Exploratory study comparing the metabolic toxicities of a lopinavir/ritonavir plus saquinavir dual protease inhibitor regimen versus a lopinavir/ritonavir plus zidovudine/lamivudine nucleoside regimen

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Objectives: To assess the safety, efficacy and metabolic toxicity of lopinavir/ritonavir + saquinavir or zidovudine/lamivudine and evaluate the pharmacokinetics of lopinavir/ritonavir + saquinavir.

Methods: HIV-1-infected, antiretroviral-naive subjects were randomized to lopinavir/ritonavir (400/100 mg) twice daily + saquinavir (800 mg) or zidovudine/lamivudine (150/300 mg) in a Phase II, 48 week study. Subjects receiving lopinavir/ritonavir + zidovudine/lamivudine initiated escalating doses of saquinavir (400, 600 and 800 mg) weekly for 3 weeks.

Results: By intent-to-treat (non-completer failure) analysis, 10/16 (63%) lopinavir/ritonavir + saquinavir-treated and 7/14 (50%) lopinavir/ritonavir + zidovudine/lamivudine-treated subjects achieved plasma HIV-1 RNA <50 copies/mL (P = 0.713) at week 48. Safety, tolerability, metabolic changes and truncal fat increases were similar between groups. Small decreases in the lower extremity fat in the zidovudine/lamivudine group (–6%) and a statistically significant increase in the lower extremity fat in the saquinavir group (+19%) were observed. Lopinavir/ritonavir co-administered with saquinavir 600 or 800 mg twice daily produced saquinavir concentrations similar to those previously reported for saquinavir/ritonavir 1000/100 mg twice daily.

Conclusions: Treatment regimens had similar efficacy and tolerability. Metabolic parameters suggested lipoatrophy in the zidovudine/lamivudine treatment group. Saquinavir 600 and 800 mg twice daily produced saquinavir concentrations similar to those previously reported for saquinavir/ritonavir 1000/100 mg twice daily.

Keywords: pharmacokinetics, lipoatrophy, HIV-1

Introduction

The use of potent combination antiretroviral regimens has had a profound positive impact on the course of HIV-1 infection. However, metabolic abnormalities including dyslipidaemia, lipoatrophy and insulin resistance have been associated with the long-term use of these treatments.¹⁻⁴ In particular, depletion of mitochondrial DNA (mtDNA) via inhibition of mtDNA polymerase γ leading to mitochondrial dysfunction and metabolic abnormalities has been described with some nucleoside reverse transcriptase inhibitors (NRTIs), most notably stavudine, didanosine, zalcitabine and zidovudine.²⁻⁷ Depletion of mtDNA by NRTIs in specific tissues is thought to be an important factor in the pathogenesis of peripheral neuropathy, hyperlactataemia, lactic acidosis and lipoatrophy²⁻⁴ and has been observed in symptomatic NRTI-related hyperlactataemia.⁸ Decreased mtDNA has also been observed in the subcutaneous fat tissue of HIV-infected subjects with lipoatrophy, who were treated with NRTIs.⁹ Because select NRTIs appear to be associated with metabolic toxicities, we hypothesized that use of an...
NRTI-sparing regimen might alleviate some of the associated metabolic abnormalities. Prior studies of dual protease inhibitor therapy administered in the absence of NRTIs have demonstrated safety, tolerability and durable antiviral activity.\textsuperscript{10} This 48 week pilot study was designed to evaluate the antiviral activity, safety and metabolic toxicities, including changes in mtDNA and body fat composition associated with two lopinavir/ritonavir-based regimens, a dual-boosted protease inhibitor, NRTI-sparing regimen of lopinavir/ritonavir plus saquinavir and a nucleoside-containing regimen of lopinavir/ritonavir plus zidovudine/lamivudine, in antiretroviral-naive subjects. In addition, the pharmacokinetics of three doses of saquinavir hard-gel capsules co-administered with lopinavir/ritonavir were evaluated and compared with historical pharmacokinetic data of saquinavir soft-gel capsules 1000 mg co-administered with ritonavir 100 mg.

