

Lack of Effect of Gastric Acid Reducing Agents on Lopinavir/ritonavir Plasma Concentrations in HIV-Infected Patients

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BACKGROUND

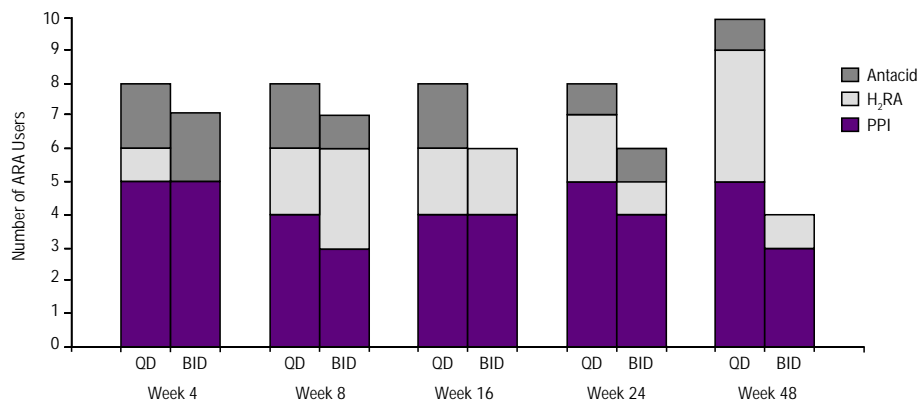
- Gastric acid reducing agents (ARAs) including proton pump inhibitors (PPIs), H₂-receptor antagonists (H₂RA) and antacids have been shown to decrease the absorption of several protease inhibitors.
- These protease inhibitors include atazanavir, fosamprenavir and indinavir; concentrations are reduced by 30 to > 50%.^{1,2,3}
- Ionized medications may bind to the divalent cations of antacids and sucralfate to result in poorly absorbed complexes.⁴ Moreover, proton pump inhibitors and H₂-receptor antagonists significantly lower intraluminal acidity, thereby reducing the solubility and decreasing the absorption of drugs that are weak bases.^{4,5} The fact that atazanavir is formulated as an acidic salt could make the drug more susceptible to changes in pH.
- Lopinavir is a nonionizable compound thus its solubility is not influenced by changes imposed by acid reducing agents. Ritonavir is a weak base with two ionizable sites that dissociate below pH 3. Therefore, acid reducing agents may not affect these drugs to the same degree as these other protease inhibitors. The effect of acid reducing agents on lopinavir/ritonavir concentrations has not been formally evaluated. In this analysis, the effect of these agents is assessed in HIV infected patients receiving lopinavir/ritonavir-based therapy in a clinical trial (Study M02-418) in which trough drug concentrations were obtained.

METHODS

- Antiretroviral-naïve, HIV infected patients (N=190) were randomized 3:2 to receive lopinavir/ritonavir, as 800/200 mg QD or 400/100 mg BID, in combination with tenofovir and emtricitabine.
- Lopinavir/ritonavir trough concentrations were collected on weeks 4, 8, 16, 24 and 48.
- Forty eight-week efficacy and safety data for this study, as well as full pharmacokinetic results, have been presented previously.^{6,7}
- Patients were classified as users of acid reducing agent if the study investigator reported they were receiving acid reducing agent(s) as concomitant therapy at the time of the PK visit, or nonusers if otherwise.
- A repeated measure analysis using mixed effects modeling was performed to compare the lopinavir/ritonavir concentrations between acid reducing agent users vs. nonusers. The trough concentrations were logarithmically transformed prior to the analysis so that the data had a near normal probability distribution.
- The dependency along time (weeks 4 to 48) was accounted for using the first-order autoregressive (AR1) model.
- The median and interquartile range were plotted for the trough concentration vs. time curve for ARA users and nonusers.

RESULT 1: CONCURRENT ARA USE

- In this study, the investigators reported concurrent administration of gastric acid reducing agents including antacids of various brand names, PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole), and H₂RA (ranitidine and famotidine).
- The number and classification of patients receiving gastric acid reducing agents are presented below:



- Among patients having trough concentration data available, 86, 95, 92, 86 and 76 patients were nonusers on week 4, 8, 16, 24 and 48, respectively, in the QD arm.
- For the BID arm, 45, 58, 57, 53 and 45 patients with available trough concentrations were classified as nonusers on week 4, 8, 16, 24 and 48, respectively.

