Lack of Interaction Between Atazanavir and Proton Pump Inhibitors in HIV-Infected Patients Treated With Ritonavir-Boosted Atazanavir

To the Editor:

Conflicting results have been recently published concerning drug interaction between atazanavir (ATV) and antacid treatments, especially proton pump inhibitors (PPIs).

In the August 1, 2005 issue of this journal, Khanlou and Farthing[1] summarized the results they collected in 10 HIV clinics in Los Angeles, saying that the use of ATV, even boosted with ritonavir (RTV), with PPIs should be avoided. These data require some comments.

In this study, the prospective method of plasma collection is not clearly defined. Were the patients interviewed by a physician on the treatment they were really taking? Did the nurse who drew the blood samples ask the patients when they had taken their last dose of ATV and antacid treatment?

The median ATV minimum concentrations (C_{min}s) reported are not in keeping with values observed in recent published studies and in our experience on HIV-infected patients treated with boosted ATV (Table 1).

Because of its chemical structure, ATV absorption is highly dependent on an appropriate gastric pH. The potential interaction between ATV and PPIs or histamine-2 receptor blockers (H_2RBs) is expected to reduce ATV exposure.

In the presence of an H_2RB, however, the median ATV C_{min} reported in this study was 2-fold higher than values observed in the previously reported series (performed in patients without antacid treatment). Such a high ATV C_{min} was found in only 1 study on healthy volunteers.[2] In presence of PPIs, the median ATV C_{min} was found to be strictly comparable to those observed in the previous studies, where a significant reduction should be expected. These results could be explained by too short a time between blood sample collection and drug intake.

Assessing the time between ATV intake and blood collection precisely is fundamental in such a study. Only ATV plasma concentrations measured 24 ± 4 hours (C_{min}) after the last intake should be taken into account in patients who have received a stable ATV regimen for at least 1 week before blood sampling. Treatments received by the patients included in this study should be detailed.

The proportion of patients receiving ATV boosted with RTV may indeed highly influence the C_{min} values observed. The results collected in such patients should therefore be distinguished from those collected in patients receiving ATV without RTV. In our prospective cohort of 184 patients, median C_{min}s measured at 24 ± 4 hours were 499 [26–2205] ng/mL and 99 [12–1159] ng/mL among the 141 patients treated with 300 mg of ATV plus 100 mg of RTV and the 43 patients receiving 400 mg of ATV alone, respectively ($P < 0.0001$).

The combination of ATV with another protease inhibitor or nonnucleoside reverse transcriptase inhibitor may lead to significant drug interactions and should also be noted.

TABLE 1. Median ATV C_{min} in Patients Treated With Boosted ATV (300/100 mg/d)

ATV C_{min} (ng/mL)	n	Reference
790	25	Gonzales de Req, CROI 2005
774	81	Winston, CROI 2005, JAC 2005
573	79	Kruse, Fifth IWCPTT 2004
564	10	Taburet, CROI 2003
504	15	Von Hentig, IAS 2004
499	141	Poirier, Guiard-Schmid (submitted)
496	61	Gibbons, Sventh ICDTHI 2004
1206	44*	Agarwala, CROI 2005
476	92	Ray, Br J Clin Pharmacol 2005

*Healthy volunteers study.

During PPI treatment, the time during which the intragastric pH is above 4.0 increases with the acid-suppressive dose, and pH can vary widely during the day in a given individual. Doses of PPIs may affect ATV absorption differently and have to be precisely described.

The time interval between ATV and antacid drug administration may also play a role. This is a possible confusion bias if patients did not state the time of their last drug intake accurately.

In our cohort, we prospectively compared ATV C_{min} in HIV-infected patients receiving ATZ plus RTV, with or without a PPI, to assess this specific drug interaction in clinical practice.

Among the first 92 patients enrolled, 13 stated that they were taking a PPI. Among these 13 patients, 10 were using omeprazole (20 mg/d, except for 1 patient who was taking 40 mg/d) and 3 were using rabeprazole (30 mg/d).

Median ATV trough concentrations were 551 ng/mL (range: 203–1976 ng/mL) in the patients receiving PPIs and 469 ng/mL (range: 65–1944 ng/mL) in the group without PPIs. Results showed that PPI treatment did not affect ATV C_{min} values in our patients.[3]

A recent case report with pharmacokinetic study showed no interaction between boosted ATV and lansoprazole. Another study showed no clinical or immunovirologic failures in 14 patients treated with ATV and PPIs after a 6-month follow-up.[4,5] Our findings are in keeping with these results.

Our conclusion is therefore completely different from that of Khanlou and Farthing[1] because we observed that PPIs seem to be compatible with boosted ATZ therapy in clinical practice. It is nonetheless recommended to monitor ATV drug concentrations in case of concomitant antacid treatment.