Materials and methods

Study design

This was a Phase II, 48 week, open-label, randomized, multicentre study conducted between 7 January 2003 and 8 April 2005 at 6 sites in the USA and Canada. Each site had research ethics and institutional review board approvals. HIV-infected, antiretroviral-naive subjects were eligible for enrolment if they had plasma HIV-1 RNA concentrations >400 copies/mL at screening. There were no CD4+/T cell count entry restrictions. Thirty subjects were randomized 1:1 to receive saquinavir (800 mg) twice daily or zidovudine/lamivudine (300/150 mg) twice daily. All subjects received lopinavir/ritonavir soft-gel capsules (400/100 mg) twice daily. The hard-gel capsule formulation of saquinavir (Invirase\textsuperscript{a}) was used throughout the study. All subjects remained on study until the last subject on treatment reached week 48. Procedures were in accordance with the Helsinki Declaration of 1975, revised in 2000.

The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at week 48. Secondary efficacy variables included the time to loss of virological response through week 48 and the mean change from baseline at each visit in CD4+ T cell count. Pharmacokinetic measures of lopinavir, ritonavir and saquinavir plasma drug concentrations were assessed when lopinavir/ritonavir plus zidovudine/lamivudine were administered with increasing doses of saquinavir.

Exploratory toxicity outcomes included changes in fasting lipids and glucose concentrations, peripheral blood mononuclear cell (PBMC) mitochondrial DNA:nuclear DNA (mtDNA:nDNA) ratio\textsuperscript{11} and changes in body fat composition as measured by dual energy X-ray absorptiometry (DEXA). A soft-tissue ‘phantom’ was scanned at each site for data calibration.

Plasma HIV-1 RNA concentrations were measured every 4 weeks through week 16 and then every 8 weeks through week 48 using the Roche Amplicor HIV-1 Ultrasensitive Quantitative PCR Assay, Version 1.5 (Roche Molecular Systems, Branchburg, NJ, USA), with a limit of quantification (LOQ) of 50 copies/mL. Fasting lipids and glucose were determined at baseline and weeks 24 and 48. Complete blood counts were taken every 4 weeks through week 16 and then every 8 weeks through week 48. The proportion of subjects with plasma HIV-1 RNA <50 copies/mL was assessed using an intent-to-treat, non-completer = failure (ITT NC = F) analysis in which missing values were considered failures unless both the immediately preceding and following values were <50 copies/mL. An observed data analysis method was also used, in which missing values were excluded from the analysis.

The cumulative incidence of adverse events through week 48 was summarized. For the purpose of analysis, all adverse events of peripheral fat wasting (including face, buttocks and limbs), central adiposity, breast enlargement, dorsal fat pad enlargement and multiple lipomas were considered events of body fat composition change.

For the assessment of steady-state pharmacokinetics, subjects receiving lopinavir/ritonavir plus zidovudine/lamivudine were given a dose escalation of saquinavir, beginning with 400 mg twice daily for 7 days and increasing to 600 mg twice daily at week 2 and 800 mg twice daily at week 3. Saquinavir was discontinued in the lopinavir/ritonavir plus zidovudine/lamivudine treatment group after week 4. Intensive pharmacokinetic sampling was performed 7 days after each dose escalation, with blood samples taken at pre-dose (0 h) and at 2, 4, 6, 8 and 12 h. Drug concentrations were measured using liquid chromatography/mass spectrometry in the which LOQ for saquinavir and ritonavir was 1 ng/mL and that for lopinavir was 5 ng/mL.

Data analysis

The study was not powered to detect a statistical difference in antiviral activity between the two treatment groups. An intention-to-treat (ITT) analysis and observed analyses were used to measure antiviral activity. Outcomes were compared between treatment groups using Fisher’s exact test. DEXA scan determinations included total body fat, total body lean mass, trunk fat, appendicular fat and lower extremity fat. The percentage change from baseline was calculated for each subject for each DEXA measurement; mean percentage changes were compared between treatment groups using an analysis of covariance (ANCOVA) that adjusted for measurements of a soft-tissue phantom scanned at each study site; mean observed fat percentage was used as the covariate for the ANCOVA. Descriptive statistics were used to evaluate safety variables. All analyses were conducted through 48 weeks. DEXA scan data were also evaluated at the final visit (representing up to 96 weeks of treatment). For the pharmacokinetic analysis, parameters within the study were compared using analysis of variance. ANCOVA was used to compare pharmacokinetic parameters for the present study with those from the historical control study, with age and weight as covariates.

