Safety and Antiviral Activity at 48 Weeks of Lopinavir/Ritonavir plus Nevirapine and 2 Nucleoside Reverse-Transcriptase Inhibitors in Human Immunodeficiency Virus Type 1–Infected Protease Inhibitor–Experienced Patients

Constance A. Benson,1 Steven G. Deeks,2 Scott C. Brun,4 Roy M. Gulick,7 Joseph J. Eron,6 Harold A. Kessler,5 Robert L. Murphy,8 Charles Hicks,9 Martin King,4 David Wheeler,10 Judith Feinberg,11 Richard Stryker,3 Paul E. Sax,12 Sharon Riddler,13 Melanie Thompson,14 Kathryn Real,1 Ann Hsu,1 Dale Kempf,4 Anthony J. Japour,4 and Eugene Sun4

The safety and antiviral activity of lopinavir (Lpv), a protease inhibitor (PI) coformulated with ritonavir (Rtv) to enhance its pharmacokinetic properties, were evaluated in 70 patients with plasma human immunodeficiency virus type 1 (HIV-1) RNA levels of 1000–100,000 copies/mL on a first PI-containing regimen. Patients were randomized to substitute only the PI with Lpv/Rtv, 400/100 mg or 400/200 mg twice daily. On day 15, nevirapine (200 mg 2×/day) was added, and nucleoside reverse-transcriptase inhibitors were changed. Despite a >4-fold reduction in phenotypic susceptibility to the preentry PI in 63% of patients, mean plasma HIV-1 RNA levels declined by 1.14 log10 copies/mL after 2 weeks of Lpv/Rtv. At week 48, 86% of subjects receiving treatment had plasma HIV-1 RNA levels of <400 copies/mL; 76% had levels <50 HIV-1 RNA copies/mL (intent-to-treat: 70% and 60%, respectively). Mean CD4 cell counts increased by 125 cells/μL. Three patients discontinued therapy for drug-related adverse events.

The widespread use of potent combination antiretroviral regimens containing human immunodeficiency virus type 1 (HIV-1) protease inhibitors (PIs) has been associated with significant reductions in HIV-1–related morbidity and mortality in developed countries [1]. The virologic, immunologic, and clinical benefits of PI antiretroviral therapy have been demonstrated in numerous clinical trials [2–5]. There is, however, a growing population of patients in whom durable adequate suppression of HIV-1 replication cannot be maintained with currently available PI-based therapies. Failure to maintain suppression of HIV-1 replication has been attributed to a variety of factors, including, but not limited to, suboptimal pharmacokinetics, marginal potency, side effects, and inadequate adherence to complicated dosing require-

Received 5 July 2001; revised 24 October 2001; electronically published 14 February 2002.
Reprints or correspondence: Dr. Constance A. Benson, University of Colorado Health Sciences Center, Div. of Infectious Diseases, 4200 E. 9th Ave., B-168, Denver, CO 80262 (constance.benson@uchsc.edu).
The Journal of Infectious Diseases  2002;185:599–607  © 2002 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/2002/18505-0005$02.00 0022-1899/2002/18505-0005$02.00
ments of regimens. Persistent viral replication as a consequence of inadequate drug levels or intermittent adherence may result in loss of antiviral activity because of the development of drug resistance.

Genotypic and phenotypic analyses show that HIV-1 isolates that contain resistance mutations and display loss of susceptibility to currently available PIs are prevalent among treated patients experiencing virologic failure with their current therapies [6, 7]. HIV-1 isolates with evidence of genotypic or phenotypic resistance also can be recovered from recently infected patients, presumably because of the transmission of drug-resistant HIV-1 strains [8]. For patients who experience virologic failure while receiving antiretroviral therapy with a PI, virologic response to a subsequent treatment regimen may be as low as 30%–40%, although the response depends, in part, on prior treatment history and the number of drugs prescribed to which the breakthrough virus remains susceptible [9–16]. The likelihood of achieving a favorable virologic response appears to diminish with failure of each successive treatment regimen [9–16]. Thus, there is a need for antiretroviral agents that are active against virus isolates with phenotypic and genotypic resistance to existing drugs.

