Steady-State Pharmacokinetics of a Double-Boosting Regimen of Saquinavir Soft Gel plus Lopinavir plus Minidose Ritonavir in Human Immunodeficiency Virus-Infected Adults

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Management of treatment-experienced human immunodeficiency virus patients has become complex, and therapy may need to include two protease inhibitors at therapeutic doses. The objective of this study was to characterize the pharmacokinetics in serum of saquinavir (1,000 mg twice daily [b.i.d.]), lopinavir (400 mg b.i.d.), and ritonavir (100 mg b.i.d.) in a multidrug rescue therapy study and to investigate whether steady-state pharmacokinetics of lopinavir-ritonavir are affected by coadministration of saquinavir. Forty patients were included (25 given ritonavir, lopinavir, and saquinavir and 15 given ritonavir and lopinavir). The median pharmacokinetic parameters of lopinavir were as follows: area under the concentration-time curve from 0 to 12 h (AUC0-12), 85.1 µg/ml · h; maximum concentration of drug in serum (Cmax), 10.0 µg/ml; trough concentration of drug in serum (Ctrough), 7.3 µg/ml; and minimum concentration of drug in serum (Cmin), 5.5 µg/ml. Lopinavir concentrations were similar in patients with and without saquinavir. The median pharmacokinetic parameters for saquinavir were as follows: AUC0-12, 22.9 µg/ml · h; Cmax, 2.9 µg/ml; Ctrough, 1.6 µg/ml; and Cmin, 1.4 µg/ml. There was a strong linear correlation between lopinavir and ritonavir and between saquinavir and ritonavir concentrations in plasma. The correlation between lopinavir and saquinavir levels was weaker. We found higher saquinavir concentrations in women than in men, with no difference in lopinavir levels. Only patients with very high body weight presented lopinavir and saquinavir concentrations lower than the overall group. Ritonavir has a double-boosting function for both lopinavir and saquinavir, and in terms of pharmacokinetics, the drug doses selected seemed appropriate for combining these agents in a dual protease inhibitor-based antiretroviral regimen for patients with several prior virologic failures.

AIDS-related morbidity and mortality have declined sharply with the use of potent antiretroviral regimens. Despite the clinical benefit observed with highly active antiretroviral therapy, inevitably most regimens fail; failure rates of 20 to 50% have been reported within the first year of triple-drug therapy (4, 21, 25). Virologic failure rates increase rapidly with successive therapeutic regimens (19, 24); thus, the management of patients who have failed several previous courses of antiretroviral therapy is a major challenge in clinical practice (9). Since a conventional drug regimen cannot be offered to these patients, multiple-drug rescue therapies have been used. Sometimes these therapies have to include dual human immunodeficiency virus (HIV) protease inhibitor (PI) combinations at therapeutic doses (5).

PIs undergo cytochrome P450-based metabolism in the gastrointestinal tract and liver, and they are subject to potentially significant drug-drug interactions. In addition, all PIs are substrates for transport by the P-glycoprotein drug transport protein (18, 27). Such interactions may be beneficial when two PIs are administered simultaneously. For example, ritonavir is a potent inhibitor of some cytochrome P450 isoenzymes and of the P-glycoprotein, and when it is coadministered with other PIs there is a considerable increase in their concentrations in plasma (14, 22). Saquinavir was the first PI available for the treatment of patients with HIV infection. The bioavailability of saquinavir is low, but when it is coadministered with ritonavir, concentrations of saquinavir in plasma increase enormously (28). The first combination of PIs used was saquinavir and ritonavir, each at doses of 400 mg (3). The combination of 1,000 mg of saquinavir and 100 mg of ritonavir, both twice daily (b.i.d.), results in higher exposure to saquinavir than that obtained with a 400-mg–400-mg b.i.d. combination of saquinavir and ritonavir (28, 31). With regard to saquinavir concentration, the boosting effects of different doses of ritonavir ranging from 100 to 400 mg b.i.d. are similar (15), and with the 100-mg dose, the toxic effects of higher doses are minimized (11). Ritonavir was the first commercially marketed PI coformulated with ritonavir to achieve good bioavailability. The usual regimen is 100 mg of ritonavir and 400 mg of lopinavir b.i.d. (6). This fixed combination of lopinavir and low-dose ritonavir (Kaletra) facilitates the simultaneous boosting of another PI.

