Randomized Study of Saquinavir with Ritonavir or Nelfinavir Together with Delavirdine, Adefovir, or Both in Human Immunodeficiency Virus–Infected Adults with Virologic Failure on Indinavir: AIDS Clinical Trials Group Study 359

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This study compared antiretroviral activity among 6 “salvage” therapy regimens. The study was a prospective, randomized, 2 X 3 factorial, multicenter study of the AIDS Clinical Trials Group. The study enrolled 277 human immunodeficiency virus (HIV)-infected patients naive to nonnucleoside analogues who had taken indinavir >6 months. The patients had 2000–200,000 HIV RNA copies/mL. Patients received saquinavir with ritonavir or nelfinavir together with delavirdine and/or adefovir and were followed for safety and antiretroviral response between baseline and week 16. At week 16, 30% (77/254) of patients had ≤500 HIV RNA copies/mL. Virologic response did not differ significantly between pooled ritonavir and nelfinavir groups (28% vs. 33%; P = .50) or between pooled delavirdine and delavirdine/adefovir groups (40% vs. 33%; P = .42). Pooled delavirdine groups had a greater virologic response rate than did adefovir groups (40% vs. 18%; P = .002). Overall, one-third of patients who experienced virologic failure on an indinavir-containing regimen suppressed virus load levels while they were taking a new salvage regimen.

Standard treatment for human immunodeficiency virus (HIV) infection is a regimen consisting of 2 nucleoside analogue reverse-transcriptase inhibitors and a potent protease inhibitor (or nonnucleoside reverse-transcriptase inhibitor) [1, 2]. This recommendation is supported, in part, by clinical trial data showing that most patients taking such regimens suppress HIV RNA levels for ≥2 years [3–9]. However, ≥20% of patients taking potent protease inhibitor–containing regimens on clinical trials experience virologic failure [3–9], and the rate of virologic failure may be even higher in general clinical use [10–15]. Current guidelines for the treatment of patients who experience virologic failure while receiving potent antiretroviral therapy are based on expert opinion [1, 2] and recommend combinations of drugs that the patient has not yet taken. Although there are some published observational data on the use of such “salvage” regimens [12, 16–18], no published prospective, randomized clinical trial data are available.

We conducted a prospective clinical trial in a population of treatment-experienced patients with virologic failure who were taking indinavir. The patients were randomized to receive saquinavir in combination with a second protease inhibitor together with a nonnucleoside analogue reverse-transcriptase inhibitor and/or a nucleotide analogue reverse-transcriptase inhibitor.

Methods

Study design. This was a randomized, partially double-blinded, multicenter factorial study of 6 oral antiretroviral regimens that included combinations of open-label saquinavir soft gelatin cap-
sules (Roche Pharmaceuticals, Nutley, NJ) with ritonavir (Abbott Laboratories, Abbott Park, IL) or nelfinavir (Aguon Pharma
ceuticals, San Diego), together with blinded delavirdine (Pharmacia and Upjohn, Kalamazoo, MI) and/or adefovir dipivoxil (Gilead
Sciences, Foster City, CA; table 1). The randomization was based
on permuted blocks with dynamic balancing by participating site.
Patients discontinued their current antiretroviral regimens, in-
cluding all nucleoside analogues, and received randomized treat-
ment for 24 weeks. Patients with geometric mean HIV RNA levels at
weeks 12 and 16 of either ≤5000 copies/mL or ≥1 log₁₀ below
baseline could continue randomized study treatment for an addi-
tional 24 weeks.

Study population. Eligible patients were ≥16 years old with
documented HIV infection who had taken indinavir for ≥6 months
and for 2 weeks immediately before study entry and had screening
plasma HIV RNA levels of 2000–200,000 copies/mL (Amplicor
HIV Monitor test; Roche Diagnostic Systems, Branchburg, NJ;
lower limit of quantification, 500 copies/mL). Patients could have
taken ritonavir or saquinavir hard gelatin capsule for <2 weeks but
could not have taken any nonnucleoside reverse-transcriptase
inhibitor, other protease inhibitors, or adefovir dipivoxil. Patients
were not pregnant or breast-feeding and had not received inves-
tigational therapy within 30 days of entry.

