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Decrease of Atazanavir and Lopinavir Plasma Concentrations in a Boosted Double Human Immunodeficiency Virus Protease Inhibitor Salvage Regimen▽

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The human immunodeficiency virus protease inhibitor combination of atazanavir (ATV)-lopinavir-ritonavir was reported to exhibit a mutual pharmacoenhancement of plasma lopinavir and ATV concentrations which may be beneficial for salvage patients. We identified 17 patients in our pharmacokinetic database taking this combination and found conflicting results. Plasma concentrations of both ATV and lopinavir were modestly, although not significantly, decreased when the drugs were coadministered. Therefore, patients should be selected carefully for this regimen and frequent clinical and therapeutic drug monitoring is strongly advised.

A nucleoside-free combination of lopinavir (LPV)-ritonavir (RTV) and ATV can be an alternative therapy regimen for human immunodeficiency virus type 1 (HIV-1)-infected patients who have no further options with nucleoside reverse transcriptase inhibitors (NRTI) due to toxicity or resistance, as previously shown for other protease inhibitor combinations (12, 13, 17). Both LPV and ATV are highly potent against HIV-1; i.e., they have a low in vivo 50% inhibitory concentration for wild-type HIV-1 replication (Kaletra package insert, Abbott Laboratories, Chicago, IL; Reyataz Product Information, Bristol Myers-Squibb Company, Princeton, NJ). Their diverging resistance profiles may even increase the antiretroviral efficacy of this regimen compared to that of each separate substance (4).

Moreover, a pharmacokinetic interaction between LPV and ATV has been suggested to further increase the therapeutic efficacy of this combination and supersede therapeutic drug monitoring (TDM). When given in combination, 1.4 to 2 times larger areas under the LPV plasma concentration-versus-time curves, AUC, and maximum plasma LPV concentrations, $C_{max,}$ and twofold higher minimum plasma ATV concentrations, $C_{min,}$ were observed compared to historical controls having received single therapy with either drug (9). This so-called double boosting may be explained by a mutual inhibition of the cytochrome P450 3A-mediated metabolic clearance of LPV and ATV.

However, that previously reported (9) pronounced and probably therapeutically relevant increase in plasma LPV and ATV concentrations contrasts with other published results showing a more modest effect of the pharmacokinetic drug interaction (3, 8, 14, 16). In light of these discrepant reports and because this regimen is prescribed especially to extensively pretreated HIV-1-infected patients in whom sufficient plasma protease inhibitor concentrations are of crucial importance, we reappraised the extent of the mutual boosting in an LPV-RTV-ATV combination by retrospectively analyzing available pharmacokinetic data. We selected 17 patients (group 1) from our pharmacokinetic database receiving LPV-RTV at 400 and 100 mg twice daily (BID) plus ATV at 300 mg once a day (QD), partly plus NRTI ($n = 4$) and enfuvirtide ($n = 3$). As controls matched for sex, age (within 4 years), ethnicity, and body weight (within 8 kg), a random sample was drawn from the database consisting of patients receiving either ATV and RTV at 300 and 100 mg QD (group 2, $n = 17$) or LPV and RTV at 400 and 100 mg BID (group 3, $n = 17$), each together with NRTI. Groups 1, 2, and 3 included 16 men and 1 woman of Caucasian ethnicity with mean (95% confidence interval [CI]) ages of 43.0 (39.9 to 46.1), 41.7 (38.1 to 45.4), and 42.2 (39.3 to 45.1) years and mean (95% CI) body weights of 73.4 (66 to 80.7), 72.0 (62.9 to 81.0), and 72.1 (64.7 to 79.5) kg. The mean baseline CD4 cell counts and HIV-1 RNA copy numbers were 170 cells/mm^3 and 4.34 $\log_{10}$ copies/ml, 332 cells/mm^3 and 3.1 $\log_{10}$ copies/ml, and 270 cells/mm^3 and 4.2 $\log_{10}$ copies/ml in group s 1, 2, and 3, respectively. Patients on comedication known to induce or inhibit cytochrome P450 3A and patients with documented noncompliance were not included in the analysis. Two patients in group 1 (ATV–LPV-*r*), nine patients in group 2 (ATV-RTV plus NRTI), and one patient in group 3 (LPV-*r* plus NRTI) took tenofovir-DF as part of the NRTI comedication, which is nevertheless not expected to impair plasma ATV concentrations if boosted with low-dose RTV (15).