The administration of two PIs boosted with low doses of ritonavir can produce complex drug interactions with unexpected results. A decrease in the concentration of both PIs has been described when lopinavir-ritonavir is administered with
amprenavir (6). This unfavorable reaction does not seem to occur when lopinavir-ritonavir is administered with saquinavir (6, 28), but there is little pharmacokinetic data to support the use of this combination.

This study reports the steady-state pharmacokinetics of lopinavir, saquinavir and ritonavir administered as a dual-boosted PI combination in HIV-infected adults with multiple prior therapeutic failures and investigates whether the steady-state serum pharmacokinetics of lopinavir-ritonavir are affected by coadministration of saquinavir. (This work was presented in part at the XIV International AIDS Conference, Barcelona, Spain, 2002 [abstract TuPe B4545].)

MATERIALS AND METHODS

Study population and design. All 29 patients from Vall d’Hebron Hospital included in a multiple-drug rescue therapy study (Retrogen study) (29) between September 2001 and February 2002 were asked to participate in an intensive pharmacokinetic study. One of them did not accept. Three patients were excluded because of self-reported poor adherence to the study medications or drug changes due to severe intolerance of PIs. A total of 25 patients were included in this study. Briefly, the Retrogen study evaluated the efficacy of a five-drug salvage regimen (29). All patients received the same antiretroviral therapy, as follows: didanosine enteric coated capsules (400 or 250 mg once a day according to weight), lamivudine (150 mg b.i.d.), abacavir (300 mg b.i.d.), saquinavir soft gel capsules (1,000 mg b.i.d.), and lopinavir-ritonavir (400 and 100 mg b.i.d., respectively). HIV-infected patients were eligible for enrollment in the Retrogen study if they had received at least two different three-drug, PI-including combination regimens for at least 6 months, had experienced failure with all previously received treatments, and had two consecutive plasma HIV type 1 (HIV-1) RNA loads of >1,000 copies/ml, without restrictions for CD4 cell counts. Patients included in the study had previously failed a median of eight antiretroviral drugs, and their genotypic data showed a median of six mutations associated with reverse transcriptase inhibitor resistance and five mutations associated with PI resistance.

A concurrent comparison group of 15 consecutive patients who received lopinavir-ritonavir (400 mg and 100 mg b.i.d., respectively) and two nucleosides (participants in the ABT-378–ritonavir expanded access trial) (7) were also enrolled in the study. The main criterion for a patient to be eligible for the ABT-378–ritonavir expanded access trial was that it was impossible to construct a viable treatment regimen for him or her without lopinavir-ritonavir.

The exclusion criteria for both groups included concomitant use of other drugs known to interfere with PI pharmacokinetics, particularly nonnucleosides, rifamycins, or azoles.

Blood collection and drug concentration assays. Blood samples for the measurement of lopinavir, ritonavir, and saquinavir concentrations were collected at steady state, after at least 3 days of antiretroviral therapy (mean ± standard deviation, 78 ± 26 days). All subjects were instructed to take these drugs at 9:00 a.m. and at 9:00 p.m. with breakfast and dinner, respectively, during the week before the day of intensive pharmacokinetic assessment of drug concentrations. On that day, patients came to the hospital between 8:15 and 8:50 a.m. after an overnight fast. Both study drugs were administered at the hospital at 9:00 a.m. with a standard breakfast. Blood samples were drawn before dosing and at 1, 2, 3, 4, 6, 8, and 12 h postdosing. All samples were centrifuged at 1,500 g for 20 min, and serum was stored at −80°C until assay.

