Antiretroviral therapy in Thai adults and children with HIV-1 Infection
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Chapter 2:
Pharmacokinetic study of saquinavir hard gel caps/ritonavir in HIV-1-infected patients: 1600/100 mg once-daily compared with 2000/100 mg once-daily and 1000/100 mg twice-daily

Pharmacokinetic study of saquinavir hard gel caps/ritonavir in HIV-1-infected patients: 1600/100 mg once-daily compared with 2000/100 mg once-daily and 1000/100 mg twice-daily


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Objectives: A pharmacokinetic comparison of three dosing regimens of saquinavir/ritonavir was carried out: 1600/100 mg once-daily with 2000/100 mg twice-daily, and 1600/100 mg once-daily with 2000/100 mg once-daily.

Methods: Twenty patients on saquinavir hard gel caps/ritonavir 1600/100 mg once-daily in combination with two nucleoside reverse transcriptase inhibitors for at least 4 weeks were enrolled and randomized to either saquinavir hard gel caps/ritonavir 1000/100 mg twice-daily or 2000/100 mg once-daily. Two pharmacokinetic curves were plotted, at baseline (day 0) and 7 days after the switch. Plasma concentrations were measured at 0, 2, 4, 6, 8, 10, 12 (and 24 for once-daily dosing) hours after drug intake by validated high-performance liquid chromatographic assay (HPLC). The area under the plasma concentration–time curve (AUC_{1-24} or AUC_{1-12}), maximum and minimum concentration (C\text{max} and C\text{min}) and elimination half-life were calculated using a non-compartmental model.

Results: Compared with saquinavir/ritonavir 1600/100 mg once-daily dosing, the saquinavir AUC and C\text{max} improved significantly when dosed as 1000/100 mg twice-daily (53% and 299%, respectively), and as 2000/100 mg once-daily (71% and 65%, respectively). Low C\text{min} in three subjects at baseline was corrected after switch to the other dosages. Saquinavir/ritonavir 2000/100 mg once-daily was also associated with a significant increase in saquinavir C\text{max} (52%) compared with saquinavir/ritonavir 1600/100 mg once-daily.

Conclusions: Saquinavir/ritonavir when dosed as 2000/100 mg once-daily or 1000/100 mg twice-daily achieves higher saquinavir plasma levels compared with saquinavir/ritonavir 1600/100 mg once-daily. Taking the convenience of once-daily dosing into consideration, dosage of 2000/100 mg once-daily may be preferred.

Keywords: protease inhibitors, HIV, Thailand, pharmacokinetics

Introduction

Saquinavir is an HIV protease inhibitor. It is used as part of a therapeutic regimen for HIV-1 or HIV-2 infection. Saquinavir is frequently combined with low dose ritonavir to improve the pharmacokinetics of saquinavir. Ritonavir and saquinavir are metabolized through the same pathways, predominantly by cytochrome P450 isoenzyme 3A4. Furthermore, inhibition of
P-glycoprotein, by ritonavir, has been suggested to play a role in the boosting effect. Improvement of saquinavir pharmacokinetic parameters enables the use of lower and less frequent saquinavir dosing.¹

Two formulations of saquinavir are available: the saquinavir hard gel capsule and the saquinavir soft gel capsule. Pharmacokinetic studies have shown that the formulations are bioequivalent when boosted by ritonavir.² Furthermore, in the HIV-NAT 001 study series, virological response was maintained and immunological recovery continued out to 48 weeks when saquinavir soft gel caps/ritonavir was replaced with saquinavir hard gel caps/ritonavir. Reasons to use saquinavir hard gel caps instead of saquinavir soft gel caps, include better tolerability, smaller capsule size, the absence of need for refrigerated storage and lower cost in most countries.³,⁴

The recommended dose for saquinavir with low dose of ritonavir is 1000/100 mg twice-daily. However, a 1600/100 mg dose has been tested as a once-daily dosing regimen. When dosed as 1600/100 mg, the total daily dose is lower than that received with the recommended 1000/100 mg twice-daily dose, possibly leading to suboptimal exposure to saquinavir and virological failure. Furthermore, for all other protease inhibitors, the total daily dose is similar for once-daily and twice-daily regimens. Therefore, a once-daily dosing regimen of 2000/100 mg may result in better exposure to saquinavir than 1600/100 mg.

