/100mg BID Treatment B N=22
No. (%) Subjects Reporting Any AE	12 (71%)	19 (86%)
Nervous system disorders (any event)	6 (35%)	12 (55%)
Headache	6 (35%)	10 (45%)
Renal and urinary disorders (any event)	10 (59%)	13 (59%)
Chromaturia	10 (59%)	11 (50%)
Pollakiuria	0	4 (18%)
Gastrointestinal disorders (any event)	6 (35%)	12 (55%)
Diarrhea	2 (12%)	7 (32%)
Nausea	0	4 (18%)
Investigations (any event)	6 (35%)	9 (41%)
Neutrophil count decreased	3 (18%)	3 (14%)
ALT increased	0	5 (23%)
Neutrophil count increased	0	3 (14%)
General disorders and administration site conditions (any event)	3 (18%)	7 (32%)
Fatigue	0	4 (18%)
Chills	0	3 (14%)
Pain	2 (12%)	1 (5%)
Musculoskeletal and connective tissue disorders (any event)	2 (12%)	5 (23%)
Myalgia	0	4 (18%)
Skin and subcutaneous tissue disorders (any event)	0	6 (27%)
Rash generalized	0	2 (9%)
Blood and lymphatic system disorders (any event)	3 (18%)	3 (14%)
Neutropenia	2 (12%)	1 (5%)
Thrombocytopenia	0	3 (14%)
Psychiatric disorders (any event)	5 (29%)	1 (5%)
Insomnia	4 (24%)	1 (5%)

Discussion

Following co-administration of RFB 150mg QOD + FPV/r 700/100mg BID, RFB AUC(0-48) was equivalent to that following RFB 300mg QD. dAc-RFB AUC(0-48) was increased 11-fold, from less than 10% of parent to approximately 80% of parent, relative to RFB 300mg QD. As a result of the significant increase in dAc-RFB, which is equipotent to RFB on a molar basis (1), the total antimycobacterial exposure was increased 64%.

Based on the impact of LPV/r on 50% reduced RFB, it is predicted that co-administration of LPV/r with 75% reduced RFB (RFB 150mg QOD) would have increased RFB, dAc-RFB, and total antimycobacterial AUC(0-48) 1.5-, 24-, and 2.9-fold, respectively, relative to RFB 300mg QD. By comparison, the 11-fold and 64% increase in dAc-RFB and total antimycobacterial AUC(0-48) values observed in this study are acceptable at less than half those predicted for the currently recommended RFB QOD regimen with LPV/r.

Co-administration of dose-adjusted RFB with FPV/r 700/100mg BID in this study increased plasma APV AUC(0-t) by 35%, and Cmax by 36%, but had no effect on Ct. This small increase in APV PK may reflect differences in study populations; the true effect of RFB QOD on APV PK is unclear without intrasubject comparisons. A 75% dose reduction of RFB to RFB 150mg QOD is appropriate when coadministered with FPV/r 700/100mg BID.

Conclusions

- The combination of RFB 150mg every other day and FPV/r 700/100mg BID for 14 days was well tolerated in this study.
- Following co-administration of FPV/r 700/100mg BID with RFB 150mg every other day, RFB AUC(0-48) was unchanged and Cmax was decreased modestly by 14%. 25-O-desacetyl-rifabutin AUC(0-48) and Cmax were increased by 11-fold and 6-fold, respectively. Total antimycobacterial AUC(0-48) was increased by 64%.
- Co-administration of RFB 150mg every other day with FPV/r 700/100mg BID increased plasma APV AUC(0-t) by 35% and Cmax by 36%, but Ct was increased 17% compared to historical controls.

RFB 150mg QOD is recommended when co-administered with FPV/r 700/100mg BID

References

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