Serum concentration-time data were analyzed by noncompartmental methods. The area under the serum concentration-time curve from 0 to 12 h (AUC0–12) was calculated by using the trapezoidal rule in the Abbottbase Pharmacokinetic Systems (Abbott Laboratories, Abbott Park, Ill.). The highest concentration of drug in serum (Cmax), with the corresponding sampling time (tmax), the concentration of drug in serum before the morning dose (Ctough, equal to C12-h), the lowest concentration of drug in serum (Cmin), and the concentration 12 h after ingestion of the drugs, before the night dose (Cnight, equal to C12-h) were determined directly from the concentration-time data. Total oral clearance (CLoral) was calculated by dividing the dose by the AUC0–12.

Concentrations of lopinavir, ritonavir, and saquinavir in serum were simultaneously measured with a sensitive, validated method developed in our laboratory, consisting of linear gradient reverse-phase ion-paired high-performance liquid chromatography with UV detection at 220 nm (lopinavir) and 240 nm (saquinavir and ritonavir). Drugs were extracted from serum by liquid-liquid extraction. Standard curves containing blank serum and lopinavir, saquinavir, and ritonavir were prepared at a concentration range of 0.05 to 10 μg/ml and treated in the same way as the patient samples. Briefly, 1 ml of serum was pipetted into glass tubes, and 50 μl (100 μg/ml) of internal standard (A-86093) and sodium hydroxide (0.1 M; 0.4 ml) was added. Tube contents were mixed thoroughly. Test samples and standards were extracted with diethyl ether (5 ml) for 10 min. After centrifugation for 10 min at 1,500 × g the organic phase was transferred to clean glass tubes and evaporated to dryness. Extracts were reconstituted in 200 μl of methanol-water (50:50) and washed with hexane (1 ml). Tube contents were mixed thoroughly for 30 s. After centrifugation for 10 min at 1,500 × g, the hexane was subsequently discarded, washed extracts were transferred to vials, and 100-μl volumes were injected into the chromatograph. High-performance liquid chromatography separation was performed in a Waters chromatograph (Milford, Mass.) equipped with a Model 2695 Alliance (separation module) and a Model 2467 UV dual λ absorbance detector. The analytical column was an X Terra RP18 (150- by 4.6-mm inside diameter, 3.5-μm particle size), with an incorporated X Terra RP18 guard column (20- by 3.9-mm inside diameter, 3.5-μm particle size) (Waters). The mobile phase consisted of 10 mM phosphate buffer (containing 10 mM triethylamine, pH 5.5)–acetonitrile. In the gradient elution the acetonitrile was increased linearly from 35 to 65% during the 16 min of chromatography time at a flow rate of 1.0 ml/min. Acetonitrile content was returned to 35% for 2 min and equilibrated for 5 min before the next injection. Mean recoveries were 98.7, 97.0, and 92.7% for saquinavir, ritonavir, and lopinavir, respectively. Within-day and between-day variations of quality control samples of saquinavir, ritonavir, and lopinavir in serum were 2.31 to 4.86 and 2.68 to 8.84%, respectively. Method accuracy was 105.0, 106.7, and 108.8% for saquinavir, ritonavir, and lopinavir, respectively. The lower limit of quantification was 25 ng/ml for saquinavir, ritonavir, and lopinavir. The assay was linear up to concentrations of at least 10 μg/ml.

Statistical analysis. The SPSS software for Windows (version 10.0; SPSS, Chicago, Ill.) was used to perform the statistical analyses. All analyses were performed by nonparametric tests. For quantitative variables, the medians and interquartile ranges (25th to 75th percentiles) were used as measures of central tendency and dispersion. For qualitative variables, the number of patients in each category and the corresponding percentages are given. The between-group characteristics were compared by the Mann-Whitney or Wilcoxon tests for quantitative variables and the chi-square test for qualitative variables, with the continuity correction for the chi-square when a subgroup included five or fewer subjects. Correlations were analyzed by Spearman’s rank test. All statistical tests were two-tailed and were performed at a level of statistical significance of 0.05.

