

# Effect of Concomitant Rifampin on the Pharmacokinetics and Safety of Twice-Daily Atazanavir: ACTG Protocol A5213

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## BACKGROUND

- Rifampin (RIF) is a cornerstone of effective antituberculosis therapy.
- RIF is a potent inducer of hepatic cytochrome P450 (CYP) 3A expression which significantly lowers plasma concentrations of HIV protease inhibitors.<sup>1</sup>
- Although RIF may be co-administered with efavirenz and nevirapine, there are many situations where concomitant use of these agents together are not the agents of choice.
- Additional safe and effective strategies are needed to treat co-infection with HIV and *Mycobacterium tuberculosis*.
- Atazanavir (ATV), a widely prescribed PI, undergoes hepatic metabolism by CYP3A to generate 2 metabolites that lack antiviral activity.<sup>2</sup>
- Although approved dosages for ATV are 400 mg once daily (QD) or 300 mg boosted with ritonavir 100 mg QD, these doses are unlikely to be sufficient with concomitant RIF administration.<sup>1,3</sup>

## OBJECTIVES

- To characterize the steady-state pharmacokinetics (PK) of twice daily ATV alone and when co-administered with RIF in healthy, HIV-seronegative volunteers
- To characterize the safety of ATV and RIF in healthy, HIV-seronegative volunteers
- To address whether higher-than-approved, twice daily dosing of ATV without RTV could maintain adequate plasma concentrations with concomitant RIF

## METHODS

### Study Subjects and Design

- Phase I, open-label, single-arm PK interaction study with 3 sequential periods of ATV ± RIF
- 15 healthy volunteers between 18 and 55 years of age were selected to participate. A sample size of 18 had 90% power to test if the estimated ATV AUC<sub>24</sub> values were at least 70% of the historic mean AUC<sub>24</sub> for ATV 400 every 24 hours.
- Dosing for each period included:
  - Period 1: ATV 300 mg q 12h for at least 8 days but no more than 11 days
  - Period 2: ATV 300 mg q 12h + RIF 600 mg q 24h for at least 11 days but no more than 14 days
  - Period 3: ATV 400 mg q 12h + RIF 600 mg q 24h for at least 8 days but no more than 11 days

- Intensive sampling for concentration determinations was completed at the end of each period; a standard meal was provided
- Safety assessments including AST and ALT determinations were performed during PK sampling visits, the midpoint of each study period, and 14 to 21 days after the last dose of study drug.

### Bioanalytical and Pharmacokinetic Methods

- Plasma was collected within 15 minutes before the morning dose and 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours after observed ingestion of study medications.
- ATV was quantitated using a validated HPLC method at the University of Alabama at Birmingham that was linear over a concentration range of 25 to 20,000 ng/mL
- Rifampin and desacetyl rifampin assays were performed at Covance (Princeton, NJ) using a validated liquid chromatography-tandem mass spectrometry assay.
- PK parameter estimates were determined using a non-compartmental approach with WinNonlin version 4.01, Pharsight Corp., Mountain View, CA. AUC<sub>12(24)</sub> was determined using the linear/log trapezoidal method and the elimination rate constant was determined by linear regression of the terminal elimination phase concentration-time points.

### Statistical Design

- Wilcoxon signed rank test was applied to the within-subject differences in the untransformed ATV AUC and C<sub>12h</sub> values to test the null hypothesis of no difference in these parameters before initiation of RIF (period 1) versus after dosing to steady state (period 2 and 3).
- The paired t-test was used on log-transformed AUC and C<sub>12h</sub> values as a confirmatory test.
- Wilcoxon rank sum test was applied to the untransformed AUC, C<sub>min</sub>, and C<sub>max</sub> values to test the null hypothesis of no difference in RIF PK parameters when compared to historic controls.
- The t-test was used on the log-transformed AUC, C<sub>min</sub> and C<sub>max</sub> values as a confirmatory test.
- The geometric mean ratios of the PK parameters with 90% confidence intervals were derived to compare exposure during each treatment period.
- Bilirubin concentrations were compared by the exact Kruskal-Wallis test.