RESULT 2: LOPINAVIR CONCENTRATIONS

Lopinavir trough concentrations ($\mu\text{g/mL}$) are summarized below:

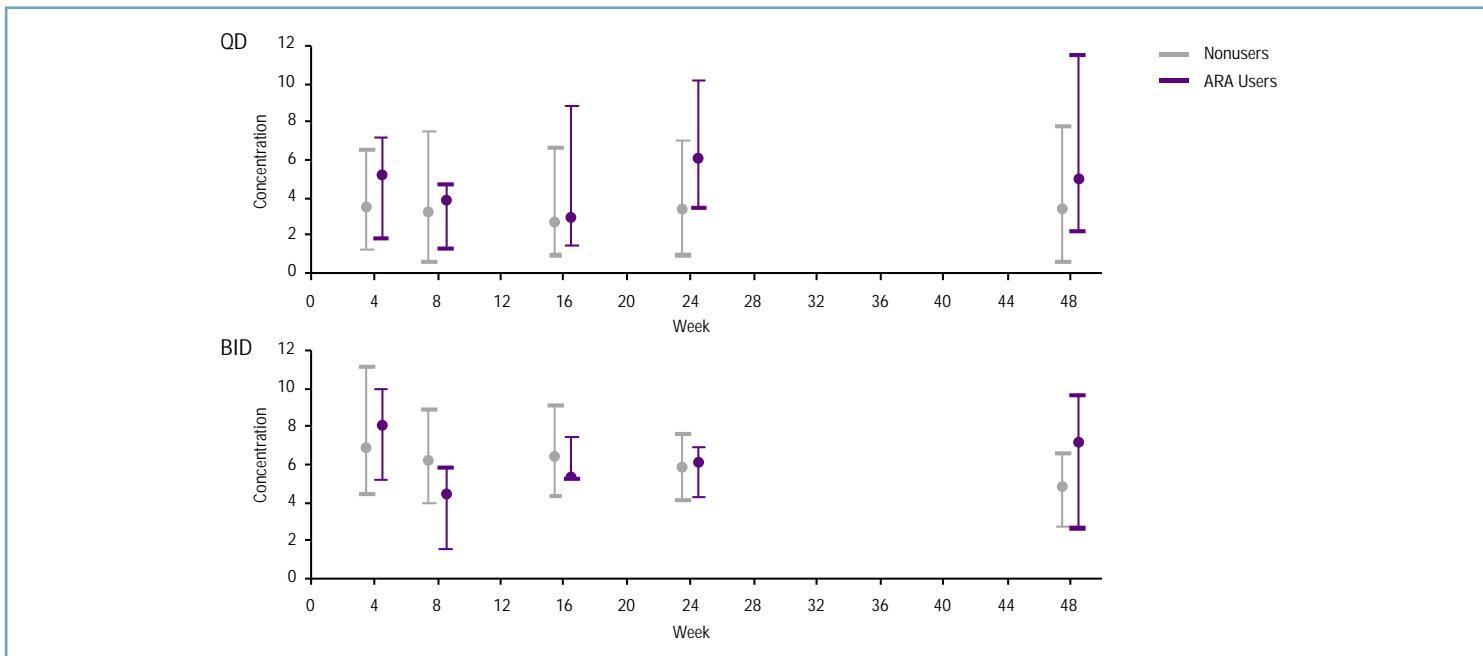
Week	QD				BID			
	N	Nonuser Mean \pm SD	N	ARA User Mean \pm SD	N	Nonuser Mean \pm SD	N	ARA User Mean \pm SD
4	86	4.70 \pm 4.30	8	5.14 \pm 4.00	45	7.65 \pm 4.71	7	8.06 \pm 3.95
8	95	4.56 \pm 4.57	8	3.65 \pm 2.52	58	7.00 \pm 4.72	7	5.41 \pm 5.45
16	92	4.38 \pm 4.45	8	6.32 \pm 7.77	57	7.32 \pm 4.17	6	5.72 \pm 2.05
24	86	4.69 \pm 4.63	8	7.05 \pm 5.10*	53	6.28 \pm 4.05	6	6.03 \pm 1.86
48	76	4.83 \pm 5.21	10	8.38 \pm 10.37 [†]	45	5.21 \pm 3.46	4	6.14 \pm 4.61

* P=0.01, statistically significantly higher concentration in users

[†] P=0.06, marginally significantly higher concentration in users

Note: no significant differences during 48 weeks for BID ($p>0.44$).