Lopinavir (Lpv; formerly known as ABT-378) is an HIV-1 PI that is 10-fold more potent in vitro than ritonavir (Rtv) in the presence of human serum [17]. The compound is coformulated with a low dose of Rtv (Lpv/Rtv) that inhibits the 3A4 isoenzyme of the cytochrome P450 system to which the breakthrough virus remains susceptible [9–16]. The likelihood of achieving a favorable virologic response appears to diminish with failure of each successive treatment regimen [9–16]. Thus, there is a need for antiretroviral agents that are active against virus isolates with phenotypic and genotypic resistance to existing drugs.

The ratio of trough concentration (C_{trough}) to effective IC_{50} of wild-type HIV-1 isolates, as measured under physiologically relevant conditions (e.g., in the presence of 50% human serum [17]), represents a pharmacodynamic indicator of in vivo antiviral activity [20, 21]. Although other methods exist for correcting for plasma protein binding, protein-corrected IC_{50}s provide a reasonable surrogate for actual conditions in vivo, because the free fraction of Lpv measured in tissue culture media with 50% human serum approximates the free fraction in patient plasma at typical therapeutic concentrations [22]. The ratio of C_{trough} to IC_{50}, (inhibitory quotient) of Lpv/Rtv for wild-type HIV-1 as calculated by this method is $>75$ at a 400/100-mg twice-daily dose [19]. On the basis of its high inhibitory quotient and data from a previous phase 2 study that demonstrated that Lpv/Rtv has good antiviral activity and tolerability in treatment-naive patients [23, 24], we designed the present study to assess the safety, tolerability, and antiviral activity of 2 Lpv/Rtv doses in combination with nevirapine (Nvp) and 2 nucleoside reverse-transcriptase inhibitors (NRTIs) in single PI–experienced, nonnucleoside reverse-transcriptase inhibitor (NNRTI)–naïve, HIV-1–infected patients experiencing virologic failure with their current regimen.

**Methods**

**Study design.** This was a prospective, multicenter, randomized, double-blind study of 2 different doses of Lpv/Rtv in HIV-1–infected viremic patients receiving treatment with 1 PI and 1 or 2 NRTIs.

**Eligibility criteria.** Patients were eligible for the study if they were $\geqslant 18$ years, had a Karnofsky Score $\geqslant 70$, had no evidence of acute illness or active opportunistic infection, were experiencing virologic failure (plasma HIV-1 RNA level of 1000–100,000 copies/mL) with current treatment with a PI-containing regimen that had not changed in the previous 12 weeks, had no history of prior NNRTI therapy, and were naive to or had received $<8$ weeks of treatment with $\geqslant 1$ other NRTI. Up to 20% of those enrolled were permitted to be positive for hepatitis B surface antigen (HBsAg) and/or anti–hepatitis C virus (HCV) antibody at screening.

Patients were excluded if they had a history of active substance abuse or a positive test result for drugs of abuse (excluding cannabis), were pregnant or lactating, had clinically significant electrocardiographic abnormalities, or baseline test results for hemoglobin or platelet count of $<5.5$ g/dL, absolute neutrophil count of $<1000$ cells/µL, platelet count of $<50,000$ cells/µL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels $>2.5$ times the upper limit of normal (ULN), or creatinine levels $>1.5$ times the ULN. Participants must not have had prior treatment with $\geqslant 1$ PI concurrently, previous exposure to another PI for $>6$ weeks before their current regimen, or exposure to an investigational drug (other than amprenavir) within the 28 days before randomization.

**Study medications.** After screening, patients were randomized to receive oral Lpv/Rtv at a dose of either 400/100 mg or 400/200 mg twice daily. Separate capsules of Lpv and Rtv were used during the study until coformulated capsules became available. The Rtv dosage was not revealed to the investigator, study staff, and the patient throughout the study; Lpv, Nvp, and the NRTIs were administered as open-label medication. On day 1, each patient had his or her current PI discontinued and replaced with Lpv/Rtv. From days 1 through 14, patients received Lpv/Rtv in 1 of 2 doses, as described above, plus the 2 NRTIs they were receiving at baseline. On day 15, the NRTI regimen was changed to include $\geqslant 1$ NRTI not previously received, and Nvp (Viramune; Boehringer Ingelheim Pharmaceuticals) was added at an initial oral dose of 200 mg once daily for 14 days and increased to 200 mg twice daily thereafter.