Study procedures. Patients had visits twice before entry, at entry,
at weeks 1, 2, and 4, and then every 4 weeks through week 24. At
all visits, a clinical assessment and laboratory tests were done. Plasma
was processed and stored at −70°C twice at baseline, then every 4
weeks, and was later assayed for HIV RNA in batch (baseline
through week 16) at a central laboratory (University of North Caro-
olina, Chapel Hill, or University of Washington, Seattle) with the
Amplicor Monitor assay (Roche Diagnostic Systems). Specimens
from weeks 16 or 24 with HIV RNA <500 copies/mL were retested
with the Ultrasensitive assay (Roche Diagnostic Systems; lower limit
of detection, 50 copies/mL). T lymphocyte subsets were quantified
by flow cytometry twice at baseline and every 4 weeks.

Adverse events were graded by using standardized AIDS Clinical
Trials Group (ACTG) guidelines from the date of entry to 30 days
after permanent discontinuation of study treatment. Moderate
(grade 2 or higher) intensity adverse events, including signs and
symptoms and laboratory abnormalities, were recorded, to evaluate
the safety and tolerability of the study treatments. In June 1998,
the protocol was amended to include laboratory monitoring, tox-
icity and, management, and dose reduction of adefovir dipivoxil for
proximal renal tubular dysfunction (PRTD), because of new
information about the toxicity provided by Gilead Sciences.
The protocol definition of PRTD was as follows: serum creatinine ≥0.5
mg/dL above baseline and serum phosphate <2.0 mg/dL, or 1 of
these abnormalities plus 2 of the following: proteinuria (≥2+),
glycosuria (≥1+) in the absence of hyperglycemia, hypokalemia
(<3.0 mEq/L), or serum bicarbonate <19 mEq/L. The dose of ade-
fovir dipivoxil (or matching placebo) was reduced to 60 mg a day
after completion of 16 weeks of study. After that time, patients
could continue adefovir dipivoxil or substitute or add ≥1 nucleo-
side analogues.

Interim analyses. One planned efficacy and safety interim anal-
ysis was performed in April 1998. The analysis was based on re-
peated confidence bands [19] and adoption of the O’Brien-Fleming
spending function. A second unscheduled interim analysis focusing
only on safety was undertaken in October 1998. In both analyses,
the Data and Safety Monitoring Committee recommended that the
trial be continued. Because of the conservative spending function,
the P value for a significant result at the final analysis (P = .044)
was close to the nominal P = .05 level, and, hence, we report the
nominal P values.

Statistical analysis. The primary study objective was to eval-
uate and compare the treatment regimens with respect to the pro-
portion of patients with plasma HIV-1 RNA levels ≤500 copies/
Ml at 16 weeks and the safety and tolerability of the regimens.
Patients were to remain on their randomized treatment for 24 weeks
to allow time for the processing of their weeks 12 and 16 HIV
RNA levels, which were used to determine their eligibility for the
open-label portion of the study. The primary comparisons focused
on the 2 factors in the 2 × 3 factorial study design: between rito-
navir and nelfinavir and among delavirdine, adefovir dipivoxil, and
the combination of delavirdine plus adefovir dipivoxil. By using
the factorial design, the levels of each factor were compared, after
we pooled the treatment groups over the levels of the other factor.
Secondary objectives included comparisons of the individual treat-
ment groups, assessment of other virologic and immunologic re-
ponses, and durability of virologic response in patients who
achieved suppression by week 16.

The sample size was determined initially as 50 patients per study
arm. This yielded 150 patients per group for the comparison of
ritonavir versus nelfinavir and 100 patients per group for the com-
parison of delavirdine, adefovir dipivoxil, or the combination. For
the first of these comparisons, this yielded a power of 98% to detect
a difference of 15% versus 35% in the proportion of patients who
suppressed their virus loads to ≤500 copies/mL by week 16, based
on a 2-sided test of size 0.05, allowing for a 10% dropout rate. For
the second, this yielded a power of 89% to detect a difference of
15% and 35%, allowing for a 10% dropout rate. Because of a
subsequent slowdown in accrual rate, the team closed the study to
accrual at a total of 277 randomized patients. This slightly lowered
the powers to 96% and 86%, respectively.