The objective of this study was to investigate the pharmacokinetics of 1600/100 mg once-daily, 2000/100 mg once-daily and 1000/100 mg twice-daily in HIV-1 infected patients.

Materials and methods

Patient selection, screening and study design

This was a single-centre, open-label, pharmacokinetic study in asymptomatic HIV-infected individuals conducted as a sub-study of the STACCATO trial.⁵ Twenty patients were recruited from The Thai Red Cross Society’s Anonymous Clinic. Patients were taking saquinavir hard gel caps 1600/100 mg once-daily together with stavudine and didanosine. Before enrolment in STACCATO, patients had participated in the HIV-NAT 001 trial series, which started in 1997, with 1 year of dual nucleoside reverse transcriptase inhibitors (NRTI) followed by protease inhibitor-based highly active antiretroviral therapy (HAART).⁶,⁷

Patients were considered eligible if they were taking saquinavir/ritonavir for at least 4 weeks and had stable virological and immunological profiles. Patients were excluded if they were taking any agents that interfered with the pharmacokinetics of saquinavir and ritonavir. Selection of patients was done randomly, based on selecting the first 20 patients that were eligible. Following the first pharmacokinetic assessment, patients were randomized to receive either 2000/100 mg once-daily (arm 1) or 1000/100 mg twice-daily (arm 2) saquinavir hard gel caps/ritonavir for 1 week. After 1 week, all patients reverted to their original dose of saquinavir hard gel caps/ritonavir 1600/100 mg. The NRTI backbone, stavudine and didanosine, remained unchanged. Before the study, each patient signed informed consent and approval was obtained from the Institutional Review Board of King Chulalongkorn University.

Safety assessment

Safety and tolerability were assessed at screening and on both pharmacokinetic study days. During these visits, the patient history was recorded and a physical examination carried out.

Pharmacokinetic analysis

Two pharmacokinetic curves per patient were recorded on day 0 and day 7 after randomization. On the pharmacokinetic study days, all patients received the study treatment with a standardized breakfast (approximately 500 calories and 12 g of fat). Other meals were also standardized, and no other foods were allowed. Furthermore, patients were counselled to maintain their lifestyle (smoking, consumption of alcohol and exercise level) during the entire study.

Blood was sampled before (t = 0) and 2, 4, 6, 8, 10 and 12 h after treatment intake, and, for the once-daily arm (arm 1), an additional sample was taken at 24 h. The blood samples were centrifuged at 1500 r.p.m. and the separated plasma was stored at −20°C until analysis.

Plasma concentrations of saquinavir and ritonavir were analysed at the HIV-NAT pharmacokinetic laboratory by validated high-performance liquid chromatographic assay (HPLC). The HIV-NAT pharmacokinetic laboratory participates in an international quality control and quality assessment (QA/QC) pharmacokinetic programme, and therefore has cross-validation with other international pharmacokinetic laboratories.⁸ The lower limit of quantification (LLOQ) was 0.04 mg/L for both protease inhibitors.

Determination of pharmacokinetic parameters was based on individual plasma concentration data versus time by non-compartmental analysis. The area under the curve, AUC₀₋₁₂ or AUC₀₋₂₄, was defined as the area under the plasma concentration–time curve until the last measurable plasma concentration calculated with the linear trapezoidal method. Depending on the dosing regimen—twice-daily or once-daily—AUC₀₋₁₂ or AUC₀₋₂₄ was calculated. In order to compare AUC₀₋₁₂ with AUC₀₋₂₄, AUC₀₋₁₂ was multiplied by two where needed. This method, however, is limited because multiplication by two implies that the drug levels do not show diurnal variation. Diurnal variation has been shown for ritonavir.⁹ The maximum observed plasma concentration during the dosing interval was defined as Cmax (mg/L). The observed time to reach Cmax was defined as Tmax (h). The minimum observed concentration just before the next dosing interval was defined as Cmin (mg/L). Finally, t₁/₂ (h) was calculated using ln(2)/λ. The definition of t₁/₂ was the apparent elimination half-life associated with the terminal slope of a semi-logarithmic concentration–time curve in which λ is the elimination rate constant.