**Evaluations performed.** Subjects were evaluated every 2 weeks to week 12 (with a visit at week 1 to measure plasma HIV-1 RNA only), then every 4 weeks to week 24, and then every 12 weeks to week 48. Plasma HIV-1 RNA levels, CD4 and CD8 T cell counts, clinical chemistry, and hematology evaluations were done at each visit. Plasma HIV-1 RNA levels were quantified by use of the Amplicor HIV-1 Monitor assay (Roche Molecular Diagnostics; lower limit of quantitation, 400 HIV-1 RNA copies/mL) and the LCx HIV RNA quantitative assay (in development by Abbott Diagnostics; lower limit of quantitation, 50 HIV-1 RNA copies/mL) [25, 26]. Phenotypic resistance testing of baseline virus isolates obtained from patient plasma was done by Virco (Mechelen, Belgium) by the Antivirogram method. These samples were tested after study enrollment was complete, and individual results were not provided to the investigators. Blood samples for pharmacokinetics evaluations were collected over 12 h after dosing from a subset of 12
patients (7 receiving Lpv/Rtv 400/100 mg 2×/day and 5 receiving
400/200 mg 2×/day) at weeks 6 and 24.

Statistical analyses. The planned sample size was 35 patients
per treatment group. This sample size was based on the ability to de-
tect, with at least 95% confidence, a true incidence of adverse events
and antiviral activity rates within 20% of the observed rate (assum-
ing an overall discontinuation rate of ≥20% within each arm). All patients who received ≥1 dose of study drug were included in the
analyses.

The primary efficacy variables were the proportion of subjects
with plasma HIV-1 RNA levels of <400 copies/mL at weeks 24
and 48. Plasma HIV-1 RNA levels were assessed using both on-
treatment and intent-to-treat analyses. The on-treatment analysis
excluded subjects with missing measurements and any measure-
ments obtained while treatment was interrupted for ≥3 days. Intent-
to-treat analyses were performed with missing values considered
treatment failures (missing = failure). Adverse events were sum-
marized by using the Coding Symbols for Thesaurus of Adverse
Reaction Terms (COSTART) V dictionary [27]. Comparison of
baseline measurements was done by using one-way analysis of var-
iance, Wilcoxon rank sum test, or the Fisher’s exact test. All re-
ported P values are based on 2-sided tests of significance; values
<.05 were considered to be significant for all comparisons.

Results

Baseline characteristics. Seventy patients received ≥1 doses
of Lpv/Rtv; 36 were randomized to the 400/100-mg twice-daily
group, and 34 were randomized to the 400/200-mg twice-daily
group. Table 1 summarizes baseline characteristics. There were
no statistically significant differences in these characteristics for
the 2 groups (table 1).

Baseline virus isolates for 57 of 70 subjects were analyzed
retrospectively for PI phenotypic susceptibility. For the remaining
subjects, either samples were not available (n = 1) or virus
could not be amplified because of insufficient plasma HIV-1
RNA levels (n = 12). Baseline phenotypic susceptibility data
are summarized in table 2.

For the 56 patients with baseline phenotypic susceptibility
data available for all the drugs in the preentry regimen, ≥4-fold
increase in IC50 for 1, 2, or 3 previously received drugs was dem-
onstrated for 36% (20/56), 45% (25/56), and 16% (9/56) of
patients, respectively. The baseline phenotypic susceptibility to
Lpv was 0.7–26-fold (mean, 2.8-fold) above that of wild-type
HIV-1 strain HXB2.

Patient disposition at week 48. Twelve patients discon-
tinued the study at or before week 48: 3 because of adverse events
related to the study drug; 1 because of persistent intermittent
diarrhea after ~36 weeks of study therapy; 1 because of nausea,
vomiting, flatulence, and diarrhea during the first 2 days of dos-
ing; and 1 because of a rash that developed 5 days after the onset
of Nvp administration. Additional reasons for discontinuation
before week 48 included adverse events not attributed to study
drug (n = 1; myocardial infarction on day 1 of study medica-
d), death not attributed to study drug (n = 2; metastatic lung
carcinoma, rhabdomyolysis/acute renal failure following tra-
umatic falls in a patient with pneumonia and progressive multifocal
leukoencephalopathy), subject choice (n = 2), noncompliance
(n = 2), and loss to follow up (n = 2).