Results

Study subjects and disposition

Demographic and other baseline characteristics of the 30 subjects enrolled in the study are summarized in Table 1. Lower baseline CD4+ T cell count in the lopinavir/ritonavir plus zidovudine/lamivudine group was the only statistically significant difference between treatment groups ($P = 0.045$). Three subjects in the lopinavir/ritonavir plus saquinavir group discontinued the study prior to week 48: one due to an adverse event, one due to virological failure and one was lost to follow-up. In the lopinavir/ritonavir plus zidovudine/lamivudine group, five subjects discontinued prematurely; one died due to progressive multifocal leukencephalopathy, three discontinued due to adverse events, and one was withdrawn from the study by the investigator due to non-adherence.
Safety/tolerability of a lopinavir/ritonavir and saquinavir regimen

Table 1. Baseline demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>LPV/r plus SQV</th>
<th>LPV/r plus ZDV/3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>16 (100)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>10 (63)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>2 (13)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>2 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>2 (13)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>42 (25–64)</td>
<td>40 (21–59)</td>
</tr>
<tr>
<td>Hepatitis B/C positive(a), n (%)</td>
<td>4 (25)</td>
<td>5 (39)</td>
</tr>
<tr>
<td>Median baseline plasma HIV-1 RNA, log(10) copies/mL (range)</td>
<td>5.0 (3.7–5.9)</td>
<td>5.3 (4.1–6.2)</td>
</tr>
<tr>
<td>Baseline CD4+ T cell count, cells/mm(^3)</td>
<td>269 (3–687)</td>
<td>120 (9–428)</td>
</tr>
<tr>
<td>number with &lt;200 cells/mm(^3) (%)</td>
<td>6 (38)</td>
<td>10 (71)</td>
</tr>
</tbody>
</table>

LPV/r, lopinavir/ritonavir; SQV, saquinavir; ZDV/3TC, zidovudine plus lamivudine.

\(a\)Hepatitis B surface antigen positive or hepatitis C virus antibody positive, or both.

**P = 0.045 between treatment groups.

Virological and immunological activity

By the ITT (NC = F) analysis, 10/16 (63%) lopinavir/ritonavir plus saquinavir-treated subjects and 7/14 (50%) lopinavir/ritonavir plus zidovudine/lamivudine-treated subjects achieved plasma HIV-1 RNA <50 copies/mL (P = 0.71) at week 48 (Figure 1). Similarly, in the observed data analysis, 10/13 (77%) saquinavir-treated subjects and 7/9 (78%) zidovudine/lamivudine-treated subjects achieved plasma HIV-1 RNA <50 copies/mL (P > 0.99, Figure 2). Three subjects in the saquinavir group and two in the zidovudine/lamivudine group had plasma HIV-1 RNA >50 copies/mL at week 48; all five of these subjects had plasma HIV-1 RNA <80 copies/mL at this timepoint.

Overall, four subjects discontinued due to adverse events. One subject in the lopinavir/ritonavir plus saquinavir treatment group and two subjects in the lopinavir/ritonavir plus zidovudine/lamivudine treatment group discontinued study due to adverse events of the digestive system, and one subject in the lopinavir/ritonavir plus zidovudine/lamivudine group discontinued due to Grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations (>10 \times \text{upper limit of normal}) in the presence of hepatitis C. One additional subject died 31 days after discontinuation of the study medication. Death was considered not related to study medication and attributed to an HIV-related event of progressive multifocal leukencephalopathy.

Laboratory abnormalities were generally mild and, with the exception of haematological abnormalities attributable to zidovudine, occurred with similar frequency in the two treatment groups. Four subjects demonstrated Grade 3 AST and ALT determinations (more than five times the upper limit of normal), one in the lopinavir/ritonavir plus saquinavir group and three in the lopinavir/ritonavir plus zidovudine/lamivudine group. All occurred in subjects with underlying hepatitis B or C, and only one resulted in study drug discontinuation.

Significant increases in mean CD4+ T cell count from baseline were observed at all visits after week 4. Through week 48, the median [interquartile range (IQR)] changes from baseline in median CD4+ T cell count were 93 (72, 174) cells/mm\(^3\) in the lopinavir/ritonavir plus saquinavir group and 163 (94, 225) cells/mm\(^3\) in the lopinavir/ritonavir plus zidovudine/lamivudine group (P = 0.55 for the comparison between treatment groups).