RESULTS

Study population. A total of 40 subjects (25 in the study group and 15 in the comparison group) were included in the study. There were 30 men and 10 women, with a median age of 38 years. Twenty subjects (50%) had hepatitis C virus (HCV) coinfection, and 15 (37.5%) had chronic hepatitis. At the time that the pharmacokinetic study was performed, the patients had a median CD4 cell count of 361 cells/μl (interquartile range, 269 to 643 cells/μl) and 50% had HIV RNA levels of less than 50 copies/ml. There were no significant differences in baseline characteristics between the patients who received saquinavir, lopinavir, and ritonavir (group 1, n = 25) and patients treated with lopinavir and ritonavir (group 2, n = 15) without saquinavir (Table 1).

Pharmacokinetic analysis. The plasma concentration-time profiles of lopinavir, saquinavir, and ritonavir of patients with double-boosting PI therapy are shown in Fig. 1, and pharmacokinetic parameters are summarized in Table 2. No measurements of lopinavir or saquinavir were below the quantitation limit. After ingestion of the drug, lopinavir continued decreasing, reaching Cmin at 2 h (Ctough, 7.3 μg/ml, and Cmin, 5.5 μg/ml, P < 0.001, Wilcoxon test). The night Ctough was significantly lower than the morning level (Ctough night, 5.8 μg/ml, 2004 PHARMACOKINETICS OF SAQUINAVIR-LOPINAVIR-RITONAVIR 4257

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The concentration of saquinavir in plasma increased faster than that of lopinavir after ingestion, with similar trough and minimum concentrations. The night trough was also significantly lower than the morning level (C_{trough} night, 1.01 \mu{g/ml}; versus C_{trough} morning, 1.56 \mu{g/ml}; P < 0.01, Wilcoxon test).

The pharmacokinetic profiles of lopinavir were similar in patients with and without saquinavir.

Factors related to lopinavir and saquinavir concentrations (Table 3). (i) Sex. The study group included 18 men and seven women. The AUC, C_{max}, and C_{trough} values for both saquinavir and ritonavir were significantly higher in women than in men.

### TABLE 1. Baseline characteristics at the time that pharmacokinetic studies were performed in patients treated with lopinavir-ritonavir and saquinavir (group 1) or with lopinavir-ritonavir without saquinavir (group 2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 25)</th>
<th>Group 2 (n = 15)</th>
<th>P (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37 (33–41)</td>
<td>40 (36–44)</td>
<td>0.15</td>
</tr>
<tr>
<td>Male sex</td>
<td>18 (72%)</td>
<td>12 (80%)</td>
<td>0.57</td>
</tr>
<tr>
<td>HIV risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous drug user</td>
<td>8 (32%)</td>
<td>6 (40%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Homosexual male</td>
<td>6 (24%)</td>
<td>5 (33%)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>10 (40%)</td>
<td>3 (20%)</td>
<td></td>
</tr>
<tr>
<td>HCV positive</td>
<td>14 (56%)</td>
<td>7 (47%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Chronic hepatitis or cirrhosis</td>
<td>10 (40%)</td>
<td>5 (33%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.0 (61.2–80.1)</td>
<td>69.6 (59.6–75.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.5 (22.2–27.9)</td>
<td>23.7 (20.8–25.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>CD4 count (cells/\mu{l})</td>
<td>325 (224–551)</td>
<td>438 (337–661)</td>
<td>0.16</td>
</tr>
<tr>
<td>HIV RNA &lt; 50 copies/\mu{l}</td>
<td>13 (52%)</td>
<td>7 (47%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hemoglobin (mmol/liter)</td>
<td>14.2 (13.4–15.3)</td>
<td>14.3 (13.1–15.5)</td>
<td>0.97</td>
</tr>
<tr>
<td>ALT (U/liter)</td>
<td>37 (24–68)</td>
<td>32 (19–65)</td>
<td>0.27</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>40 (25–7.1)</td>
<td>32 (18–58)</td>
<td>0.25</td>
</tr>
<tr>
<td>Creatinine (\mu{mol/liter})</td>
<td>1.0 (0.9–1.1)</td>
<td>0.9 (0.8–1.1)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