Efficacy analyses used an intent-to-treat approach and included
all available measurements on all randomized patients. Safety anal-
yses were based on patients who received ≥1 dose of study medi-
cation. Follow-up times were calculated from the randomization
date. The baseline HIV RNA level was calculated as the geometric
mean of the preentry and entry determinations. Baseline CD4 cell

<table>
<thead>
<tr>
<th>Table 1. Antiretroviral study treatments.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>E</td>
</tr>
<tr>
<td>F</td>
</tr>
</tbody>
</table>

NOTE. In addition, all patients received L-carnitine supplement, 500 mg once daily (qd), bid, 2×/day; sgc, soft gelatin capsule; tid, 3×/day.
Table 2. Baseline characteristics of the human immunodeficiency virus (HIV)-infected patients among the antiretroviral study treatment groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 277)</th>
<th>SQV + RTV + DLV (n = 47)</th>
<th>SQV + RTV + ADV (n = 47)</th>
<th>SQV + RTV + DLV + ADV (n = 45)</th>
<th>SQV + NFV + DLV (n = 45)</th>
<th>SQV + NFV + ADV (n = 45)</th>
<th>SQV + NFV + DLV + ADV (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>231 (83)</td>
<td>39</td>
<td>38</td>
<td>38</td>
<td>41</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Female</td>
<td>46 (17)</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>8</td>
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<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (non-Hispanic)</td>
<td>137 (49)</td>
<td>26</td>
<td>19</td>
<td>24</td>
<td>27</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Black (non-Hispanic)</td>
<td>80 (29)</td>
<td>13</td>
<td>19</td>
<td>11</td>
<td>11</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Hispanic</td>
<td>53 (19)</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>11</td>
<td>10</td>
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<tr>
<td>Other</td>
<td>7 (3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<td>0</td>
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<tr>
<td>Injection drug use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>243 (88)</td>
<td>44</td>
<td>36</td>
<td>42</td>
<td>44</td>
<td>36</td>
<td>41</td>
</tr>
<tr>
<td>Current</td>
<td>2 (1)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Previous</td>
<td>32 (2)</td>
<td>3</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Median age, years</td>
<td>40</td>
<td>39</td>
<td>42</td>
<td>37</td>
<td>41.5</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Prior treatment for HIV-related opportunistic infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>203 (73)</td>
<td>30</td>
<td>37</td>
<td>28</td>
<td>35</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>No</td>
<td>74 (27)</td>
<td>17</td>
<td>10</td>
<td>17</td>
<td>13</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Prior indinavir use, median no. of months</td>
<td>14.4</td>
<td>13.0</td>
<td>12.2</td>
<td>14.3</td>
<td>15.5</td>
<td>15.1</td>
<td>15.4</td>
</tr>
<tr>
<td>Prior nucleoside analogue use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>97 (9.6)</td>
<td>13 (7.7)</td>
<td>17 (7.7)</td>
<td>20 (12.1)</td>
<td>16 (7.4)</td>
<td>13 (8.8)</td>
<td>18 (17.2)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>268 (16.8)</td>
<td>47 (15.4)</td>
<td>47 (17.7)</td>
<td>40 (16.5)</td>
<td>47 (18.3)</td>
<td>42 (16.6)</td>
<td>44 (17.9)</td>
</tr>
<tr>
<td>Stavudine</td>
<td>146 (12.2)</td>
<td>24 (11.6)</td>
<td>29 (13.0)</td>
<td>22 (12.5)</td>
<td>30 (12.8)</td>
<td>22 (13.9)</td>
<td>19 (14.7)</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>56 (12.5)</td>
<td>6 (9.8)</td>
<td>6 (9.8)</td>
<td>14 (8.3)</td>
<td>15 (15.9)</td>
<td>6 (22.4)</td>
<td>12 (11.0)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>252 (22.3)</td>
<td>43 (24.3)</td>
<td>38 (21.7)</td>
<td>42 (33.3)</td>
<td>46 (21.9)</td>
<td>40 (16.3)</td>
<td>43 (23.3)</td>
</tr>
<tr>
<td>Median baseline HIV RNA, copies/mL</td>
<td>31,746</td>
<td>28,950</td>
<td>48,466</td>
<td>35,704</td>
<td>22,428</td>
<td>32,122</td>
<td>22,551</td>
</tr>
<tr>
<td>Median baseline CD4 cell count, cells/mm³</td>
<td>229</td>
<td>228</td>
<td>230</td>
<td>242</td>
<td>202</td>
<td>193</td>
<td>258</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, except where noted. ADV, adefovir dipivoxil; DLV, delavirdine; NFV, nelﬁnavir; RTV, ritonavir; SQV, saquinavir.

* No. of patients (median duration of use, in months).

count was computed as the arithmetic average of preentry and entry values. When 1 of these values was missing, the available value was used. Specimens were obtained within 2–4 weeks of the target week visit. Missing values were assumed to occur at random in the analysis. All tests were 2-tailed, and the significance level was set at \( P = .05 \).