Safety and tolerability

No statistically significant differences between treatment groups in frequency of specific adverse events of any severity or relationship to study drug were noted. Among moderate or severe adverse events probably or possibly related to lopinavir, digestive system events were most common, occurring in 6/16 (38%) saquinavir-treated versus 8/14 (57%) zidovudine/lamivudine-treated subjects (P = 0.46), with nausea, vomiting and diarrhoea each being reported in three or four subjects in each treatment group.

Figure 1. Proportion of subjects with HIV-1 RNA <50 copies/mL in analysis. LPV/r, lopinavir/ritonavir; SQV, saquinavir; ZDV/3TC, zidovudine plus lamivudine.

Figure 2. Proportion of subjects with plasma HIV-1 RNA <50 copies/mL in observed data analysis.
Metabolic assessments

Fasting blood samples were obtained at all study visits. There were no statistically significant changes between baseline and week 48 in blood glucose in either treatment arm. The mean increase in total cholesterol from baseline to week 48 was 60 mg/dL in each treatment group. One subject in each treatment group experienced Grade 3 total cholesterol elevation (>300 mg/dL). The median (IQR) increases through week 48 in the high-density lipoprotein (HDL) concentration were 5.8 (2.0, 9.0) mg/dL for the lopinavir/ritonavir plus saquinavir group and 6.6 (0.4, 11.2) mg/dL for the lopinavir/ritonavir plus zidovudine/lamivudine group. No statistically significant change between baseline and week 48 in total cholesterol/HDL ratio was observed in either the saquinavir (5.3 versus 5.7, \( P = 0.51 \)) or zidovudine/lamivudine (4.5 versus 5.5, \( P = 0.164 \)) treatment groups. Increases in triglycerides through week 48 were also similar in the lopinavir/ritonavir plus saquinavir (median 52 mg/dL, IQR 4–80 mg/dL) and lopinavir/ritonavir plus zidovudine/lamivudine (median 39 mg/dL, IQR 32–105 mg/dL) groups. Increases in triglycerides through week 48 were also similar in the lopinavir/ritonavir plus saquinavir (median 52 mg/dL, IQR 4–80 mg/dL) groups. One subject (lopinavir/ritonavir plus zidovudine/lamivudine (median 52 mg/dL, IQR 32–105 mg/dL) and lopinavir/ritonavir plus zidovudine/lamivudine-treated subject with mid-section weight gain and one lopinavir/ritonavir were noted in one saquinavir-treated group. Increases in triglycerides through week 48 were also similar in the lopinavir/ritonavir plus saquinavir (median 52 mg/dL, IQR 4–80 mg/dL) groups. One subject (lopinavir/ritonavir plus zidovudine/lamivudine group) experienced a Grade 3 triglyceride elevation (>300 mg/dL). The subject was not treated with lipid-lowering agents.

Assessment of change in PBMC mtDNA:nDNA ratios between baseline and week 48 was successfully performed in 10 lopinavir/ritonavir plus saquinavir and 7 lopinavir/ritonavir plus zidovudine/lamivudine-treated subjects. No statistically significant changes from baseline were observed at any visit (weeks 8, 16, 32 and 48) in either treatment group. Adverse events of body fat composition changes thought to be related to lopinavir/ritonavir were noted in one saquinavir-treated subject who experienced mid-section weight gain and one lopinavir/ritonavir plus zidovudine/lamivudine-treated subject with asymmetric gynaecomastia described as right breast tissue irregularity.

Baseline, week 48 and final visit DEXA scans were available for 13 subjects in the lopinavir/ritonavir plus saquinavir group and 9 subjects in the lopinavir/ritonavir plus zidovudine/lamivudine group. For eight subjects in each group, the final visit occurred at week 96. A significant difference between groups was noted at the final visit for the ratio of truncal fat to lower extremity fat (\( P = 0.01 \)), apparently driven by a small decrease in the lower extremity fat in the zidovudine/lamivudine group (–6%) and a statistically significant increase in the lower extremity fat in the saquinavir group (+19%, Table 2). Both groups demonstrated small but statistically significant increases in total lean body mass through the final visit. Non-significant changes of note included increases in truncal fat in both the lopinavir/ritonavir plus saquinavir and lopinavir/ritonavir plus zidovudine/lamivudine treatment groups (19% and 17%, respectively, through the final visit).