\(^a\) Values are expressed as medians (interquartile ranges) or numbers (percentages).
\(^b\) Mann-Whitney U or chi-square test.
\(^c\) Chronic hepatitis was defined as persistently increased ALT level and detectable RNA HCV. Cirrhosis diagnosis was based on clinical, biological, and sonographic data.
\(^d\) Normal ranges for both ALT and aspartate aminotransferase are 10 to 40 IU/liter.

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**FIG. 1.** (A) Median concentration-time curves at steady state of lopinavir, saquinavir, and ritonavir in patients treated with lopinavir at 400 mg b.i.d., saquinavir at 1,000 mg b.i.d., and ritonavir at 100 mg b.i.d. (B) Median concentration-time curves at steady state of lopinavir in patients treated with lopinavir at 400 mg b.i.d., saquinavir at 1,000 mg b.i.d., and ritonavir at 100 mg b.i.d. and in patients treated with lopinavir at 400 mg b.i.d. and ritonavir at 100 mg b.i.d. Error bars indicate interquartile ranges (25th and 75th percentiles).
There were no significant differences in any of the pharmacokinetic parameters for lopinavir between men and women. The slight tendency toward lower weight in women than in men was not significant \((P = 0.27)\), and body mass indexes were identical between sexes.

(ii) Chronic liver disease. Ten patients (40%) had chronic liver disease, including nine with chronic hepatitis, as defined by persistently increased alanine aminotransferase (ALT) level (>40 IU/liter) and detectable HCV RNA, and one with cirrhosis, established on the basis of clinical, analytical, and sonographic data. Significant differences were observed only in the \(C_{\text{max}}\) of lopinavir, which was lower in patients with chronic liver disease than in those without.

(iii) Virological response. At the time that the pharmacokinetic studies were performed, 13 patients had undetectable viral loads and 12 had viral loads of >50 copies/ml, with a median of 3,467 copies/ml. There was a tendency toward higher drug concentrations in patients with undetectable viral loads, but only saquinavir \(C_{\text{trough}}\) concentrations were significantly higher. CD4 lymphocyte counts were higher in patients with undetectable viral loads than in those without.

(iv) Weight. Body weight ranged from 52 to 94 kg, with a median of 71 kg. In analysis of only the group of patients treated with lopinavir, ritonavir, and saquinavir \((n = 25)\), the correlation between weight and lopinavir and saquinavir concentrations was very weak (coefficient of correlation \(r\) between \(-0.15\) and \(0.36\) and nonsignificant. In analysis of all the patients studied \((n = 40)\), the correlation between lopinavir concentrations \((AUC, C_{\max}, C_{\text{trough}}, C_{\text{min}}\) and weight was significant, although at a low magnitude \((r\) between \(-0.30\) and \(-0.41\)). Only patients with very high body weight presented lopinavir and saquinavir concentrations somewhat lower than those of the overall series of patients.