Antiviral activity and relationship with baseline viral pheno-
type. A rapid reduction in plasma HIV-1 RNA level was ob-
served in the first 2 weeks of the study, with 94% of patients
experiencing a reduction from baseline of ≥0.5 log10 HIV-1
RNA copies/mL or to a level of <400 HIV-1 RNA copies/mL,
and 80% experiencing a reduction from baseline of ≥1.0 log10
HIV-1 RNA copies/mL to <400 HIV-1 RNA copies/mL. The
mean decline from baseline in plasma HIV-1 RNA by week 2
was 1.21 log10 HIV-1 RNA copies/mL for the 400/100-mg twice-
daily group and 1.07 log10 HIV-1 RNA copies/mL for the 400/
200-mg twice-daily group, a mean reduction of 1.14 log10 HIV-1
RNA copies/mL overall. The reduction in plasma HIV-1 RNA
level by week 2 was of comparable magnitude, regardless of
the preentry PI taken. In a comparison between patients with

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of patients enrolled.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Race/ethnicitya</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
</tr>
<tr>
<td>Asian/Pacific</td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
</tr>
<tr>
<td>Hepatitis B/C positiveb</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA level, log10 copies/mL</td>
</tr>
<tr>
<td>Mean ± SE</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>CD4 T cell count, cells × 10^3/L</td>
</tr>
<tr>
<td>Mean ± SE</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>Baseline antiretroviral medication</td>
</tr>
<tr>
<td>Amprenavir</td>
</tr>
<tr>
<td>Indinavir</td>
</tr>
<tr>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Ritonavir</td>
</tr>
<tr>
<td>Saquinavir</td>
</tr>
<tr>
<td>Didanosine</td>
</tr>
<tr>
<td>Lamivudine</td>
</tr>
<tr>
<td>Stavudine</td>
</tr>
<tr>
<td>Zidovudine</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, except where noted. HIV-1, human
immunodeficiency virus type 1.

a Patients may have contributed to >1 race/ethnicity category.

b Hepatitis B surface antigen and/or hepatitis C antibody positive.
Table 2. Baseline susceptibility to protease inhibitors (PIs) and nucleoside reverse-transcriptase inhibitors included in the baseline regimen, compared with wild-type human immunodeficiency virus type 1 (n = 57).

<table>
<thead>
<tr>
<th>Baseline antiretroviral</th>
<th>Fold increase in IC_{50}</th>
<th>Percentage of patients with &gt;4-fold increase in IC_{50} (no/total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir</td>
<td>2.8</td>
<td>19 (11/57)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>7.4</td>
<td>67 (16/24)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>19.1</td>
<td>62 (13/21)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>23.0</td>
<td>100 (3/3)</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>9.5</td>
<td>44 (4/9)</td>
</tr>
<tr>
<td>Didanosine</td>
<td>1.9</td>
<td>0 (0/7)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>&gt;90.8</td>
<td>100 (48/48)</td>
</tr>
<tr>
<td>stavudine</td>
<td>2.1</td>
<td>13 (4/50)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>10.6</td>
<td>40 (10/25)</td>
</tr>
</tbody>
</table>

<4-fold or >4-fold reduced susceptibility to Lpv at baseline, there was no difference in the reduction in mean plasma HIV-1 RNA level by week 2 (1.11 vs. 1.21 log_{10} HIV-1 RNA copies/mL, respectively, P = .55). Similarly, linear regression analysis relating baseline log_{10} fold change in Lpv IC_{50} to log_{10} HIV-1 RNA decline from baseline to week 2 demonstrated no relationship between these variables (R^2 = .016).

