

## LOPINAVIR-RITONAVIR VERSUS NELFINAVIR FOR THE INITIAL TREATMENT OF HIV INFECTION

SHARON WALMSLEY, M.D., BARRY BERNSTEIN, M.D., MARTIN KING, PH.D., JOSÉ ARRIBAS, M.D., GILDON BEALL, M.D., PETER RUANE, M.D., MARGARET JOHNSON, M.D., DAVID JOHNSON, M.D., RICHARD LALONDE, M.D., ANTHONY JAPOUR, M.D., SCOTT BRUN, M.D., AND EUGENE SUN, M.D., FOR THE M98-863 STUDY TEAM\*

## ABSTRACT

**Background** Lopinavir is a newly developed inhibitor of human immunodeficiency virus (HIV) protease that, when formulated with ritonavir, yields mean trough plasma lopinavir concentrations that are at least 75 times as high as that needed to inhibit replication of wild-type HIV by 50 percent.

**Methods** We conducted a double-blind trial in which 653 HIV-infected adults who had not received antiretroviral therapy for more than 14 days were randomly assigned to receive either lopinavir-ritonavir (400 mg of lopinavir plus 100 mg of ritonavir twice daily) with nelfinavir placebo or nelfinavir (750 mg three times daily) with lopinavir-ritonavir placebo. All patients also received open-label stavudine and lamivudine. The primary efficacy end points were the presence of fewer than 400 HIV RNA copies per milliliter of plasma at week 24 and the time to the loss of virologic response through week 48.

**Results** At week 48, greater proportions of patients treated with lopinavir-ritonavir than of patients treated with nelfinavir had fewer than 400 copies of HIV RNA per milliliter (75 percent vs. 63 percent,  $P < 0.001$ ) and fewer than 50 copies per milliliter (67 percent vs. 52 percent,  $P < 0.001$ ). The time to the loss of virologic response was greater in the lopinavir-ritonavir group than in the nelfinavir group (hazard ratio, 2.0; 95 percent confidence interval, 1.5 to 2.7;  $P < 0.001$ ). The estimated proportion of patients with a persistent virologic response through week 48 was 84 percent for patients receiving lopinavir-ritonavir and 66 percent for those receiving nelfinavir. Both regimens were well tolerated, with the rate of discontinuation related to the study drugs at 3.4 percent among patients receiving lopinavir-ritonavir and 3.7 percent among patients receiving nelfinavir. Among patients with more than 400 copies of HIV RNA per milliliter at some point from week 24 through week 48, resistance mutations in HIV protease were demonstrated in viral isolates from 25 of 76 nelfinavir-treated patients (33 percent) and none of 37 patients treated with lopinavir-ritonavir ( $P < 0.001$ ).

**Conclusions** For the initial treatment of HIV-infected adults, a combination regimen that includes lopinavir-ritonavir is well tolerated and has antiviral activity superior to that of a nelfinavir-containing regimen. (N Engl J Med 2002;346:2039-46.)

Copyright © 2002 Massachusetts Medical Society.

PROTEASE inhibitor-based combination antiretroviral therapy has led to dramatic improvements in morbidity and mortality associated with human immunodeficiency virus (HIV) infection.<sup>1-4</sup> However, virologic failure occurs within 12 months in up to 50 percent of patients in whom combination antiretroviral therapy is initiated.<sup>5-7</sup> Major factors contributing to failure are poor tolerability and toxicity of the drugs, incomplete adherence to the regimen on the part of patients, and pharmacokinetic properties that result in trough concentrations close to or below the levels required to inhibit HIV replication effectively.<sup>8,9</sup> Lopinavir is a novel peptidomimetic protease inhibitor with potent in vitro activity against HIV<sup>10</sup>; it has been formulated with low-dose ritonavir, a cytochrome P450 3A4 enzyme inhibitor, to enhance its pharmacokinetic profile. When administered at a dose of 400 mg of lopinavir and 100 mg of ritonavir twice daily, the resulting mean trough lopinavir concentrations are at least 75 times as high as the protein binding-corrected concentration needed to inhibit the replication of wild-type HIV by 50 percent ( $EC_{50}$ ).<sup>11</sup> The combination of lopinavir and ritonavir was developed to exploit this pharmacokinetic advantage, with the goal of minimizing the risk of treatment failure and maximizing the durability of a treatment response.