(v) Correlation among plasma concentrations of lopinavir, ritonavir, and saquinavir. There was a strong positive linear correlation between the \(AUC\), \(C_{\max}\), \(C_{\text{trough}}\), \(C_{\min}\) and \(C_{\text{trough}}\) night of lopinavir and the 100 mg of ritonavir contained within the lopinavir formulation \((r = 0.63, 0.76, 0.57, 0.60, \text{and 0.58 for the respective parameters; all } P < 0.001, \text{Spearman test})\) and of saquinavir and ritonavir \((r = 0.62, 0.69, 0.61, 0.65,\text{and 0.71 for the respective parameters; all } P < 0.001, \text{Spearman test})\). The correlation between lopinavir and saquinavir concentrations was weaker but also significant \((r = 0.35, P = 0.10; r = 0.46, P = 0.02; r = 0.65, P < 0.001; r = 0.50, P = 0.001;\) and \(r = 0.37, P = 0.08\) for \(AUC, C_{\max}, C_{\text{trough}}, C_{\min},\) and \(C_{\text{trough}}\) night, respectively; Spearman test).

\[C_{\max} = 0.62C_{\text{trough}}, C_{\min} = 0.65C_{\text{trough}}\]

DISCUSSION

In the present study, b.i.d. administration of saquinavir (1,000 mg) with lopinavir (400 mg) and ritonavir (100 mg) achieved high saquinavir and lopinavir levels in plasma. The low dose of 100 mg of ritonavir had a double-boosting function for both lopinavir and saquinavir, and there were no unfavorable pharmacokinetic interactions among the three PIs.

The median pharmacokinetic parameters for lopinavir were as follows: \(AUC_{0-12} = 85.1\ \text{µg/ml·h}; C_{\max} = 10.0\ \text{µg/ml}; C_{\text{trough}} = 7.3\ \text{µg/ml};\) and \(C_{\min} = 5.5\ \text{µg/ml}\). These concentrations of lopinavir were similar to those of our comparison group of patients treated with the same doses of lopinavir and ritonavir without saquinavir, and they were also similar to the concentrations reported in some studies with the same doses of lopinavir and ritonavir without saquinavir (6, 8). la Porte et al. (17) found similar concentrations of lopinavir in seven patients treated with lopinavir, saquinavir, and ritonavir at the same doses used in our patients. The drop in plasma lopinavir concentration that we observed in the majority of patients during the first hour or the first 2 h after ingestion of the drug \((C_{\text{trough}} > C_{\min})\) has been reported in other studies (8, 17).

The median pharmacokinetic parameters for saquinavir were as follows: \(AUC_{0-12} = 22.9\ \text{µg/ml·h}; C_{\max} = 2.9\ \text{µg/ml}; C_{\text{trough}} = 1.6\ \text{µg/ml};\) and \(C_{\min} = 1.4\ \text{µg/ml}\). In the small number of studies analyzing saquinavir pharmacokinetic parameters in patients receiving the same doses of saquinavir and ritonavir as those used in the present study, without ritonavir (28, 30, 31; M. Kurowski, A. A. Arslan, K. Arasteh, C. Moecklinghoff, and A. Hill, 8th Dtsch. AIDS Kongr., abstr. FOR062, 2002) or with ritonavir (30; B. Duque, A. J. Carcas-Sansuán, J. González-García, J. R. Arribas, M. Aguilar, J. M. Peña, A. Casinillo, and J. Frias-Iniesta, 9th Eur. AIDS Conf., abstr. 4.1/3, 2003), the \(AUC_{0-12}\) and \(C_{\max}\) were similar to the values that we found, with ranges of 15.1 to 23.4 \(\mu\text{g/ml·h}\) and 1.4 to 3.9 \(\mu\text{g/ml}\), respectively. la Porte et al. (17) reported lower saquinavir exposure. The \(C_{\min}\) of saquinavir has been analyzed in patients receiving the same doses of saquinavir-ritonavir-lopinavir, ranging from 0.4 and 1.2 \(\mu\text{g/ml}\), in some other studies (17, 30; G. H. R. Smith, M. B. Kilen, T. Murphy, J. D. Macleod, J. P. Routy, R. P. LeBlanc, P. Rene, N. Gilmore, and R. G. Double,
### TABLE 3. Baseline characteristics and pharmacokinetic parameters for lopinavir (400 mg b.i.d.), ritonavir (100 mg b.i.d.), and saquinavir (1,000 mg b.i.d.) according to sex, chronic hepatitis, and viral load