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Response to: Lack of Interaction Between Atazanavir and Proton Pump Inhibitors in HIV-Infected Patients Treated With Ritonavir-Boosted Atazanavir

To the Editor:

The authors thank Dr. Guiard-Schmid and colleagues for their interest in our article.[2] In our study, the drug levels were obtained before the next dose due time and we eliminated nonadherent patients by interview. Atazanavir (ATV) absorption is clearly altered by administration of acid-modifying agents; the degree to which this occurs is dependent on the potency of acid-suppressing agents.[3–5] Current recommendations are to avoid the proton pump inhibitors (PPIs) and to separate histamine-2 blockers (H_2Bs) by 12 hours from ATV dosing.[5] One should be quite cautious in interpreting drug levels because of major patient intervariability.

In fact, the data from Guiard-Schmid and colleagues attest to high interpatient variability, where the range was 203 to 1976 ng/mL for the ATV/ritonavir combined with PPI group and 65 to 1944 ng/mL for the non-PPI group, allowing some patients to have inadequate levels. We are surprised by these findings, because the PPI group has slightly better levels than non-PPI group. It would be helpful to know the lower levels of sensitivity and the coefficient of variation for their assays.

Furthermore, the median levels obtained by Guiard-Schmid et al (551 ng/mL in the PPI group vs. 469 ng/mL in the non-PPI group) may be adequate for naive patients but would be inadequate in patients with antiretroviral experience. Recent studies have shown that higher ATV concentration trough (C_{trough}) levels (ie, 774–850 ng/mL) were more likely to reduce viral load (VL) in experienced patients.[6–8] We are starting to understand the relation between drug levels and antiviral activity of the agents better, but many questions are still unanswered. One interesting issue is the intracellular levels of these agents and their relation to other drugs, particularly ritonavir, and viral suppression.

We have seen patients in our cohort with undetectable serum levels of ATV and <50 HIV RNA copies/mL. There are also other reports showing lack of failure in these types of patients.[9] Our group is currently in the process of investigating the intracellular levels and their relation to viral suppression. Until this information is available, it would be wise to follow the current recommendation on avoiding PPIs and separating H_2Bs with ATV.

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Proton Pump Inhibitor Therapy in Atazanavir-Treated Patients: Contraindicated?

To the Editor:

Atazanavir (ATV; Reyataz, Bristol-Myers Squibb, Princeton, NJ) has become a popular protease in hibitor owing to its simplified dosing and diminished effect on serum glucose and lipids as compared with other protease inhibitors. However, its use is limited in patients concomitantly receiving agents that reduce gastric pH, as acidity is required for solubility and absorption.[1] In a survey of 110 HIV-infected patients, 42% received proton pump inhibitor (PPI) therapy since beginning protease inhibitor–based highly active antiretroviral therapy (HAART),[2] suggesting the number of patients affected by this possible interaction is substantial.

A pharmacokinetic study evaluated the effect of the PPI omeprazole in 48 healthy subjects receiving atazanavir 300 mg plus ritonavir 100 mg daily (ATV/r). Following 10 days of therapy with ATV/r, patients were randomly assigned to receive 1 of 3 regimens with omeprazole 40 mg daily for 10 days: ATV/r + omeprazole, ATV/r + omeprazole + 8 oz cola, or ATV/r 400/100 + omeprazole. When comparing ATV/r alone vs. with omeprazole, substantial reductions in C_{max} (72%), area under the concentration curve (76%), and C_{min} (78%) were observed. The authors concluded that PPI use should be avoided in patients taking ATV.[3,4] Furthermore, the complexity of this uncertain pharmacokinetic picture deepens for patients receiving tenofovir (TDF), which reduces ATV concentrations; the manufacturer recommends using ATV/r in such patients to ensure adequate ATV concentrations.[1]

Interpatient variability of ATV pharmacokinetic parameters has been reported in HIV-infected patients regardless of whether it is boosted with ritonavir or combined with TDF.[5] In addition, plasma concentrations in healthy subjects may not correlate with those of HIV-infected patients,[1] B. Smith, August 10, 2005, oral communication). Gonzalez et al,[6] in an attempt to correlate ATV C_{min} with clinical outcome in HIV-infected patients, concluded that maintaining ATV concentrations between 150–850 ng/mL resulted in virologic response (defined as viral load <50 or viral load decrease of $>\log_{10}$ 2) in 85% of patients at 12 weeks.

Most recently, Guiard-Schmid et al [7] compared ATV C_{min} in patients receiving ATV/r alone vs. those receiving a PPI (omeprazole 20 mg daily in 9 patients and 40 mg daily in 1 patient; 3 patients received rabeprazole 20 mg daily). Median C_{min} was 551 ng/mL (203–1976) and 469 ng/mL (65–1944) in those treated with and without a PPI, respectively. This was significantly lower (2.5-fold) than values previously reported in healthy subjects. Furthermore, these workers found no difference in C_{min} in 3 patients prior to and after discontinuing PPI therapy. The authors concluded that neither PPI therapy nor TDF coadministration significantly affected C_{min} values in HIV-infected patients.