The activity of lopinavir-ritonavir in HIV-infected patients was first demonstrated in a phase 2 study of lopinavir-ritonavir in combination with stavudine and lamivudine, in patients who had not previously been treated with antiretroviral drugs. An intention-to-treat analysis showed that HIV RNA was suppressed to fewer than 50 copies per milliliter in 78 percent of these patients after 48 weeks of treatment.<sup>12</sup> On the basis of initial observations from that study,

From Toronto Hospital, University Health Network, University of Toronto, Toronto (S.W.); Abbott Laboratories, Abbott Park, Ill. (B.B., M.K., A.J., S.B., E.S.); Servicio VIH-Medicina Interna II, Hospital Universitario La Paz, Madrid (J.A.); Harbor UCLA Medical Center, Torrance, Calif. (G.B.); Tower Infectious Diseases, Los Angeles (P.R.); Royal Free Hospital, London (M.J.); Johannesburg, South Africa (D.J.); and Montreal Chest Institute, Royal Victoria Hospital, Montreal (R.L.). Address reprint requests to Dr. Walmsley at Toronto General Hospital, Division of Infectious Diseases, Rm. EN G-219, 200 Elizabeth St., Toronto, ON M5G 2C4, Canada, or at sharon.walmsley@uhn.on.ca.

\*The investigators participating in the M98-863 study are listed in the Appendix.

we conducted a randomized, double-blind, multicenter trial to compare the safety and efficacy of lopinavir–ritonavir with that of nelfinavir.

## METHODS

### Patients

Patients were recruited from 93 centers in 13 countries in North America, South America, Europe, Africa, and Australia. The patients were at least 12 years old, had more than 400 copies of HIV RNA per milliliter of plasma (measured by Roche Amplicor HIV-1 Monitor), a Karnofsky score over 70, and no prior treatment with stavudine or lamivudine or prior treatment with any other antiretroviral therapy for more than 14 days at any time. There was no restriction on the CD4+ cell count. The patients had not been treated for an active opportunistic infection within 30 days before screening. The exclusion criteria also included pregnancy and alanine aminotransferase or aspartate aminotransferase levels more than three times the upper limit of normal. All patients gave written informed consent.

### Study Design

We conducted a randomized, double-blind, comparative study. The primary outcome measures were the proportion of patients with fewer than 400 copies of HIV RNA per milliliter of plasma at 24 weeks and the time to the loss of virologic response through 48 weeks. Secondary efficacy outcomes included the proportion of patients with fewer than 50 copies of HIV RNA per milliliter at weeks 24 and 48 (as determined with the Roche Amplicor HIV-1 Monitor) and changes in the CD4+ cell count. To assess safety, the frequency and severity of treatment-related adverse events, the incidence of laboratory abnormalities, and changes from base line in clinical and laboratory values were compared between the two treatment groups.

### Treatment Regimens

Patients were centrally assigned according to a computer-generated randomization schedule in a 1:1 fashion either to receive lopinavir–ritonavir (Kaletra, Abbott Laboratories) at a dose of 400 mg of lopinavir and 100 mg of ritonavir twice daily, plus nelfinavir placebo three times daily, or to receive nelfinavir (Viracept, Agouron) at a dose of 750 mg three times daily plus a lopinavir–ritonavir placebo twice daily. No stratification was used in the randomization. After approval by the Food and Drug Administration of the nelfinavir regimen consisting of 1250 mg twice daily, the protocol was amended to allow nelfinavir to be taken either three or two times daily by patients who had completed at least 24 weeks of study treatment. Thirty patients made this change before week 48. All patients also received twice-daily open-label lamivudine (150 mg; Epivir, GlaxoSmithKline) and stavudine (40 mg; Zerit, Bristol-Myers Squibb) (patients weighing less than 60 kg received 30 mg). If adverse events related to stavudine or lamivudine occurred, the drug could be discontinued and replaced with another nucleoside drug at the discretion of the investigator.

### Assessment and Monitoring

The patients were evaluated at base line, every four weeks through week 24, then every eight weeks through week 48. At each visit an interim history was taken and a physical examination was performed, adverse events were recorded, nonfasting hematologic and blood-chemistry evaluation were performed, and the HIV RNA level and CD4+ cell count were determined. Peripheral fat wasting, central adiposity, breast hypertrophy, development of a dorsal fat pad, multiple lipomas, and a cushingoid appearance were all considered to be adverse events associated with lipodystrophy or lipatrophy. Patients' rates of adherence to the regimens were

determined by pill counts of the active protease inhibitor at each study visit.