Statistical analysis

Statistical analysis was carried out using SPSS software version 9.0 (SPSS, Chicago, USA, Inc., 1989–1999) and Excel 1997 (Microsoft Corporation, 1985–1997). Pharmacokinetic parameters were logarithm-transformed before statistical analysis. The geometric mean ratio (GMR) and associated 90% confidence interval (CI) were calculated for each pharmacokinetic parameter. Patient characteristics such as age, sex, height and weight are tabulated.

Results

Sixteen females and four males participated in the study, with a median age of 33 years (interquartile range 29–35 years), and all 20 patients completed it. Baseline characteristics of study participants are illustrated in Table 1.

One patient, randomized to 1000/100 mg twice-daily, had diarrhoea on day 0 and day 7; the investigator did not feel that this was related to study medication. The patient had comparable pharmacokinetic results to other patients in the study and was included in the pharmacokinetic analysis. No other side effects
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OD arm (1)</th>
<th>BD arm (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.0</td>
<td>34.4</td>
</tr>
<tr>
<td>s.d</td>
<td>4.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Median</td>
<td>31.0</td>
<td>34</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>44.3</td>
<td>54.5</td>
</tr>
<tr>
<td>s.d</td>
<td>5.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Median</td>
<td>44.0</td>
<td>54.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>154.5</td>
<td>159.5</td>
</tr>
<tr>
<td>s.d</td>
<td>5.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Median</td>
<td>154.5</td>
<td>157.0</td>
</tr>
<tr>
<td>Gender, MF</td>
<td>1.9</td>
<td>37</td>
</tr>
</tbody>
</table>

OD, once-daily; BD, twice-daily; M, male; F, female.

were reported. Five patients had used other co-medications during the study period, but this was categorized as unlikely to interfere with the pharmacokinetics of saquinavir or ritonavir.

The median plasma concentrations of saquinavir are plotted (Figure 1). In the first arm, patients were randomized to receive 2000/100 mg saquinavir/ritonavir once-daily. By means of visual inspection, the rates of the absorption phase of 1600/100 mg once-daily and 2000/100 mg once-daily appear quite similar.

The mean AUC of saquinavir in the 2000/100 mg once-daily regimen was 71% higher than the mean AUC of saquinavir when dosed at 1600/100 mg once-daily. Furthermore, a parallel increase in mean saquinavir Cₘₐₓ and Cₘₜₐₓ of 65% and 52%, respectively, was seen in the 2000/100 mg once-daily group compared with the 1600/100 mg once-daily group. The interpatient variability in the 2000/100 mg once-daily arm (arm 1), at day 7, was less than the interpatient variability at the first pharmacokinetic assessment (1600/100 mg once-daily).

Looking at the pharmacokinetic parameters for ritonavir, the mean Cₘₜₐₓ and Cₘₐₓ were, as expected, similar in the 1600/100 mg once-daily group and the 2000/100 mg once-daily group. However, there was a modest increase of 23% in mean ritonavir AUC (90% CI 4–46%) (Tables 2 and 3). Median plasma concentrations of ritonavir are plotted in Figure 2.

In the second arm, patients were randomized to 1000/100 mg twice-daily saquinavir/ritonavir. The absorption of 1000/100 mg twice-daily appeared to be slower than the absorption of 1600/100 mg once-daily or 2000/100 mg once-daily (Figure 1). Comparing the saquinavir pharmacokinetic parameters of 1000/100 mg twice-daily with those of 1600/100 mg once-daily, there was a large increase in Cₘₜₐₓ when dosed as 1000/100 mg twice-daily. Additionally, the mean saquinavir AUC increased by 53% when dosed as 1000/100 mg twice-daily. The values for mean saquinavir Cₘₐₓ of both regimens were similar.