Binary responses were analyzed by using Fisher’s exact and \( \chi^2 \) tests; quantitative responses were analyzed by using the Wilcoxon rank sum test. Failure time end points were analyzed by using the Kaplan-Meier estimator and log-rank test. Regression analyses were based on simple linear regression and, in the case of binary responses, logistic regression.

Results

In total, 277 patients were enrolled between September 1997 and October 1998 at 42 units of the adult ACTG. The median length of prior indinavir use was 14 months, median baseline HIV RNA was 31,746 (4.5 log₁₀) copies/mL, and CD4 cell count was 229 cells/mm³. There were 13 (5%) patients with virus loads <2000 copies/mL at study entry, 99 (36%) with 2000–20,000 copies/mL, and 162 (58%) with >20,000 copies/mL. Major baseline measures were well balanced among the 6 treatment groups (table 2).

Follow-up of study patients. We followed 262 (95%) patients through at least the week 16 visit (table 3). Two patients did not start study treatment after randomization but remained in study follow-up, 15 patients (5%) withdrew from the study before week 16, and 57 (21%) discontinued study treatment early but remained in follow-up. There were no significant differences among the groups with respect to duration of study treatment (\( P = .31 \), log-rank test).

HIV RNA. Median HIV RNA levels (figure 1) for all groups decreased at study weeks 4 and 8. By week 16, virus load levels trended back toward baseline levels with median virus load changes from baseline (log₁₀ HIV RNA copies/mL) of −0.41 (arm A; see table 1), −0.16 (arm B), −0.21 (arm C), −0.61 (arm D), −0.08 (arm E), and −0.05 (arm F). Figure 2A shows the proportion of patients with <500 HIV RNA copies/mL through week 16, by treatment group. Overall, 77 (30%) of 254 patients had <500 HIV RNA copies/mL at week 16. Arm D had the...
Table 3. Disposition of the study patients among the antiretroviral study treatment groups.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SQV + RTV + DLV</th>
<th>SQV + RTV + ADV</th>
<th>SQV + RTV + DLV + ADV</th>
<th>SQV + NFV + DLV</th>
<th>SQV + NFV + ADV</th>
<th>SQV + NFV + DLV + ADV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received intervention as allocated</td>
<td>47</td>
<td>47</td>
<td>45</td>
<td>47</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>No intervention as allocated</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawn from study before week 16</td>
<td>Patient request (1); lost to follow-up (2)</td>
<td>Patient request (1); patient moved (1)</td>
<td>Patient request (1); lost to follow-up (2)</td>
<td>Patient request (1); death (1)</td>
<td>Patient request (1); other (1)</td>
<td>Patient request (1); death (2); patient ineligible (1)</td>
</tr>
<tr>
<td>Completed 16 weeks of follow-up</td>
<td>44</td>
<td>45</td>
<td>42</td>
<td>46</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>Discontinued study treatment during first 16 weeks of study</td>
<td>Patient request (2); increased virus load (2); noncompliant (1)</td>
<td>Patient request (1); increased virus load (4); noncompliant (1); toxicity end point (1); prohibited concomitant medications (1)</td>
<td>Patient request (3); increased virus load (6); noncompliant (1); moved (1)</td>
<td>Patient request (5); increased virus load (4); toxicity end point (3)</td>
<td>Patient request (2); increased virus load (6); toxicity end point (1)</td>
<td>Patient request (6); increased virus load (3); toxicity end point (3)</td>
</tr>
<tr>
<td>Completed 16 weeks of treatment</td>
<td>39</td>
<td>37</td>
<td>31</td>
<td>33</td>
<td>34</td>
<td>28</td>
</tr>
</tbody>
</table>

NOTE. Numerals indicate no. of patients. ADV, adefovir dipivoxil; DLV, delavirdine; NFV, nelﬁnavir; RTV, ritonavir; SQV, saquinavir.
Figure 1. Median change in human immunodeficiency virus (HIV) RNA from baseline (log_{10} copies/mL; 25th, 75th percentiles) for 16 weeks among treatment groups A–F: ADV, adefovir dipivoxil; DLV, delavirdine; NFV, nelfinavir; RTV, ritonavir; SQV, saquinavir soft gel capsules.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number of samples at baseline</th>
<th>Number of samples at week 4</th>
<th>Number of samples at week 8</th>
<th>Number of samples at week 12</th>
<th>Number of samples at week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>46</td>
<td>41</td>
<td>42</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>B</td>
<td>46</td>
<td>41</td>
<td>42</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>C</td>
<td>46</td>
<td>41</td>
<td>42</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>D</td>
<td>48</td>
<td>43</td>
<td>43</td>
<td>42</td>
<td>42</td>
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<tr>
<td>E</td>
<td>44</td>
<td>41</td>
<td>42</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>F</td>
<td>45</td>
<td>43</td>
<td>43</td>
<td>42</td>
<td>42</td>
</tr>
</tbody>
</table>