Fifty-eight patients completed 48 weeks of the study. At week 48, results from the on-treatment analysis demonstrated that 86% of patients (48/56) had a virus load of <400 HIV-1 RNA copies/mL. The corresponding result from the intent-to-treat (missing = failure) analysis was 70% (49/70; figure 1). Suppression of viral replication to <50 HIV-1 RNA copies/mL occurred in 76% of patients (41/54) on-treatment and in 60% of patients (42/70) by intent-to-treat analysis (figure 1). Of note, 2 patients were excluded from all on-treatment analyses because they were not receiving study treatment at week 48; another 2 patients did not have samples available for ultrasensitive virus load testing at week 48. No statistically significant difference (P < .05) was observed between the 400/100-mg and 400/200-mg twice-daily dose groups at any visit, although a trend favoring greater efficacy of the 400/200-mg dose group was evident at week 48 (P = .056) but not at subsequent follow-up (figure 1).

Mean plasma trough concentrations of Lpv in the pharmacokinetics subgroups treated with the 400/100-mg and 400/200-mg twice-daily doses were higher than the protein binding–corrected IC_{50} of Lpv for all baseline virus isolates (n = 57) tested (figure 2). As the ranges of Lpv trough concentrations were 1.8–7.9 ng/mL for the 400/100-mg dose and 3.6–16.6 μg/mL for the 400/200-mg dose group, the lowest trough concentrations observed were at (n = 1) or above the protein binding–corrected Lpv IC_{50} for all baseline isolates tested. A >4-fold reduction in baseline phenotypic susceptibility to Lpv was not associated with a diminished virus load response at week 24 (P = .327) or week 48 (P > .999) by a limit of quantitation of 400 HIV-1 RNA copies/mL (figure 2) or 50 HIV-1 RNA copies/mL (data not shown).

Immunologic response. The mean CD4 T cell count increased rapidly following initiation of study therapy, and a statistically significant increase from baseline was observed in both dose groups at and after week 8 (P < .001). By week 48, the mean increase from baseline in CD4 T cell count was 125 cells/μL, with a mean of 504 cells/μL (n = 58; figure 3). CD4 T cell count increases were similar in the 2 dose groups, with a mean increase of 140 and 108 cells/μL, respectively, in the 400/100-mg and 400/200-mg twice-daily groups.

Safety and tolerability. The most commonly reported adverse effects of at least moderate severity that were possibly related to study drug were diarrhea (defined as >3 loose stools per day: 19% of patients in the 400/100-mg twice-daily and 24% in the 400/200-mg twice-daily dose groups) and asthenia (3% and 9%, respectively; table 3). Most adverse events were of mild-to-moderate severity, and with the exception of gastrointestinal effects, most were reported by the investigator to be probably not or not related to Lpv/Rtv. There was no statistically significant difference in the incidence rates of adverse events between the 400/100-mg and 400/200-mg twice-daily dose groups.

All laboratory values were obtained without regard to fasting. Elevated cholesterol, triglycerides, AST, ALT, and γ-glutamyl transferase levels were observed through 48 weeks of treatment (table 3). At week 48, mean cholesterol levels increased by 30

![Figure 1](image-url)
mg/dL and 38 mg/dL, respectively, from baseline in the 400/100-mg and 400/200-mg twice-daily groups (P < .001 in each group, compared with baseline). Mean triglyceride levels increased by 135 and 124 mg/dL, respectively (P < .05 in each group, compared with baseline). Although there were more grade 3 or higher lipid elevations (>300 mg/dL for total cholesterol and >750 mg/dL for triglycerides) in the 400/200-mg twice-daily group than in the 400/100-mg twice-daily group, the difference was not statistically significant at week 48 (P = .162 for total cholesterol and P = .403 for triglycerides), possibly as a consequence of the relatively small sample size. Patients with baseline cholesterol values >200 mg/dL or baseline triglyceride levels >400 mg/dL were more likely to develop grade 3 or higher lipid elevations during the study.