A standardized TDM procedure (6, 17) had been carried out after at least 2 weeks (median, 5 weeks) on therapy under steady-state-conditions as part of the clinical routine diagnostic procedures used between 03/2003 and 03/2006. Patients underwent a pharmacokinetic assessment immediately before and 1, 2, 4, 6, 9, and 12 h (and 24 h in ATV-containing regimens) after dosing. The drugs were taken together with a breakfast of

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TABLE 1. Comparison of the pharmacokinetic, demographic, and clinical baseline data of three groups of adult HIV-1 infected patients[a]

Parameter	ATV			LPV	
	ATV-LPV/*r* GeoMean (90% CI), group 1[b]	ATV-RTV GeoMean (90% CI), group 2[b]	Group 1 vs group 2 GMR (*P* value)	ATV-LPV-*r* GeoMean (90% CI), group 1[b]	LPV/*r* GeoMean (90% CI), group 3[b]
C_{min} (ng/ml)	390 (288–529)	329 (223–483)	1.19 (0.633)	2,232 (1,700–2,930)	2,827 (2,218–3,603)
C_{max} (ng/ml)	2,257 (1,740–2,926)	2,745 (2,125–3,548)	0.82 (0.540)	5,252 (4,356–6,333)	6,847 (5,776–8,117)
AUC (ng · h/ml)	26,412 (20,552–33,943)	30,329 (22,848–40,260)	0.87 (0.388)	48,465 (39,849–58,944)	59,726 (51,085–69,829)
$t_{1/2}$ (h)	7.79 (6.56–9.24)	7.21 (6.35–8.20)	1.08 (0.484)	6.56 (5.34–8.06)	8.21 (6.78–9.94)
CL/F (ml/min)	185 (144–236)	154 (116–204)	1.20 (0.463)	133 (109–162)	99 (81–122)

[a] The patients compared were taking either ATV at 300 mg QD plus LPV and RTV at 400 and 100 mg BID or ATV and RTV at 300 and 100 mg QD ($n = 17$) plus NRTI or LPV and RTV at 400 and 100 mg BID ($n = 17$) plus NRTI. Patient pairs were matched for sex, age, ethnicity, and body weight. Results were compared between the groups by means of analysis of variance and post-hoc Bonferroni-corrected *t* tests. LPV/*r*, LPV-RTV gel capsule formulation; GeoMean, geometric mean; GMR, geometric mean ratio; C_{trough}, trough plasma drug concentration immediately before dosing (at 0 h); $t_{1/2}$, half-life; CL/F, oral clearance; m/f, male/female.
[b] $n = 17$.

approximately 2,500 kJ, 21% of which was from fat. The standardized TDM protocol ensures the comparability of the data while reproducing the field conditions under which antiretroviral therapy is commonly taken.

Plasma drug concentrations were determined by validated liquid chromatography-tandem mass spectrometry methods in an externally quality-controlled laboratory (5), and basic pharmacokinetic parameters were obtained by noncompartmental standard analyses. Group comparisons of pharmacokinetic parameters were performed by means of analyses of variance, with post-hoc *t* tests in the case that this produced significant results.