highest response rate of 47% (20/43 patients), compared with arm F (36%, 15/42 patients), arm A (33%, 14/42 patients), arm C (31%, 12/39 patients), arm B (20%, 9/44 patients), and arm E (16%, 7/44 patients). Of 69 patients with samples available with HIV RNA levels \( \leq 500 \) copies/mL at week 16, 38 (55%) also had \( \leq 50 \) copies/mL by the ultrasensitive assay.

Figure 2B presents the proportion of patients with \( \leq 500 \) HIV RNA copies/mL by week for the pooled ritonavir and nelfinavir groups. The proportions (95% pointwise confidence intervals [CIs]) of virologic suppression at week 16 were 28% (20%-36%) for ritonavir versus 33% (24%-41%) for nelfinavir (\( P = .50 \), Fisher’s exact test). Figure 2C presents the proportion of patients with \( \leq 500 \) HIV RNA copies/mL by week for the pooled delavirdine, adefovir dipivoxil, and combination groups. The respective proportions (95% pointwise CIs) were 40% (27%-54%) for delavirdine, 18% (7%-23%) for adefovir dipivoxil, and 33% (23%-50%) for the combination. Using 3 pairwise tests, the proportion of patients with virologic suppression for the delavirdine and combination groups was significantly greater than that of the pooled adefovir dipivoxil groups (\( P = .002 \) and .03, respectively, Fisher’s exact test). The difference between the delavirdine and combination groups was not significant (\( P = .42 \), Fisher’s exact test).

Multivariate logistic regression models were used to examine the effects of baseline factors on virologic response. Patients with higher baseline CD4 cell counts (odds ratio [OR], 1.1 per 100 cells/mm\(^3\); \( P = .003 \)), lower baseline HIV RNA levels (OR, 0.34 per log_{10} copies/mL; \( P < .001 \)), shorter duration of prior indinavir use (OR, 0.93 per month; \( P = .002 \)), and female sex (OR, 0.40; \( P = .04 \)) were significantly associated with a higher probability of virus load levels \( \leq 500 \) copies/mL by week 16. After we adjusted for these factors, the delavirdine groups continued to have a significantly greater virologic response rate than did the adefovir dipivoxil groups (\( P = .002 \) and did not differ from the combination (\( P = .37 \)).

Of 221 study patients with available samples, 60 (27%) had \( \leq 500 \) HIV RNA copies/mL at week 24. Arm D had the highest response rate of 41% (15/37 patients), compared with arms C (31%, 11/36 patients), A (30%, 11/37 patients), F (22%, 8/36 patients), B (20%, 7/35 patients), and E (20%, 8/40 patients). In total, 76% of patients with \( \leq 500 \) copies/mL of HIV RNA at week 16 with available samples remained suppressed at week.
Figure 2. Proportion of patients with human immunodeficiency virus (HIV) RNA < 500 copies/mL for 16 weeks and confidence intervals. A. Treatment groups (A–F); B, pooled ritonavir (RTV) and nelfinavir (NFV) groups; C, pooled delavirdine (DLV), adefovir dipivoxil (ADV), and combination groups. SQV, saquinavir soft gel capsules.

24, and there were no differences between the ritonavir and nelfinavir groups ($P = .57$) or among the delavirdine, adefovir dipivoxil, and delavirdine plus adefovir dipivoxil combination groups ($P = .69$) with respect to continued virologic suppression. Of 54 patients with samples available with HIV RNA levels ≤ 500 copies/mL at week 24, 32 (59%) had ≤ 50 copies/mL. The available data showed that 86% of patients with HIV RNA levels ≤ 50 copies/mL at week 16 had ≤ 500 copies/mL at week 24.

**CD4 cell count.** The overall median change in CD4 cells from baseline was +19 cells/mm$^3$ (range, 5–44 cells/mm$^3$). There was no significant difference in the number of CD4 cells from baseline to week 16 between the ritonavir and nelfinavir groups ($P = .25$, Wilcoxon rank sum test) or among the 3 pairwise comparisons, delavirdine versus adefovir dipivoxil versus the combination ($P = .38$, .75, and .50, respectively, Wilcoxon rank sum test). Multiple linear regression analysis revealed no significant association between baseline factors and change in CD4 cell count.