The interpatient variability for saquinavir Cₘₜₐₓ was in a similar range (68% versus 73%), expressed as coefficient of variation. The saquinavir Cₘₜₐₓ and AUC of 1000/100 mg twice-daily dose were associated with an increase in interpatient variability. The total daily dose of ritonavir in the 1000/100 mg twice-daily arm (arm 2) was double the dose of the once-daily regimen. As expected, mean Cₘₜₐₓ Cₘₐₓ and AUC for ritonavir showed increases when dosed at 1000/100 mg twice-daily (Tables 2 and 3). Three patients on 1600/100 mg once-daily had a saquinavir trough level lower than the recommended trough level of 0.1 mg/L of saquinavir. All three levels increased above the recommended trough level on day 7.

Discussion

The pharmacokinetics of both saquinavir/ritonavir 1000/100 mg twice-daily and saquinavir/ritonavir 1600/100 mg once-daily in HIV-1-infected patients have been described before. In this study, the pharmacokinetics of two doses, saquinavir/ritonavir of 2000/100 mg once-daily and 1000/100 mg twice-daily, were compared with the pharmacokinetics of 1600/100 mg once-daily. Saquinavir/ritonavir when dosed as 2000/100 mg once-daily by 53% and 1000/100 mg twice-daily showed increased AUC and Cₘₜₐₓ compared with when dosed as 1600/100 mg once-daily. Only the saquinavir Cₘₜₐₓ increased in the 2000/100 mg once-daily arm (arm 1), whereas there was no change in saquinavir Cₘₜₐₓ in the 1000/100 mg twice-daily arm (arm 2). Overall, pharmacokinetic parameters improved with the 2000/100 mg once-daily dose, whereas the Cₘₜₐₓ improved markedly with the 1000/100 mg twice-daily dose.

Increasing the dose of saquinavir from 1600/100 mg once-daily to 2000/100 mg twice-daily gave a higher saquinavir exposure. Two observations can be made from these findings.

First, the increase in saquinavir exposure is more than dose proportional, thereby suggesting non-linear kinetics of saquinavir when combined with low doses of ritonavir. The increase can be explained as the result of ongoing processes: the continuation of saquinavir absorption; the inhibition of P450 enzymes in the gut and liver leading to decreased first-pass metabolism and, perhaps, inhibition of P-glycoprotein.

Second, the absorption of saquinavir is not maximal when dosed as 1600 mg once-daily. This observation is in contrast to healthy volunteer data for saquinavir/ritonavir. Dosing of saquinavir/ritonavir as 1800/100 mg once-daily led to lower saquinavir plasma exposure. However, there were limitations in the healthy volunteer study: a relatively small number of patients; a lack of intrapatient comparison; and a different dietary composition from that of this study. In the 1000/100 mg twice-daily arm, both the saquinavir and ritonavir daily dosages were higher than with the 1600/100 mg
Once-daily dosing. As might be expected, the exposure of saquinavir was higher. The marked increase in Cmax is striking, most likely because of increased ritonavir exposure, which enhances the inhibiting effect of P450 in the gut and the liver. Again, the role of P-glycoprotein cannot be excluded. The lack of difference between the Cmax values of the 1600/100 mg once-daily and the 1000/100 mg twice-daily dosing suggests that the absorption of saquinavir is lower for 1000/100 mg twice-daily dosing.

Drug levels in this study were higher than reported levels for Caucasian patients.\(^1\) This can be partly explained by the high number of females in this study (4:1).\(^1\) A recent study showed that female HIV-infected patients had a higher saquinavir level compared with male HIV-infected patients.\(^1\) Other potential factors that might be of influence are the characteristics of the patients such as body composition, life-style, genetic background and environmental factors. More studies are needed to examine the effect of these differences on the clinical pharmacokinetics of diverse patient populations.

Limitations in this study were no intrapatient comparison between 2000/100 mg once-daily and 1000/100 mg twice-daily.