We observed that most of the pharmacokinetic parameters of RTV-boosted ATV and LPV were modestly decreased, although this was not statistically significant (Table 1 and Fig. 1). Specifically, the geometric mean (90% CI) C_{max} and AUC of ATV for group 1 versus group 2 were decreased (geometric mean ratios, 0.82 [$P = 0.388$] and 0.87 [$P = 0.540$], respectively). The geometric mean (90% CI) C_{min}, C_{max}, and AUC of LPV for group 1 versus group 3 were also decreased (geometric mean ratios, 0.79 [$P = 0.312$], 0.76 [$P = 0.188$], and 0.81 [$P = 0.098$], respectively). One parameter showing a moderate and statistically insignificant increase was the geometric mean (90% CI) C_{min} of ATV for group 1 versus group 2 (geometric mean ratio, 1.19 [$P = 0.633$]). The C_{max} and AUC of RTV were significantly lower when RTV was coadministered with ATV-LPV, in contrast to ATV-NRTI (geometric mean ratios, 0.54 [$P = 0.004$] and 0.42 [$P = 0.021$], respectively). Converse differences in the C_{min} (geometric mean ratio, 2.40 [$P = 0.004$]) of RTV were due to the different RTV dosing intervals in the two regimens. It has been shown before that plasma RTV concentrations were significantly decreased when the drug was taken as part of an LPV-RTV coformulation, but it was also reported that even very low plasma RTV concentrations sufficiently enhance the plasma concentrations of other HIV protease inhibitors (13), so that the mechanisms of the interaction between LPV and ATV remain unknown.

In contrast to the report of up to doubled plasma concentrations of combined ATV-LPV compared to their plasma concentrations when given alone (9), we observed similar plasma concentrations displaying, if anything, a tendency toward a decrease compared to single therapy. Currently, the distinct simultaneous boosting of saquinavir by ATV and RTV remains an isolated finding (1, 17): neither amprenavir (11, 16; G. Kruse, H. Stocker, A. Breske, K. Arasteh, A. Plettenberg, S. Staszewski, and M. Kurowski, poster 6.6, 5th Int. Workshop Clin. Pharmacol. HIV Ther., Rome, Italy, 2004), tipranavir (2), nor darunavir (10) showed such alterations of plasma concentrations when combined with ATV-RTV. A pharmacokinetic reason for these differences might be the very low bioavailability of oral saquinavir of only 4 to 9%. As a so-called high-extraction drug, i.e., a drug that is quickly and largely metabolized when passing the site of metabolism, saquinavir is