**Adverse events.** Most signs and symptoms were moderate
was a marginally significant difference of severe or greater laboratory abnormality in intensity. The most common were diarrhea (71 patients [26%]), pain (35 patients [13%]), nausea (32 patients [12%]), and fatigue (32 patients [12%]). Forty-eight (17%) patients reported severe (grade 3 or higher) signs and symptoms (table 4). The distribution of time to first severe (grade 3 or higher) sign or symptom within the first 16 weeks of study was not significantly different between the ritonavir and nelfinavir groups ($P = .071$). However, the ritonavir groups showed a somewhat lower rate than did the nelfinavir groups after 6 weeks of treatment by comparison of the Kaplan-Meier curves of the 2 groups for the time to the first adverse event. There were no significant differences among the delavirdine, adefovir dipivoxil, or combination groups ($P = .94$) or among the 6 individual treatment groups ($P = .51$).

In all, 189 (68%) patients experienced moderate (grade 2 or higher) or severe (grade 3 or higher) laboratory toxicities: 87 (31%) moderate and 102 (37%) severe (table 4). Three (1%) patients experienced PRTD during the first 16 weeks—all took adefovir dipivoxil-containing regimens. The distribution of time to the first severe (grade 3 or higher) laboratory abnormality was not significantly different between the ritonavir and nelfinavir groups ($P = .35$, log-rank test) but was significant among the delavirdine, adefovir, and combination groups ($P = .019$, log-rank test). The adefovir dipivoxil groups had fewer severe or greater laboratory toxicities than did the other 2 groups. When all 6 treatment groups were compared, there was a marginally significant difference of severe or greater laboratory toxicities ($P = .062$, log-rank test), and adefovir dipivoxil-containing groups had lower rates.

### Discussion

This is the first prospective, randomized study to evaluate the virologic and immunologic activity of combination antiretroviral therapy in patients who experienced virologic failure on a protease inhibitor–containing regimen. Overall, in patients who experienced virologic failure on an indinavir-containing regimen, 77 (30%) of 254 had virus loads ≤500 copies/mL at week 16 (over half with ≤50 copies/mL) while taking a new regimen of dual protease inhibitors (saquinavir with ritonavir or nelfinavir), together with the nonnucleoside analogue reverse-transcriptase inhibitor, delavirdine, and/or the nucleotide analogue reverse-transcriptase inhibitor, adefovir dipivoxil. We found no difference in virologic response with ritonavir or nelfinavir as the second protease inhibitor but a significantly better virologic response in persons who received delavirdine instead of adefovir dipivoxil. The greatest absolute changes in virus loads occurred in the pooled delavirdine (without adefovir dipivoxil) groups. Virologic response rates for the groups receiving delavirdine plus adefovir dipivoxil were no better than in those receiving delavirdine without adefovir dipivoxil.

The virologic suppression rate demonstrated in this study is similar to rates described from observational studies in protease inhibitor–experienced patients [12, 16–18], although one small