These findings suggest that ATV/r may be coadministered with PPI therapy without affecting ATV C_{min}. However, these data must be viewed in light of their limitations. Pharmacokinetic parameters other than C_{min} were not reported and may have better illustrated drug disposition. In addition, clinical outcome was not assessed. Patients receiving PPIs seemingly have ATV C_{min} values between those seen with ATV 400 mg daily and ATV/r in HIV-infected patients. Pharmacokinetic modeling suggests that HIV-infected patients receiving ATV 400 mg daily will have an average C_{min} of approximately 90 ng/mL (range 0–450 ng/mL based on 5th and 95th percentiles) and those receiving ATV/r will have an average C_{min} of 800 ng/mL (range 100–2500 ng/mL based on 5th and 95th percentiles) (B. Smith, August 10, 2005, oral communication). Winston et al,[8] in a recent pharmacokinetic analysis of ATV/r-treated patients, observed mean ATV C_{min} of 774 ng/mL, which supports the aforementioned pharmacokinetic modeling. Until firm correlations between ATV C_{min} and virologic response are available, the long-term outcome of such a combination remains unclear. Clinical data are limited, but a recent case series suggests that use of acid-suppressive therapy does not negatively affect virologic outcome.[9] Additional clinical data, including the use of a control group for comparison, are needed to make clinical decisions regarding this potential drug–drug interaction. We report clinical findings on patients receiving combination ATV/r plus PPI compared with those receiving ATV/r alone.

METHODS

Pharmacy records were reviewed to identify all patients using ATV/r and a PPI for at least 6 weeks. Use of both drugs was verified by pharmacy refill records and, when indicated, patient interviews. Virologic responses were compared patients on ATV/r between with and without concomitant PPI therapy. Descriptive statistics were performed and groups compared using Fisher exact test (STATA software 8.0; Stata Corp., College Station, TX).

RESULTS

Of the 442 patients in our clinic, 76 were receiving ATV/r; 10 of these patients were treated with a PPI, and 4 of these 10 were naive to protease inhibitors. The average length of combination therapy with ATV/r + PPI was 21.6 (range 6–52) weeks. Eight patients were receiving rabeprazole 20 mg daily, 1 patient rabeprazole 40 mg daily, and 1 patient omeprazole 20 mg daily. Nine patients (90%) in the PPI group and 55 of 66 patients (83%) in the non-PPI group had viral load of <500 copies/mL (Table 1). The groups with and without PPI therapy did not differ with respect to virologic outcomes; P value = 1.00 by 2-tailed Fisher exact test (95% CI: 0.21 to 85.97). Nine patients (90%) in the PPI group were receiving a TDF-containing regimen.

DISCUSSION

Simultaneous use of ATV/r and PPI was not associated with a higher virologic

TABLE 1. Comparison of Virologic Response Rates in Patients Receiving ATV/r With and Without a PPI

Regimen	VL < 50 Copies/mL	VL 50–500 Copies/mL	VL > 500 Copies/mL
ATV/r −PPI ± TDF	42/66 (63%)	13/66 (20%)	11/66 (17%)
ATV/r + PPI ± TDF	7/10 (70%)	2/10 (20%)	1/10 (10%)
ATV/r − PPI + TDF	30/53 (56.6%)	12/53 (22.6%)	11/53 (20.8%)
ATV/r − PPI − TDF	11/13 (85%)	2/13 (15%)	0/13 (0%)
ATV/r + PPI + TDF	6/9 (67%)	2/9 (22%)	1/9 (11%)
ATV/r + PPI − TDF	1/1 (100%)	0/1 (0%)	0/1 (0%)

VL, viral load.

failure rate than was observed in those not taking a PPI. Unfortunately, pharmacokinetic parameters were not examined in this retrospective review. However, these results are in keeping with the pharmacokinetic findings from Guiard-Schmid et al, suggesting a negligible effect on clinical outcome. Although long-term studies involving both therapeutic drug monitoring and clinical response rates are needed to determine efficacy, it would seem that HIV-infected patients are less susceptible to this interaction. The reason for this is unclear, especially as this patient population has an increased prevalence of hypochlorhydria and a majority of patients included in this and other small cohorts were also receiving TDF. The specific PPI, the dose and time administered in relation to PPI administration may also play a role in the magnitude of this effect. Although confusion remains on whether this interaction is clinically significant in HIV-infected patients, limited pharmacokinetic and clinical data suggest this interaction may not prohibit the use of these 2 agents in all patients.

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ERRATUM

In the article appearing in the *Journal of Acquired Immune Deficiency Syndromes*, Vol. 40, pp. 175–181, entitled Viral, Nutritional, and Bacterial Safety of Flash-Heated and Pretoria-Pasteurized Breast Milk to Prevent Mother-to-Child Transmission of HIV in Resource-Poor Countries: A Pilot Study, the source of support footnote was incorrect, it should read:

> "Supported by the Thrasher Research Fund; North-Central California Center for AIDS Research, a National Institutes of Health-funded program (P30-AI49366-01); James B. Pendleton Charitable Trust; University of California at Davis Children's Miracle Network; and contributions from Stephen Luczo, Julie Still, and William and Denise Watkins."