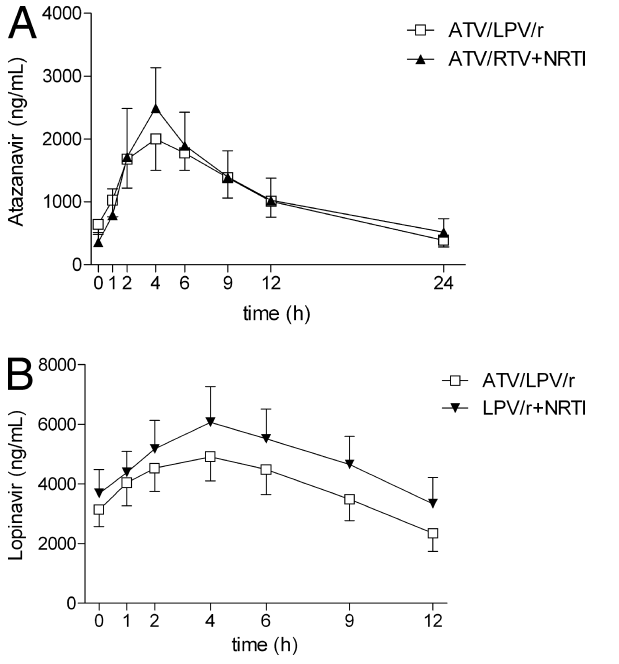

FIG. 1. (A) Geometric mean (90% CI) plasma ATV concentration-time curves, at steady state, of HIV-1-infected adult patients taking either ATV at 300 mg QD plus LPV and RTV at 400 and 100 mg BID ($n = 17$) or ATV and RTV at 300 and 100 mg QD plus NRTI ($n = 17$). Patient pairs were matched for sex, age, ethnicity, and body weight. LPV/*r*, LPV-RTV gel capsule formulation. (B) Geometric mean (90% CI) plasma LPV concentration-time curves, at steady state, of HIV-1-infected adult patients taking either ATV at 300 mg QD plus LPV and RTV at 400 and 100 mg BID ($n = 17$) or LPV and RTV at 400 and 100 mg QD plus NRTI ($n = 17$). Patient pairs were matched for sex, age, ethnicity, and body weight. LPV/*r*, LPV-RTV gel capsule formulation.

TABLE 1—*Continued*

LPV	RTV				
Group 1 vs group 3 GMR (*P* value)	ATV-LPV-*r* GeoMean (90% CI), group 1[b]	ATV-RTV GeoMean (90% CI), group 2[b]	LPV/*r* GeoMean (90% CI), group 3[b]	Group 1 vs group 2 GMR (*P* value)	Group 1 vs group 3 GMR (*P* value)
0.79 (0.312)	101 (75–137)	42 (30–59)	111 (87–141)	2.40 (0.004)	0.91 (0.770)
0.76 (0.188)	468 (358–611)	869 (625–1207)	525 (378–727)	0.54 (0.004)	0.89 (0.974)
0.81 (0.098)	3,293 (2,528–4,289)	7,773 (5,843–10,341)	3,584 (1,781–4,619)	0.42 (0.021)	0.92 (0.618)
0.80 (0.219)	4.06 (3.36–4.91)	4.58 (4.08–5.15)	4.03 (3.46–4.70)	0.89 (0.979)	1.01 (0.938)
1.33 (0.104)	437 (321–595)	199 (149–265)	440 (342–567)	2.20 (0.037)	0.99 (0.974)

vulnerable to changes in first-pass metabolism, an important part of which already occurs in the intestinal mucosa (7). Thus, ATV-RTV increases the absorption and decreases the clearance of saquinavir (17). In contrast, RTV-boosted LPV, with its slower extraction and high bioavailability, is unlikely to be influenced by this mechanism. The results of the present study suggest that neither the bioavailability nor the clearance of LPV-RTV or ATV was significantly mutually changed by their coadministration. These results are supported by those of a recently reported phase I study with 15 HIV-negative volunteers in whom a combination of ATV-LPV-RTV exhibited geometric mean ratios of the C_{max} and AUC of ATV of 0.83 ($P = 0.057$) and 0.92 ($P = 0.280$) compared to a standard regimen of ATV-RTV-NRTI. Also, the pharmacokinetics of LPV were comparable to those of historical controls. Exclusively, the C_{min} of ATV was significantly (1.45-fold, $P = 0.006$) enhanced in this study (8).

A limitation of our study may have been a selection bias, i.e., that those patients who are in need of a salvage regimen generally provide low plasma protease inhibitor concentrations as one reason for previous highly active antiretroviral treatment failure. However, plasma RTV concentrations were similar between group 1 and group 3 and the ATV concentration-time curve showed only moderate alterations between group 1 and group 2, which argues against cofactors such as malabsorption, pharmacogenomics, or noncompliance impairing plasma protease inhibitor concentrations in these patients.

In conclusion, we showed that a combination of ATV with LPV-RTV may produce only small changes in the respective plasma drug concentrations in patients. An increase in plasma protease inhibitor concentrations, as reported by Ribera et al. (9), should not be taken as a rule, especially as this suggests that this regimen offers superior pharmacokinetic safety with no need of TDM.

In fact, our results argue for the frequent monitoring of therapeutically effective plasma ATV-LPV-RTV concentrations, especially when these drugs are administered to extensively pretreated patients, in whom it is crucial to avoid subtherapeutic drug concentrations.

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