### Table 4. Number of patients experiencing adverse events among the antiretroviral study treatment groups.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>SQV + RTV + DLV (n = 47)</th>
<th>SQV + RTV + ADV (n = 47)</th>
<th>SQV + RTV + DLV + ADV (n = 45)</th>
<th>SQV + NFV + DLV (n = 48)</th>
<th>SQV + NFV + ADV (n = 45)</th>
<th>SFV + NFV + DLV + ADV (n = 45)</th>
<th>Total (N = 277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs and symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10, 2</td>
<td>6, 3</td>
<td>10, 1</td>
<td>15, 2</td>
<td>13, 4</td>
<td>17, 4</td>
<td>71, 16</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8, 0</td>
<td>6, 2</td>
<td>8, 0</td>
<td>4, 0</td>
<td>2, 0</td>
<td>4, 2</td>
<td>32, 4</td>
</tr>
<tr>
<td>Fever</td>
<td>2, 1</td>
<td>3, 0</td>
<td>3, 1</td>
<td>5, 3</td>
<td>2, 0</td>
<td>0, 0</td>
<td>15, 5</td>
</tr>
<tr>
<td>Nausea</td>
<td>4, 1</td>
<td>9, 3</td>
<td>7, 1</td>
<td>4, 0</td>
<td>3, 0</td>
<td>5, 1</td>
<td>32, 8</td>
</tr>
<tr>
<td>Pain</td>
<td>3, 1</td>
<td>6, 1</td>
<td>7, 0</td>
<td>6, 2</td>
<td>7, 1</td>
<td>6, 1</td>
<td>35, 6</td>
</tr>
<tr>
<td>Rash</td>
<td>3, 1</td>
<td>1, 0</td>
<td>5, 0</td>
<td>8, 2</td>
<td>1, 1</td>
<td>2, 0</td>
<td>30, 4</td>
</tr>
<tr>
<td>Laboratory finding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT &gt;5× normal</td>
<td>7, 4</td>
<td>3, 0</td>
<td>11, 1</td>
<td>4, 3</td>
<td>10, 0</td>
<td>4, 2</td>
<td>39, 10</td>
</tr>
<tr>
<td>Amylase &gt;2× normal</td>
<td>1, 0</td>
<td>2, 1</td>
<td>1, 0</td>
<td>1, 1</td>
<td>1, 1</td>
<td>0, 0</td>
<td>6, 3</td>
</tr>
<tr>
<td>Absolute neutrophil count &lt;750 cells/mm³</td>
<td>1, 3</td>
<td>2, 3</td>
<td>2, 1</td>
<td>1, 8</td>
<td>2, 1</td>
<td>1, 3</td>
<td>9, 18</td>
</tr>
<tr>
<td>AST &gt;5× normal</td>
<td>3, 4</td>
<td>2, 0</td>
<td>7, 2</td>
<td>4, 4</td>
<td>2, 0</td>
<td>3, 1</td>
<td>21, 11</td>
</tr>
<tr>
<td>Creatine phosphokinase &gt;4× normal</td>
<td>4, 3</td>
<td>5, 2</td>
<td>2, 5</td>
<td>2, 4</td>
<td>4, 3</td>
<td>5, 2</td>
<td>22, 19</td>
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<tr>
<td>Glucose, nonfasting &gt;250 mg/dL</td>
<td>2, 0</td>
<td>4, 1</td>
<td>2, 0</td>
<td>4, 4</td>
<td>2, 1</td>
<td>3, 3</td>
<td>17, 9</td>
</tr>
<tr>
<td>Phosphorus &lt;1.5 mg/L</td>
<td>2, 0</td>
<td>2, 0</td>
<td>0, 1</td>
<td>3, 1</td>
<td>3, 1</td>
<td>0, 1</td>
<td>10, 4</td>
</tr>
<tr>
<td>Total bilirubin &gt;2.5× normal</td>
<td>5, 2</td>
<td>3, 1</td>
<td>0, 1</td>
<td>1, 2</td>
<td>0, 0</td>
<td>1, 1</td>
<td>10, 7</td>
</tr>
<tr>
<td>Triglycerides &gt;750 mg/dL</td>
<td>13, 13</td>
<td>10, 7</td>
<td>14, 8</td>
<td>11, 8</td>
<td>12, 0</td>
<td>6, 1</td>
<td>66, 35</td>
</tr>
<tr>
<td>Uric acid &gt;120 mg/dL</td>
<td>0, 0</td>
<td>2, 2</td>
<td>0, 1</td>
<td>0, 0</td>
<td>0, 1</td>
<td>0, 0</td>
<td>2, 4</td>
</tr>
</tbody>
</table>

NOTE. Data are moderate (grade 2) events and severe (grade 3) or greater (grade 4) events, reported at grade 3 or 4 in ≥1% of study patients for 16 study weeks. ADV, adefovir dipivoxil; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLV, delavirdine; NFV, nelfinavir; RTV, ritonavir; SQV, saquinavir.
uncontrolled study described a better response rate in nelfinavir- 
infected patients who changed to a saquinavir plus lami 
navir-based regimen [20]. The fact that we found in patients in 
whom a protease inhibitor–containing regimen failed that only a 
minority experienced virologic suppression on a subsequent 
regimen reaffirms the principle that the timing and choice of 
initial antiretroviral therapy are critical to avoid virologic fail 
ure. For patients who experience virologic failure, more effec 
tive "salvage" regimens are needed.

Studies of patients who had not previously taken protease 
 inhibitors have documented the potency of dual protease in 
hibitor–based regimens, including saquinavir plus ritonavir [6] 
or nelfinavir [21]. In the current study of indinavir-experienced 
patients, overall limited virologic response and the lack of a 
demonstrable difference in response between ritonavir and 
nelfinavir, used in combination with saquinavir, is likely due 
to significant cross-resistance among the protease inhibitors. Per 
sions in whom the indinavir-containing regimen fails develop 
with sequential substitutions in the protease gene over 3–12 months, which confers virologic cross-resistance to other 
protease inhibitors [22, 23]. In the current study, a shorter du 
ration of prior indinavir therapy was significantly associated 
with a more favorable virologic outcome at 16 weeks. This 
observation supports the principle that a change in regimen 
early after virologic rebound may produce a better virologic 
outcome. Others have noted that virologic rebound for a person 
on a protease inhibitor–containing regimen may not always be 
associated with protease inhibitor resistance [24–26] and have 
shown the benefit of resistance testing when selecting salvage 
therapy regimens [27].