### Table 2. Pharmacokinetic parameters (means ± SD)

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Day 0 SQV/RTV 1600/100 OD</th>
<th>Day 7 SQV/RTV 2000/100 OD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SQV</td>
<td>RTV</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>6.5 ± 3.59</td>
<td>1.49 ± 0.64</td>
</tr>
<tr>
<td>Cmin (mg/L)</td>
<td>0.32 ± 0.28</td>
<td>0.06 ± 0.07</td>
</tr>
<tr>
<td>AUCC-24 (mg h/L)</td>
<td>53.95 ± 29.92</td>
<td>12.87 ± 5.51</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>4.80 ± 1.03</td>
<td>4.40 ± 2.07</td>
</tr>
<tr>
<td>V/kg</td>
<td>7.13 ± 6.33</td>
<td>1.18 ± 0.67</td>
</tr>
<tr>
<td>CL/kg</td>
<td>1.03 ± 0.82</td>
<td>0.22 ± 0.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm 2</th>
<th>Day 0 SQV/RTV 1600/100 OD</th>
<th>Day 7 SQV/RTV 1000/100 OD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SQV</td>
<td>RTV</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>4.09 ± 1.84</td>
<td>1.39 ± 0.75</td>
</tr>
<tr>
<td>Cmin (mg/L)</td>
<td>0.28 ± 0.19</td>
<td>0.07 ± 0.09</td>
</tr>
<tr>
<td>AUCC-24 (mg h/L)</td>
<td>36.62 ± 18.74</td>
<td>12.33 ± 5.09</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>5.80 ± 1.48</td>
<td>5.60 ± 2.95</td>
</tr>
<tr>
<td>V/kg</td>
<td>7.04 ± 3.63</td>
<td>1.19 ± 1.14</td>
</tr>
<tr>
<td>CL/kg</td>
<td>0.99 ± 0.39</td>
<td>0.17 ± 0.06</td>
</tr>
</tbody>
</table>

Cmax, maximum observed concentration; Cmin, minimum observed concentration; AUC, area under the curve; T1/2, time to reach Cmax; t1/2, terminal half-life; V, volume of distribution; CL, clearance; SQV, saquinavir; RTV, ritonavir; OD, once-daily; BD, twice-daily.

### Table 3. Change in pharmacokinetic parameters (GMR with 90% CI)

<table>
<thead>
<tr>
<th>SQV/RTV 1600/100 mg OD → 2000/100 mg OD</th>
<th>GMR</th>
<th>90% CI</th>
<th>GMR</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQV Cmax</td>
<td>1.52</td>
<td>1.23–1.88</td>
<td>1.16</td>
<td>1.00–1.34</td>
</tr>
<tr>
<td>SQV Cmin</td>
<td>1.65</td>
<td>1.09–2.49</td>
<td>1.01</td>
<td>0.65–1.57</td>
</tr>
<tr>
<td>SQV AUCC-24</td>
<td>1.71</td>
<td>1.27–2.29</td>
<td>1.23</td>
<td>1.04–1.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SQV/RTV 1600/100 mg OD → 1000/100 mg BD</th>
<th>GMR</th>
<th>90% CI</th>
<th>GMR</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQV Cmax</td>
<td>0.97</td>
<td>0.70–1.33</td>
<td>1.57</td>
<td>1.17–2.11</td>
</tr>
<tr>
<td>SQV Cmin</td>
<td>3.99</td>
<td>2.47–6.43</td>
<td>7.11</td>
<td>4.22–11.98</td>
</tr>
<tr>
<td>SQV AUCC-24</td>
<td>1.53</td>
<td>1.08–2.16</td>
<td>2.27</td>
<td>1.75–2.93</td>
</tr>
</tbody>
</table>

GMR, geometric mean ratio; CI, confidence interval; Cmax, maximum observed concentration; Cmin, minimum observed concentration; AUC, area under the curve; T1/2, time to reach Cmax; SQV, saquinavir; RTV, ritonavir; OD, once-daily; BD, twice-daily.
dosing. Conclusions regarding comparison of these two regimens should be drawn with caution. Despite randomization, different baseline values for weight were seen between the first and the second arm. However, we can assume that the contribution to the differences between the pharmacokinetics on day 0 and day 7 is low, because of inpatient comparison.