## RESULTS

- 15 subjects received at least 1 dose of study drug, 10 subjects completed all 3 PK sampling visits
- 10 evaluable subjects yielded 80% power to detect hypothesized differences

Table 1. Study Participant Demographics

	Subjects Receiving Dose (n=15)	Evaluable Subjects (n=10)
Male, n(%)	8 (53%)	5 (50%)
White, Non-Hispanic, n(%)	9 (60%)	5 (50%)
Black, Non-Hispanic, n(%)	2 (13%)	1 (10%)
Hispanic, n(%)	3 (20%)	3 (30%)
American Indian, n(%)	1 (7%)	1 (10%)
Age [yr, mean (range)]	35 (23-51)	34 (23-48)
Weight [kg, mean (range)]	77 (55-109)	78 (55-109)

- 1 subject discontinued due to intolerance to study drug and 4 discontinued study because of nonadherence with the protocol
- Study drugs were safe and generally well tolerated
- There were no elevations of ALT, Scr, or Hgb above the normal range, and no clinically significant ECG changes.
- Elevations of unconjugated bilirubin occurred while receiving atazanavir 300 mg every 12 hours without rifampin. Bilirubin values normalized during periods 2 and 3.

Table 2. Atazanavir PK parameters during each study period

Group	Parameter	T <sub>1/2</sub> (hr)	T <sub>max</sub> (hr)	C <sub>max</sub> (ng/mL)	C <sub>12h</sub> (ng/mL)	AUC <sub>12</sub> (hr*ng/mL)	AUC <sub>24</sub> (hr*ng/mL)	V/F (L)	CL/F (L/hr)
Period 1 ATV 300 q12h	Mean	5.1	3.2	3,913	983	23,784	47,367	78	12.1
	GM	4.8	3.0	3,671	911	21,921	43,842	74	10.6
	Min	3.1	1.0	2,197	363	10,179	20,357	48	3.7
	Median	4.6	3.0	3,943	804	22,356	44,713	70	10.7
	Max	11.1	5.1	6,322	2,484	41,148	82,297	127	24.9
CV%	43	36	37	69	42	42	35	52	
Period 2 ATV 300 q12h PLUS RIF 600 mg q24h	Mean	2.2	2.7	1,432	58	5,147	10,293	252	83.6
	GM	2.2	2.6	1,263	44	4,369	8,739	209	66.3
	Min	1.8	2.0	354	13	1,019	2,038	84	25.2
	Median	2.2	2.8	1,359	47	4,769	9,539	213	60.9
	Max	2.8	4.0	2,456	187	11,273	22,546	724	285.6
CV%	17	25	46	86	56	56	74	90	
Period 3 ATV 400 q12h PLUS RIF 600 mg q24h	Mean	2.4	2.9	2,364	125	9,816	19,631	171	48.5
	GM	2.4	2.7	2,149	113	8,945	17,890	146	42.8
	Min	1.9	1.0	744	39	2,880	5,760	84	21.8
	Median	2.4	3.0	2,132	114	9,819	19,638	136	39.4
	Max	2.8	4.0	4,296	260	17,282	34,565	490	131.7
CV%	13	34	43	47	41	41	71	64	

GM, geometric mean; T<sub>1/2</sub>, elimination half-life; V/F, apparent distribution volume; CL/F, oral clearance. ATV, atazanavir; RIF, rifampin; q12h, every 12 hours; q24h, every 24 hours. Rifampin was dosed at 600 mg once daily. The AUC<sub>24</sub> was estimated by doubling the AUC<sub>12</sub>.

- RIF markedly reduced ATV exposure, C<sub>12h</sub> more so than AUC<sub>12</sub> values
- Mean ATV C<sub>12h</sub> during period 2 was 97% lower compared with period 1, during period 3 it was 83% lower (both Wilcoxon p=0.02)
- Mean ATV AUC<sub>12</sub> values were reduced by 77% (Wilcoxon p=0.002) and 55% (Wilcoxon p=0.002) during periods 2 and 3, respectively.