Pharmacokinetic results

When co-administered with lopinavir/ritonavir, saquinavir 400 mg twice daily produced generally similar concentrations (Table 3). The safety profile observed in prior clinical trials of lopinavir/ritonavir reflects the combination therapies employed and includes toxicities from both lopinavir/ritonavir and co-administered NRTIs. Select toxicities observed in these studies may be attributable either to specific antiretroviral drugs or to a combination of antiretroviral agents. The safety profile

Table 2. DEXA screen results

<table>
<thead>
<tr>
<th>Measurement</th>
<th>LPV/r plus SQV group (n = 13)</th>
<th>LPV/r + ZDV/3TC group (n = 9)</th>
<th>( P ) values comparing treatment groups (week 48/final visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline mean</td>
<td>mean percentage change from baseline to week 48</td>
<td>mean percentage change from baseline to final visit</td>
</tr>
<tr>
<td>Truncal fat (kg)</td>
<td>13.0</td>
<td>+19</td>
<td>+19</td>
</tr>
<tr>
<td>Lower extremity fat (kg)</td>
<td>6.2</td>
<td>+13</td>
<td>+19*</td>
</tr>
<tr>
<td>Truncal:lower extremity fat (ratio)</td>
<td>2.06</td>
<td>+3</td>
<td>–1</td>
</tr>
<tr>
<td>Total body fat (kg)</td>
<td>22.2</td>
<td>+15</td>
<td>+17</td>
</tr>
<tr>
<td>Total body lean mass (kg)</td>
<td>56.0</td>
<td>+2</td>
<td>+3*</td>
</tr>
<tr>
<td>Appendicular fat (kg)</td>
<td>8.2</td>
<td>+11</td>
<td>+17</td>
</tr>
</tbody>
</table>

*Statistically significant (\( P < 0.05 \)) within-group change from baseline.
observed may also reflect the specific NRTI employed, as there are data suggesting risk of metabolic toxicity is lower with abacavir, tenofovir, emtricitabine and lamivudine than with other NRTIs. A number of previous studies have examined the effect of switching NRTIs on metabolic toxicities associated with antiretroviral therapy. These studies have generally shown modest and gradual improvement in lipoatrophy and/or mtDNA abnormalities. The present study was performed to investigate the metabolic toxicities, overall safety, tolerability and antiviral activity associated with an NRTI-sparing regimen containing lopinavir/ritonavir plus saquinavir versus a nucleoside-containing ‘standard’ regimen of lopinavir/ritonavir plus zidovudine/lamivudine.

The antiviral activity and tolerability observed in this study were consistent with that observed in prior clinical trials of lopinavir/ritonavir combination therapy, as well as with a prior study demonstrating the efficacy of dual protease inhibitor therapy with saquinavir and ritonavir. Both lopinavir/ritonavir-containing regimens studied were effective, with similar proportions of subjects achieving plasma HIV-1 RNA <50 copies/mL through 48 weeks of observation in each treatment group. Similar CD4+ T cell count response was also noted in the two treatment groups. With the exception of expected haematological changes attributed to zidovudine use, adverse events and laboratory abnormalities also occurred with similar frequency in the two treatment groups. Results should be interpreted with caution, because the small sample size limited the ability to detect differences between treatment groups.

Assessment of metabolic toxicities including change in mtDNA:nDNA ratio, lipid abnormalities and reports of body fat composition changes revealed no statistically significant differences between the NRTI-sparing dual-protease inhibitor regimen (lopinavir/ritonavir plus saquinavir) and the NRTI-containing regimen (lopinavir/ritonavir plus zidovudine/lamivudine). However, changes in body fat composition were suggested by the DEXA scan, particularly in subjects who remained on their assigned treatment regimen through 96 weeks of treatment. Differences between treatment groups were manifest predominately as a significantly greater increase in the ratio of truncal to lower extremity body fat noted in the lopinavir/ritonavir plus zidovudine/lamivudine versus lopinavir/ritonavir plus saquinavir treatment groups. Of interest, this difference appears to be driven by increases in the lower extremity fat in the lopinavir/ritonavir plus saquinavir treatment group, a phenomenon which may represent normalization of lower extremity fat loss associated with HIV infection, a phenomenon also observed in the AIDS Clinical Trial Group 5005s study. Increases in the lower extremity fat were not observed in the lopinavir/ritonavir plus zidovudine/lamivudine treatment group, a finding consistent with peripheral fat wasting effects. Increases in truncal fat were noted in both regimens.