Similarly, patients with baseline AST or ALT elevations were more likely to develop grade 3 or higher AST or ALT elevations (>5 times the ULN) during the study. However, AST or ALT levels returned to baseline in most patients while they continued their assigned Lpv/Rtv dose. No patient discontinued the study as a consequence of treatment-emergent laboratory abnormalities through week 48. One episode of ALT elevation, clay colored stools, and dark urine was interpreted as hepatitis by the site investigator and was ascribed to Nvp. No episodes of clinical (symptomatic) hepatitis attributed to Lpv/Rtv were reported as adverse events. Among 10 patients with serologic evidence of chronic hepatitis B (HBsAg positive) and/or hepatitis C (HCV antibody positive) infection at baseline, 2 patients (20%) experienced grade 3 or higher AST or ALT elevations, which is comparable to the rate of such elevations in hepatitis B– and hepatitis C–negative patients (9 [15%] of 59; P = .656). However, the small number of patients with hepatitis coinfection enrolled in this study precluded detection of significant differences.

Discussion

Demonstration of the singular antiviral activity of new anti–HIV-1 drugs in the setting of combination antiretroviral therapy presents a challenge to clinical trial design. This evaluation is particularly difficult for patients in whom previous therapies failed and for whom subsequent successful treatment is dependent on the use of multiple active agents. In this ongoing study...
of single PI-experienced patients, we demonstrated the antiviral activity of Lpv/Rtv by the rapid reduction in plasma HIV-1 RNA levels observed in the first 2 weeks of therapy, when the only new drug administered was Lpv/Rtv. Following the addition of Nvp and ≥1 new NRTI, durable suppression of HIV-1 replication with Lpv/Rtv was observed in a high proportion of patients despite substantial baseline resistance to PIs and NRTIs. The durability of the virologic response is likely due to the combined effect of one or more of the following factors: the demonstrated antiviral activity of Lpv/Rtv, the antiviral activity of Nvp in this NNRTI-naive patient population, and the substitution of ≥1 new NRTI component in the study regimen. These results should also be considered in the context that patients with plasma HIV-1 RNA levels >100,000 copies/mL at screening were excluded from participation in this study, and only 3 patients had plasma HIV-1 RNA levels >100,000 copies/mL at baseline.

Few published, prospective, randomized clinical trials have addressed salvage therapy following virologic failure of a first potent combination antiretroviral regimen containing a PI in a population such as that in this study. AIDS Clinical Trials Group (ACTG) 372b evaluated 94 subjects for whom zidovudine (or stavudine), lamivudine, and indinavir treatments were failing. These patients were NNRTI naive [12]. Subjects were randomized in a factorial design to receive either investigator-selected NRTIs or abacavir plus efavirenz and adeovir dipivoxil with or without nelfinavir. Overall, 32% of subjects had plasma HIV-1 RNA levels <500 copies/mL at week 16: the highest proportion were in the arm combining abacavir, nelfinavir, efavirenz, and adeovir dipivoxil (48%) [12]. In ACTG 333, subjects who had received hard gel capsule saquinavir for ≥48 weeks and were experiencing virologic treatment failure were randomized to substitute either soft gel capsule saquinavir or indinavir plus continued background NRTIs [28]. Those randomized to indinavir had a significantly greater decline in plasma HIV-1 RNA level during the first 8 weeks of treatment than those randomized to soft gel capsule saquinavir, and, by week 16, a greater proportion of subjects who received indinavir (49%) achieved a plasma HIV-1 RNA level <500 copies/mL than subjects who received soft gel capsule saquinavir (8%; P < .001).

A number of studies have reported that dual PI–containing regimens that take advantage of pharmacokinetic enhancement with Rtv or other agents can be used effectively in treating HIV-1–infected patients who experienced virologic failure with previous therapy with ≥1 other PIs [29–32]. Tebas et al. [11] reported results for 24 patients who experienced treatment failure with a nelfinavir-containing regimen and were subsequently treated with Rtv, saquinavir, stavudine, and lamivudine. At 24 weeks, 71% of these patients had a virus load of <500 HIV-1 RNA copies/mL [11].