High saquinavir levels were seen in both arms on day 7. Low body weights at baseline in arm 1 might contribute to this effect. The relationship between body weight and saquinavir is not clear yet. However, an inverse correlation between body weight and saquinavir AUC was observed in a previous study in Thai HIV patients.11

The recommended 1000/100 mg twice-daily dose can be used in place of the 400/400 mg twice-daily dosing regimen so as to minimize side effects caused by higher doses of ritonavir.12,13 In our study, no side effects were seen in the once-daily arm (arm 1). One patient had diarrhea on both pharmacokinetic days, but this did not seem to be related to the study agents. No other side effects were reported. However, patients were tolerating saquinavir/ritonavir for a minimum of 4 weeks and a mean of 48 weeks before this pharmacokinetic study. Nevertheless, as a result of higher doses of saquinavir or ritonavir, additional side effects might have appeared with intake for longer than 1 week.

A high pill burden is a potential disadvantage of protease inhibitors in general. Changing the saquinavir dose from a twice-daily to once-daily regimen increases the number of saquinavir capsules to be taken at the same time (from five in the twice-daily regimen to between eight and 10 in the once-daily regimen).

A new 500 mg formulation of saquinavir is currently being developed.12 With the new formulation, a reduction in daily pill count can be achieved. The results from our study have shown that 2000/100 mg once-daily or 1000/100 mg twice-daily would result in more favourable pharmacokinetic parameters than the 1600/100 mg once-daily dosage and presumably the new formulation alternative dosage of 1500/100 mg once-daily as well.

The critical pharmacokinetic parameter that best predicts in vivo antiviral efficacy of boosted saquinavir has not been determined. The clinical efficacy of the saquinavir/ritonavir 1000/100 mg twice-daily regimen has been demonstrated in the MasCmin trials.21,22 There is a concern that the 1600/100 mg once-daily dose is too low compared with the recommended 1000/100 mg twice-daily regimen, resulting in a lower trough level and, consequently, an increased likelihood of selecting drug-resistant HIV strains.

In our study, three patients on 1600/100 mg once-daily had trough levels lower than the recommended target trough level for treatment-naive patients with wild-type virus.23 Despite these low levels, the patients had virological suppression up to 48 weeks. In a previous study within the HIV-NAT 001 trial series, low trough levels were also seen with saquinavir 1600/100 mg. However, patients safely switched from 1600/100 mg once-daily saquinavir soft gel caps to 1600/100 mg once-daily saquinavir hard gel caps and maintained their immunological and virological response without additional side effects. Whether this means that a lower trough level is acceptable, that the concomitant NRTIs are of more importance or that intracellular saquinavir concentration is the key parameter for predicting antiviral efficacy is difficult to say.13 Moreover, in both the previously mentioned switch study and our present study, the effects of selection bias cannot be ruled out because patients were using saquinavir hard gel caps 1600/100 mg once-daily long term.

In conclusion, dosing of saquinavir/ritonavir as 2000/100 mg once-daily or 1000/100 mg twice-daily resulted in increased saquinavir AUC and Cmax, whereas the saquinavir Cmax only increased when dosed as 2000 mg.

Both dose-regimens can be used in clinical practice. Dosing as 2000/100 mg is an attractive option because of the convenience of once-daily dosing. However, it can be hypothesized that in patients with viral resistance, the twice-daily regimen would result in better outcomes, because of high saquinavir levels during the entire dosing interval.

Whether one of these regimens has better clinical efficacy needs to be investigated in a larger clinical trial. Furthermore, studies are required to establish whether AUC, Cmax or perhaps another pharmacokinetic parameter should be the primary consideration when evaluating pharmacokinetic values associated with different saquinavir/ritonavir dosing regimens.

Acknowledgements
Ferdinand Wit (JATEC), Staccato Clinical Trial team, HIV-NAT and Thai Red Cross Aids Research Centre, Roche Pharmaceuticals, Pharmaccess and JATEC.

References

Figure 2. Median concentrations of ritonavir (RTV) (1600/100 mg) on day 0 of arm 1, ritonavir (200/100 mg) on day 7 of arm 1, ritonavir (1600/100 mg) on day 0 of arm 2 and ritonavir (1000/100 mg) on day 7 of arm 2. Diamonds, arm 1, RTV 100 mg once-daily on day 0; triangles, arm 1, RTV 100 mg once-daily on day 7; squares, arm 2, RTV 100 mg once-daily on day 0; crosses, arm 2, RTV 100 mg twice-daily on day 7.