The superior virologic effect shown in the delavirdine-con 
taining arms likely results from the fact that patients had not 
taken any nonnucleoside analogue reverse-transcriptase inhibitor 
before study entry. In a study of the combination of delavirdine 
with 2 nucleoside analogues, 68% of antiretroviral-naive patients 
suppressed HIV RNA levels at 52 weeks [28]. In addition, 
delavirdine is an inhibitor of cytochrome P450-mediated metabo 
lism and can increase plasma concentrations of saquinavir [29], 
ritonavir [29, 30], and nelfinavir [31] 2–5-fold. Salvage therapy 
regimens should include new classes of antiretroviral agents and 
exploit favorable pharmacokinetic interactions, such as those of 
delavirdine and the protease inhibitors.

The reason for the inferior virologic effect demonstrated with 
adeviovir dipivoxil is less clear. A study in which patients added 
adeviovir dipivoxil to their current therapy showed a median 
0.4 log10 decrease in HIV RNA levels at 24 weeks [32]. In a 
subset of patients from that study who underwent intensive 
virologic investigation, adevovir dipivoxil had decreased activity 
in virus with high-level lamivudine resistance but greater activ 
ity against lamivudine-resistant virus (with the M184V substi 
tution in the reverse transcriptase). Most patients in the current 
study had taken lamivudine and stavudine and lamivudine and 
changed all antiretrovirals at study entry. Whether baseline 
high-level lamivudine resistance reduced the virologic response 
to adevovir dipivoxil or whether continuing therapy with la 
mivudine, to select virus with the M184V substitution, would 
enhance the virologic effect of adevovir dipivoxil is unknown.

The lack of any additive or synergistic antiviral effect with 
the combination of delavirdine and adevovir dipivoxil may be 
due, at least in part, to drug interactions among saquinavir, 
delavirdine, and adevovir dipivoxil. An intensive pharmacok 
etic substudy conducted in 37 of the study patients indicated 
that, when saquinavir concentrations were compared according 
to the addition of reverse-transcriptase inhibitor, the area under 
the plasma concentration time curves (AUCs) were highest in 
the delavirdine arms and lowest in the delavirdine and adevovir 
dipivoxil combination arms [33]. In fact, saquinavir AUCs in 
the combination arms were reduced by ~50%, compared with 
those of the delavirdine arms. There was also evidence for an 
interaction between delavirdine and adevovir dipivoxil, because 
delavirdine AUCs were significantly lower in the combination 
arms than in the delavirdine arms.

Overall, median delavirdine concentrations were reduced by ~50% in the combination groups, compared with the delavirdine groups. These interactions were not anticipated, and the mechanism of action is unknown. Current treatment guidelines recommend use of ≥2 new drugs, to which cross-resistance is not anticipated as a 
 choice regime [1, 2]. However, pharmacokinetic interactions 
must be considered and further characterized when using com 
explex multidrug antiretroviral regimens.

Fewer than 10% of patients discontinued study medications 
for toxicity. The most common adverse events were gastroin 
testinal symptoms, as seen in prior studies of the individual 
drugs [5–7, 21, 28, 32], and the incidence did not differ among 
the treatment groups. Adevovir dipivoxil–related PRTD oc 
curred in 1% of study patients during the first 16 weeks. In 
other studies, 35% of patients taking adevovir dipivoxil devel 
oped significant increases in serum creatinine levels, and 50% 
developed significant hypophosphatemia, laboratory abnor 
malities consistent with PRTD, by 48 weeks [32].

In summary, one-third of patients experiencing virologic fail 
ure on an indinavir-containing regimen suppressed virus load 
levels when they took a new combination regimen of dual pro 
tease inhibitors, delavirdine, and/or adevovir dipivoxil. Follow 
up of these study patients will provide more information about 
the durability of the viral suppression. Future studies will need 
to define the pharmacokinetics and virologic activity of newer 
antiretroviral agents and combinations of agents active against 
resistant strains of HIV as patients continue to experience vi 
rologic failure with current antiretroviral regimens.

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References