In a study by Piketty et al. [33], 32 PI-experienced patients who were naive to saquinavir and efavirenz and who experienced treatment failure with a PI and 2 NRTIs at study entry were switched to Rtv (100 mg twice daily), saquinavir (1000 mg twice daily), efavirenz (600 mg once daily), and NRTIs [33]. An intent-to-treat analysis at 24 weeks revealed that 71% had plasma HIV-1 RNA levels <500 copies/mL, and 45% had levels <50 HIV-1 RNA copies/mL [33]. In ACTG 359, 277 subjects who were NNRTI naive and whose treatment with a first PI indinavir-containing regimen was failing were randomized to 1 of 6 salvage regimens in a factorial design that included saquinavir plus Rtv or saquinavir plus nelfinavir and either delavirdine, adeovir dipivoxil, or both. In the intent-to-treat analysis, only 30% of subjects had plasma HIV-1 RNA levels <500 copies/mL at 16 weeks [16]. The results from the current trial of Lpv/Rtv in combination with Nvp and 2 NRTIs compare favorably with and expand on these findings, demonstrating sustained viral suppression in 70% of single PI–experienced patients in the intent-to-treat analysis through 48 weeks.

The rates of virologic response observed in salvage therapy are generally lower than those seen when antiretroviral agents are administered to treatment-naive patients, even with regimens containing antiretroviral agents to which patients are naive. The use of Lpv/Rtv in PI-experienced patients also appears to be associated with a lower rate of response than when administered to antiretroviral-naive patients. In a study of 100 antiretroviral-naive patients receiving Lpv/Rtv with 2 NRTIs, a greater proportion achieved plasma HIV-1 RNA levels <400 copies/mL through 108 weeks (99% in an on-treatment analysis and 80% with an intent-to-treat analysis) than observed in the current study at 48 weeks [23].

Central to this study was the analysis of virologic response relative to the baseline phenotypic susceptibility of virus isolates. In studies where patients did not achieve durable suppression of plasma HIV-1 RNA levels with a second PI-containing regimen, this was often associated with genotypic and/or pheno-

### Table 3. Adverse events and grade 3 or 4 laboratory abnormalities reported to week 48 of study, by lopinavir/ritonavir dosage group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lopinavir/ritonavir dosage given twice a day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400/100 mg (n = 36)</td>
</tr>
<tr>
<td>Adverse event&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Grade 3/4 laboratory abnormalities&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>GGT level &gt;5 × ULN</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Total cholesterol &gt;300 mg/dL</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Triglycerides &gt;750 mg/dL</td>
<td>7 (19)</td>
</tr>
<tr>
<td>AST/ALT level &gt;5 × ULN</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamine transferase; ULN, upper limit of normal.

<sup>a</sup> Adverse events of at least moderate severity and probable, possible, or unknown relationship to lopinavir/ritonavir occurring in ≥5% of patients overall.

<sup>b</sup> Patients with grade 3/4 laboratory abnormalities occurring in ≥5% of patients overall with ≥1 postbaseline measurement. Laboratory values were obtained without regard to fasting.
tropic resistance at the time of therapy switch [6, 34, 35]. Indeed, for currently available PIs, phenotypic resistance at baseline appears to be associated with a lower clinical response to the drug in question [28, 36], and a ≥4-fold increase in IC_{50}, compared with wild-type HIV-1, may be a useful predictor of therapeutic outcome [37, 38]. However, in this study, despite baseline resistance to Lpv/Rtv and other PIs, a large proportion of patients had sustained suppression of viral replication. No relationship was observed between the initial 2-week virologic response in patients receiving Lpv/Rtv and the level of phenotypic susceptibility to Lpv/Rtv at baseline. Similarly, a ≥4-fold increase in baseline phenotypic susceptibility to Lpv was not associated with diminished virus load response at weeks 24 or 48 by using a limit of quantitation of either 400 or 50 HIV-1 RNA copies/mL. This is consistent with the high mean trough plasma levels achieved with Lpv/Rtv, which are in excess of the IC_{50} values for all baseline virus isolates obtained from patients in this study.

These data demonstrate that a relationship between drug susceptibility, as measured by in vitro phenotype assays and drug exposure in vivo, is likely to differ for individual antiviral agents and must be defined carefully to allow for clinically meaningful interpretations. For Lpv/Rtv, these data indicate that the clinically relevant “breakpoint” for phenotypic resistance is substantially >4-fold above the susceptibility of wild-type virus. An insufficient number of isolates with higher levels of reduced phenotypic susceptibility to Lpv (only 3 isolates had ≥10-fold increase in IC_{50}) prevented further delineation of this breakpoint within this study. This breakpoint was studied further in a clinical trial of multiple PI–experienced NNRTI-naive patients treated with Lpv/Rtv, efavirenz, and NRTIs. After 24 weeks of treatment, plasma HIV-1 RNA level was ≤400 copies/mL in 93% (27/29) and 65% (15/23) of patients with <10-fold and ≥10-fold, respectively, reduced susceptibility to Lpv at baseline (P < .05) [39].