Median and Interquartile Range for Lopinavir Trough Concentrations



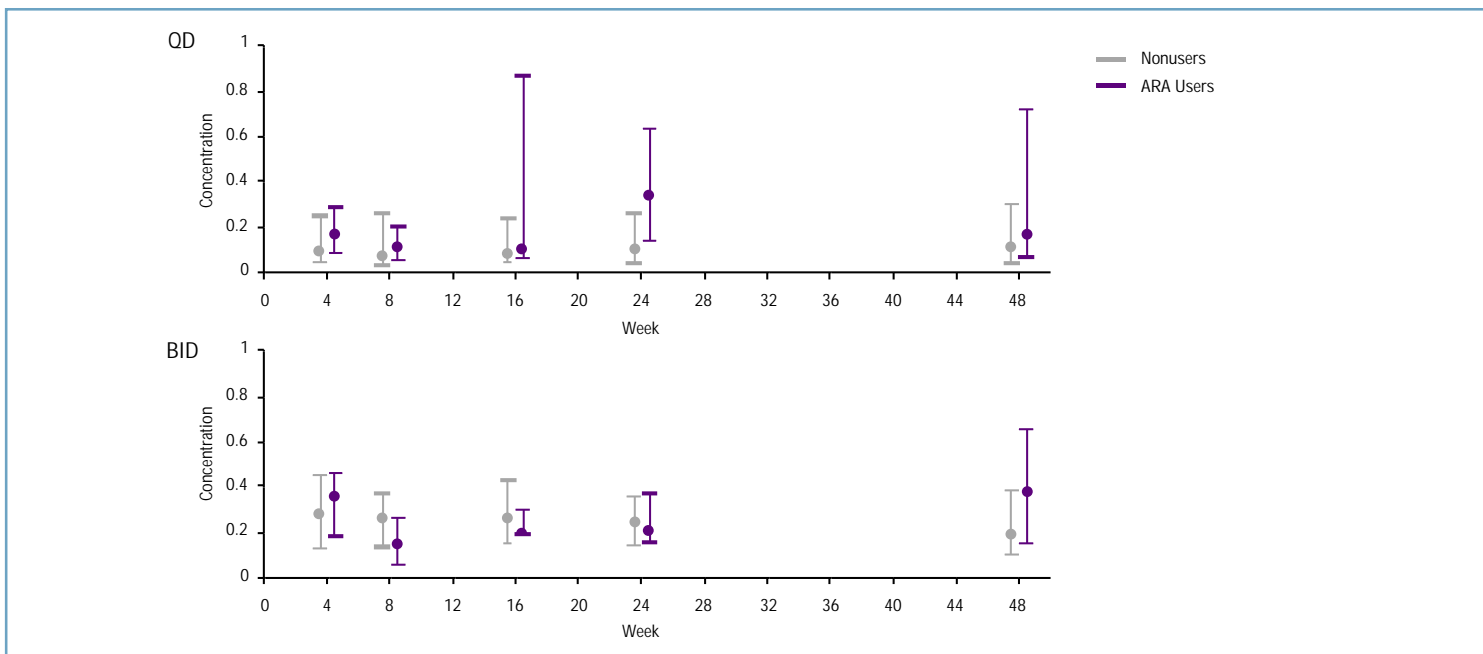
RESULT 3: RITONAVIR CONCENTRATIONS

Ritonavir trough concentrations ($\mu\text{g/mL}$) are summarized below:

Week	QD				BID			
	N	Nonuser Mean \pm SD	N	ARA User Mean \pm SD	N	Nonuser Mean \pm SD	N	ARA User Mean \pm SD
4	86	0.22 \pm 0.33	8	0.21 \pm 0.19	45	0.33 \pm 0.28	7	0.36 \pm 0.18
8	95	0.23 \pm 0.35	8	0.15 \pm 0.13	58	0.33 \pm 0.27	7	0.22 \pm 0.23
16	92	0.22 \pm 0.33	8	0.42 \pm 0.48	57	0.32 \pm 0.21	6	0.23 \pm 0.07
24	86	0.27 \pm 0.46	8	0.37 \pm 0.28 [†]	53	0.30 \pm 0.22	6	0.30 \pm 0.22
48	76	0.25 \pm 0.33	10	0.41 \pm 0.50	45	0.30 \pm 0.32	4	0.40 \pm 0.35

[†] P=0.06, marginally significantly higher concentration in users
 Note: no significant differences during 48 weeks for BID (p>0.31).

Median and Interquartile Range for Ritonavir Trough Concentrations



CONCLUSIONS

- Lopinavir/ritonavir treated patients who received acid reducing agents did not appear to have a reduction in lopinavir and ritonavir trough concentrations through 48 weeks of therapy.
- Further formal investigation of the effect of potent acid reducing agents on lopinavir/ritonavir pharmacokinetics is warranted.

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ACKNOWLEDGMENTS

- Study M02-418 subjects and study sites
- Abbott Laboratories: Amber Cekander, Michael J Fath, George Hanna, Balakrishna Hosmane, Dale Kempf, Kathryn King, Charles Locke, Michelle Long