<table>
<thead>
<tr>
<th>Characteristic or parameter</th>
<th>Sex</th>
<th>Chronic liver disease</th>
<th>HIV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n = 18)</td>
<td>Women (n = 7)</td>
<td>No (n = 15)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>37 (34–42)</td>
<td>37 (31–43)</td>
<td>37 (34–43)</td>
</tr>
<tr>
<td>Male sex</td>
<td>10 (67%)</td>
<td>8 (80%)</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.8 (63.3–82.4)</td>
<td>63.5 (60.1–83.7)</td>
<td>69.5 (60.1–83.7)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.2 (22.0–27.9)</td>
<td>25.44 (23.5–21.0)</td>
<td>24.3 (21.3–28.9)</td>
</tr>
<tr>
<td>HIV RNA &lt; 50 copies/ml</td>
<td>9 (50%)</td>
<td>4 (57%)</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Lopinavir AUC0–12 (µg/ml·h)</td>
<td>74.1 (56.8–108.8)</td>
<td>90.56 (66.2–118.5)</td>
<td>90.56 (64.4–118.5)</td>
</tr>
<tr>
<td>Lopinavir C_max (µg/ml)</td>
<td>9.64 (6.93–12.47)</td>
<td>11.82 (6.31–14.43)</td>
<td>11.23 (7.85–14.90)</td>
</tr>
<tr>
<td>Lopinavir T_max (h)</td>
<td>5 (3–6)</td>
<td>4.3 (3.7–8.3)</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td>Ritonavir AUC0–12 (µg/ml·h)</td>
<td>7.46 (3.43–8.99)</td>
<td>7.38 (6.16–11.13)</td>
<td>7.11 (3.94–11.13)</td>
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<tr>
<td>Ritonavir C_max (µg/ml)</td>
<td>6.15 (2.30–7.86)</td>
<td>5.41 (3.92–8.10)</td>
<td>6.53 (3.81–9.22)</td>
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<td>Ritonavir T_max (h)</td>
<td>6.41 (4.33–10.05)</td>
<td>13.39 (8.19–18.85)</td>
<td>7.92 (4.67–16.99)</td>
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<tr>
<td>Saquinavir AUC0–12 (µg/ml·h)</td>
<td>18.52 (8.91–36.59)</td>
<td>34.79 (30.38–44.56)</td>
<td>25.34 (14.07–36.54)</td>
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<tr>
<td>Saquinavir C_max (µg/ml)</td>
<td>2.58 (1.41–4.23)</td>
<td>4.72 (3.45–5.85)</td>
<td>3.49 (1.82–5.14)</td>
</tr>
<tr>
<td>Saquinavir T_max (h)</td>
<td>3 (2–4)</td>
<td>4 (3–4)</td>
<td>3.5 (2–4)</td>
</tr>
<tr>
<td>Saquinavir C_trough (µg/ml)</td>
<td>1.38 (0.65–2.20)</td>
<td>2.10 (1.68–2.81)</td>
<td>1.72 (0.87–2.01)</td>
</tr>
</tbody>
</table>

* Values are expressed as medians (interquartile ranges) or numbers (percentages).

Chronic liver disease includes nine patients with chronic hepatitis, defined as persistently increased ALT level and detectable RNA HCV, and one patient with liver cirrhosis, defined according to clinical, biological, and sonographic data.