Although Lpv trough concentrations remained above the IC_{50} values for virus isolates from single PI–experienced patients enrolled in this study, comparison of pharmacokinetic data from this study with data from patients receiving Lpv/Rtv without Nvp suggest that Nvp reduces trough concentrations of Lpv in the presence of low doses of Rtv (unpublished data, Abbott Laboratories). Furthermore, pharmacokinetic results from a subsequent clinical study in a pediatric population demonstrated ~40%–45% reduction in Lpv trough levels when Lpv/Rtv was coadministered with Nvp [40]. Although these data were not available to prompt modification of therapy in the first 48 weeks of this trial, consideration should be given to increasing the dose of Lpv/Rtv to 533/133 mg (4 coformulated capsules) twice daily in patients receiving Lpv/Rtv concomitantly with an NNRTI when reduced susceptibility to Lpv is clinically suspected by treatment history or laboratory evidence [39].

In addition to demonstrated antiviral efficacy, the ability of PIs to induce immune recovery is widely recognized [41]. Although no data are yet available on the effectiveness of Lpv/Rtv in restoring specific immune responses, a significant increase in CD4 T cell count was observed in both treatment groups in this study. This occurred even though patients may have already experienced a significant CD4 T cell response with their previous antiretroviral regimen.

Lpv/Rtv was well tolerated: 4% of patients (3/70) discontinued therapy because of treatment-related adverse events through week 48. The most common drug-related adverse events of at least moderate severity were gastrointestinal, and the most common laboratory abnormalities were lipid elevations. Of note, lipid measurements were made without respect to fasting, the majority of patients had lipid values exceeding the ULN at baseline, and lipid levels did not progressively increase with time. Additional follow-up of a larger number of patients for a longer period will be required to determine the clinical significance of the elevated lipid levels observed during Lpv/Rtv treatment, especially with respect to the impact on body fat distribution abnormalities and long-term cardiovascular risk.

In conclusion, for single PI–experienced, NNRTI-naive patients, the combination of Lpv/Rtv, Nvp, and NRTIs produced significant reductions in plasma HIV-1 RNA levels and increased CD4 cell counts. Factors that likely contributed to these responses are limited prior PI treatment, preentry plasma HIV-1 RNA levels <100,000 copies/mL, the use of ≥1 drug in a class not previously received (i.e., Nvp), and the high plasma levels of Lpv achieved allowing moderately decreased antiviral drug susceptibility to be overcome. The lack of a relationship between a ≥4-fold decrease in viral susceptibility to Lpv at baseline and virologic response at weeks 2, 24, and 48 is also a likely consequence of high Lpv levels achieved in combination with low doses of Rtv, further supporting this strategy to achieve improved virologic responses in treatment-experienced patient populations.

Acknowledgments

We thank the following persons who assisted substantially with the conduct of this study: Beverly Putnam and Sally Camann (University of Colorado Health Sciences Center, Denver); Dorrie Herren and Doug Raggett (San Francisco General Hospital, San Francisco); Marshall Glesby and Todd Stroberg (Weill Medical College, Cornell University, New York, NY); Cheryl Marcus and Janet Devine (University of North Carolina, Chapel Hill); Elke Narkiewicz (Rush Medical College, Chicago); James L. Bruce and Pam Donath (Northwestern University Medical School, Chicago); Julieta Giner and Carmen Elliott (Duke University, Durham, NC); Stephen B. Poretz and Tracey A. King (Infectious Disease Physicians, Ammandale, VA); Pamela Daniel and Carol Colegate (University of Pittsburgh School of Medicine, Pittsburgh); Paul Couey (AIDS Research Consortium of Atlanta, Atlanta); and Richard J. Bertz and Theresa Marsh (Abbott Laboratories, Abbott Park, IL).
References