In the pharmacokinetic substudy, saquinavir 600 or 800 mg twice daily produced exposures similar to those reported with saquinavir hard-gel capsules 1000 mg plus ritonavir 100 mg twice daily at 22 weeks. The Cmin of saquinavir exceeded the serum-adjusted IC50 of wild-type HIV-1 virus by 2.0–2.3-fold for the saquinavir 600 and 800 mg twice daily regimens, respectively, when co-administered with lopinavir/ritonavir 400/100 mg twice daily. Saquinavir 400–800 mg twice daily did not appear to affect the pharmacokinetics of lopinavir. The lopinavir Cmin exceeded the serum-adjusted IC50 of wild-type HIV-1 virus by 79–93-fold when lopinavir/ritonavir 400/100 mg twice daily was co-administered with 400–800 mg of saquinavir. These findings were consistent with an earlier report demonstrating that co-administration of lopinavir/ritonavir 400/100 mg twice daily with saquinavir soft gel capsules 1000 mg twice daily will result in therapeutic concentrations of both lopinavir and saquinavir, although the saquinavir dose was higher in this earlier study.

Several limitations of this study, which may have affected the ability to detect differences in metabolic toxicities across treatment regimens, should be noted. First, recent analyses have suggested that NRTI-induced changes in the mtDNA:nDNA ratio may be more reliably identified in adipose tissue than in PBMCs. Second, the rates of occurrence and time of onset of metabolic toxicities associated with specific NRTI therapies may vary. For example, although both stavudine and zidovudine have been associated with metabolic toxicities, the risk of metabolic abnormalities with stavudine may be substantially greater than with zidovudine. Thus, the choice of zidovudine as an NRTI used in this study may have reduced the likelihood of identifying differences in occurrence of metabolic toxicities when an NRTI-sparing regimen is compared with an NRTI-containing regimen using a different NRTI, such as stavudine. Finally, the relatively short duration of observation (48 weeks) and small sample size may have reduced the ability to detect differences in the metabolic profiles of the two regimens employed.

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**Table 3. Week 2, 3 and 4 mean ± SD steady-state saquinavir (SQV) and lopinavir (LPV) pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400 mg of SQV + 400/100 mg of LPV/r twice daily (n = 12)</td>
<td>600 mg of SQV + 400/100 mg of LPV/r twice daily (n = 12)</td>
<td>800 mg of SQV + 400/100 mg of LPV/r twice daily (n = 12)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>5.0 ± 1.8</td>
<td>3.8 ± 2.0</td>
<td>4.5 ± 1.2</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>1.22 ± 0.55*</td>
<td>2.44 ± 1.4</td>
<td>2.44 ± 0.85</td>
</tr>
<tr>
<td>Cmin (mg/L)</td>
<td>0.27 ± 0.16*</td>
<td>0.51 ± 0.28</td>
<td>0.60 ± 0.33</td>
</tr>
<tr>
<td>Cgrouph (mg/L)</td>
<td>0.45 ± 0.25*</td>
<td>0.92 ± 0.58</td>
<td>1.06 ± 0.52</td>
</tr>
<tr>
<td>AUC12 (mg h/L)</td>
<td>7.62 ± 2.42*</td>
<td>15.59 ± 7.43</td>
<td>17.47 ± 7.13</td>
</tr>
</tbody>
</table>

*Statistically significantly different from reference (800 mg of SQV + 400/100 mg of LPV/r; P < 0.05).
Nevertheless, the study suggests that large or consistent differences in metabolic parameters would be unlikely in comparisons of NRTI-sparing versus NRTI-containing regimens.

In conclusion, this pilot study demonstrated that lopinavir/ritonavir plus saquinavir, a dual-boosted protease inhibitor, NRTI-sparing regimen, had antiviral activity and safety comparable to the lopinavir/ritonavir standard combination regimen. In general, similar occurrences of lipid and metabolic abnormalities were observed, although DEXA scan results demonstrated differences in fat distribution consistent with previously reported NRTI effects. The small sample size limited the ability to discern differences between treatment groups, underscoring the need for additional, larger studies to evaluate potential long-term metabolic benefits of dual-boosted protease inhibitor-based regimens sparing NRTIs associated with metabolic toxicities.

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Transparency declarations

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