<table>
<thead>
<tr>
<th>^c</th>
<th>^d</th>
</tr>
</thead>
<tbody>
<tr>
<td>^c</td>
<td>P &lt; 0.05, Mann-Whitney U test.</td>
</tr>
<tr>
<td>^d</td>
<td>c, copies.</td>
</tr>
</tbody>
</table>
XIV Int. AIDS Conf., abstr. TuPeB4547, 2002; J. Hellinger.
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We found higher saquinavir and ritonavir concentrations in women
than in men, with no difference in lopinavir concentrations,
even though there were no significant differences in
weight or body mass indexes between men and women. In
two very recent studies (10, 23) plasma saquinavir concentrations
were also found to be higher in women than in men. In the
report by Fletcher et al. (10) the higher saquinavir AUC and
C_{min} in women remained after adjustment by weight. More-
over, a significantly larger percentage of women than of men
had a viral load below 500 copies/ml at week 16, and this
finding was attributed to a sex-related difference in saquinavir
concentrations. In our study, patients with an undetectable
viral load had a higher saquinavir C_{tough} than did patients with
virologic failure.

Arribas et al. (J. R. Arribas, F. Pulido, J. Z. Peng, S. Kem-
mis, J. L. Li, A. Lorenzo, C. Cepeda, T. Reisch, J. Moseley, K.
Grebner, J. A. Cabanillas, B. Da Silva, B. Bernstein, Y. L.
found higher concentrations of lopinavir, particularly of free
drug, in patients with hepatic cirrhosis (hepatic insufficiency-
liver failure) than in those without chronic liver disease. Our 10
patients with chronic liver disease had lower lopinavir C_{max}
values than did patients without; however, only one of these
patients had liver cirrhosis. All the patients in the study by
Arribas et al. had liver cirrhosis; there was no control group
with chronic hepatitis but no cirrhosis. Other PI studies have
shown significant reductions in the clearance of these drugs
in patients with liver dysfunction (1). We do not know the signif-
icance of the decreased C_{max} of lopinavir in our chronic hep-
itis patients; the number studied was small, and we cannot
rule out a confounding effect of overlap with liver disease or
other factors.

The C_{tough} values of lopinavir and saquinavir were signifi-
cantly lower in the morning than in the evening, suggesting
circadian variation of these drugs. Circadian variations of nelfi-
vir and ritonavir are well documented (2, 12). In a small
study, Justesen and Pedersen (13) recently reported that morn-
ing C_{tough} values of indinavir, amprenavir, and saquinavir are
higher than evening C_{tough} values. With regard to lopinavir, no
circadian variation has been reported; however, the reported
concentration-time curves in some studies suggest that these
drugs may be affected by circadian rhythms (8, 17).

In HIV-infected patients (Kurowski et al., 8th Dtsch. AIDS
Kongr., abstr. FOR062, 2002) and healthy volunteers (16) Ku-
rowski et al. found that saquinavir boosting by ritonavir with
the hard gel capsule (HGC) formulation results in saquinavir
plasma levels at least as high as those achieved with the soft gel
capsule (SGC) formulation, apparently with better tolerance in
terms of gastrointestinal system disorders. This may be because
the SGC formulation of saquinavir is suspended in Capmul, a
substance that has shown gastrointestinal toxicity in animal
studies. This fact may be important when the saquinavir, lopi-
navir, and ritonavir combination is used, since the lopinavir-
ritonavir coformulation also contains Capmul. In fact, some of
our patients presented slight to moderate diarrhea, which did
not require discontinuation of the treatment. This side effect
improved when saquinavir SGC was changed to HGC, and
some patients showed better tolerance when the lopinavir-
ritonavir capsules were substituted for syrup.

With regard to pharmacokinetics, the doses selected for
lopinavir-ritonavir and saquinavir seemed to be appropriate
for combining these agents in a dual PI-based antiretroviral
regimen for patients with several prior virologic failures. The
ritonavir from the lopinavir-ritonavir coformulation has a dou-
ble-boosting function for both lopinavir and saquinavir. No
negative pharmacokinetic interactions were found among lopi-
avir, saquinavir, and ritonavir, and the high concentrations of
lopinavir and saquinavir attained in serum can be especially
useful in patients with moderate resistance to PIs (26). Dual
PI-boosted regimens with these drugs may be particularly use-
ful, since in vitro synergy between lopinavir and saquinavir has
been described elsewhere (20).

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