Table 3. RIF and desacetyl RIF PK parameters during each study period

Group	Parameter	T <sub>1/2</sub> (h)	T <sub>max</sub> (hour)	C <sub>max</sub> (ng/mL)	C <sub>min</sub> (ng/mL)	AUC <sub>24</sub> (hr*ng/L)	V/F (L)	CL/F (L/hr)
Period 2 Rifampin	Mean	1.6	2.7	9492	329	45.7	32.1	15.1
	GM	1.5	2.6	9222	197	42.4	30.7	14.1
	Min	1.1	2.0	5080	99	23.0	21.7	6.6
	Median	1.3	2.6	9600	159	38.9	28.5	15.4
	Max	2.7	4.0	13000	1770	91.5	64.4	26.1
CV%	34	30	24	158	45	38	35	
Desacetyl rifampin	Mean	1.6	3.2	1653	128	8.3	200.4	89.5
	GM	1.6	3.1	1543	104	7.3	183.2	81.7
	Min	1.3	2.0	864	55	4.1	81.3	30.4
	Median	1.5	3.0	1590	95	7.0	214.9	86.1
	Max	1.9	5.0	2930	432	19.7	375.7	148.2
CV%	12	34	41	91	59	44	41	
Period 3 Rifampin	Mean	1.4	2.7	10110	360	41.7	33.0	16.5
	GM	1.4	2.5	9421	212	38.7	31.2	15.5
	Min	1.0	1.0	5270	91	23.7	20.7	7.3
	Median	1.3	2.0	9755	156	36.5	29.2	16.6
	Max	2.2	4.0	17100	1280	82.7	64.5	25.3
CV%	29	43	39	129	45	39	35	
Desacetyl rifampin	Mean	1.5	3.7	1714	118	8.4	158.6	75.6
	GM	1.5	3.6	1637	93	8.6	148.2	70.0
	Min	1.4	2.0	944	54	4.7	73.2	28.3
	Median	1.4	4.0	1680	76	8.2	145.1	72.9
	Max	1.8	4.0	2940	416	21.2	279.9	128.8
CV%	9	19	33	38	52	39	39	

GM, geometric mean; T<sub>1/2</sub>, elimination half-life; V/F, apparent distribution volume; CL/F, oral clearance. Rifampin was dosed at 600 mg once daily.

- Plasma RIF exposure did not differ substantially between periods 2 and 3
- Desacetyl RIF AUC<sub>24</sub> was slightly higher during period 3 than during period 2; exposure (AUC) during both periods were higher than historic controls (p=0.004)

Figure 1. ATV steady-state concentration-time curves for the three study periods

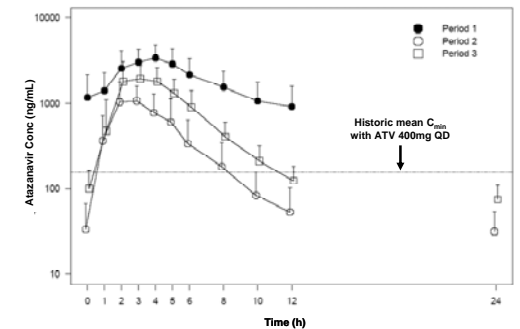
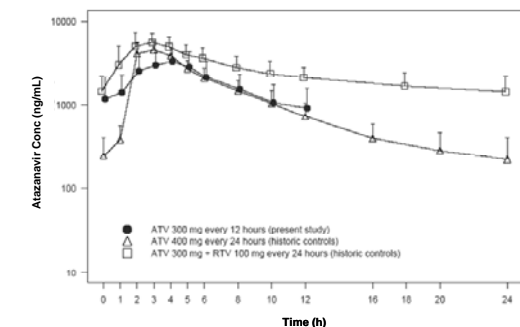


Figure 2. Atazanavir concentration-time profiles from three different dosing regimens



### Geometric Mean Ratios (GMR) and 90% CI Results

- ATV C<sub>max</sub> (Period 2/Period 1 and Period 3/Period 1) GMRs were 0.34 (0.24, 0.50) and 0.59 (0.44, 0.79), respectively.
- Similarly, ATV AUC<sub>12</sub> GMRs were 0.20 (0.13, 0.30) and 0.41 (0.30, 0.57), respectively.
- ATV C<sub>12h</sub> GMRs were 0.054 (0.03, 0.090) and 0.14 (0.09, 0.21), respectively.
- RIF AUC<sub>24</sub> GMRs for Periods 2 and 3 versus historic controls were 1.32 (1.06, 1.65) and 1.22 (0.96, 1.53), respectively.
- RIF C<sub>max</sub> GMRs were 1.14 (0.97, 1.35) and 1.17 (0.92, 1.49), respectively.
- Desacetyl rifampin AUC<sub>24</sub> GMRs for Periods 2 and 3 versus historic controls were 2.89 (2.12, 3.93) and 3.37 (2.546, 4.46), respectively, and the C<sub>max</sub> GMRs were 2.29 (1.78, 2.96) and 2.43 (1.97, 3.00), respectively.

## CONCLUSIONS

- ATV + RIF was safe and generally well tolerated, without untoward symptoms or laboratory abnormalities
- ATV 300mg or 400mg q12h will likely not provide adequate plasma ATV exposure to effectively treat HIV infection when co-administered with once daily RIF, as the ATV C<sub>min</sub> falls well below historical data for 400 mg once daily without RTV

## REFERENCES

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