### Viral Genotyping and Phenotypic Analysis

Viral genotyping (GeneSeq, ViroLogic) was performed on samples from all patients who had more than 400 copies of HIV RNA per milliliter at any study visit between weeks 24 and 48. Phenotypic analysis (PhenoSense, ViroLogic) was also conducted on samples from patients treated with lopinavir–ritonavir. For patients with multiple genotypic results, the latest sample was used for data analysis. Resistance to nelfinavir was defined as the presence of a D30N or L90M mutation in HIV protease.<sup>13</sup> Genotyping was also performed on stored isolates obtained at base line from nelfinavir-treated patients with a D30N or L90M mutation at any time between week 24 and week 48. In the absence of data on new mutations selected by lopinavir *in vivo*, resistance to lopinavir was defined conservatively as the development of any primary or active-site protease mutation (i.e., a mutation at amino acid 8, 30, 32, 46, 47, 48, 50, 82, 84, or 90).<sup>14</sup> Lamivudine resistance was defined as the presence of the M184V/I mutation in reverse transcriptase.

### Statistical Analysis

The planned sample size of 330 patients per treatment group provided the study, at the two-sided 0.05 level of significance, with 80 percent power to detect an absolute difference of 10 percent in the proportion of patients with fewer than 400 copies of HIV RNA per milliliter, based on a predicted response rate of 70 percent at week 24 for nelfinavir-treated patients. It also provided 85 percent power to detect an absolute difference of 12 percent (62 percent vs. 50 percent) in the proportion of patients with a virologic response that persisted through week 48. As specified in the protocol, only patients who actually received the study drugs were included in the analyses. The proportion of patients with fewer than 400 or fewer than 50 copies of HIV RNA per milliliter was summarized, with missing values considered to be greater than or equal to 400 copies per milliliter or greater than or equal to 50 copies per milliliter, respectively. Treatment groups were compared by Fisher's exact test. The distribution of values for time to the loss of virologic response through week 48 was estimated with use of a Kaplan–Meier procedure, and the treatment groups were compared by means of the Cox proportional-hazards model. The time of the loss of virologic response was defined as day 0 for patients who never had fewer than 400 copies of HIV RNA per milliliter or as the date of the first of the following: the first of two consecutive HIV RNA values greater than or equal to 400 copies per milliliter after any HIV RNA value of less than 400 copies per milliliter, the use of an antiretroviral agent not allowed by the protocol, or premature discontinuation of the study drug for reasons related to treatment. The rates of incidence of adverse events were compared by Fisher's exact test. A one-way analysis of variance was used to evaluate mean changes from base line. All statistical tests were two-sided.

The data were gathered at study centers by site investigators and research nurses and forwarded to Abbott Laboratories for data entry and statistical analysis. The principal investigator (Dr. Walmsley) was provided with the data set, drafted the manuscript, and then revised it on the basis of comments from all the other authors. No restrictions were imposed by Abbott on the interpretation of the data or the writing of the manuscript.

## RESULTS

Of 859 patients screened, 686 met the eligibility criteria and were randomly assigned to treatment between March 30, 1999, and September 30, 1999. Thirty-three patients (17 assigned to lopinavir–ritonavir and 16 to nelfinavir) never received a study drug;

the remaining 653 patients were included in the analysis. The base-line characteristics were similar in the two study groups (Table 1). A total of 56 patients in the lopinavir-ritonavir group and 77 patients in the nelfinavir group withdrew from the study before week 48. Study drug-related adverse events resulted in discontinuation in 3.4 percent of patients treated with lopinavir-ritonavir and 3.7 percent of those treated with nelfinavir, and discontinuation due to virologic failure occurred more frequently among patients treated with nelfinavir than among those treated with lopinavir-ritonavir (9.2 percent vs. 0.6 percent,  $P<0.001$ ) (Table 2). Although discontinuation of the randomly assigned therapy was not required for patients meeting protocol-defined virologic end points, all patients who discontinued the study with an investigator-specified reason of virologic failure had reached a protocol-defined virologic end point. Unblinding occurred in less than 2 percent of patients and was generally related to the management of clinically significant medical events.

**Antiviral Activity**

In the primary analysis at week 24, 259 of 326 patients treated with lopinavir-ritonavir (79 percent)

and 233 of 327 nelfinavir-treated patients (71 percent) had fewer than 400 copies of HIV RNA per milliliter ( $P<0.05$ ). The response rates at week 48 were 75 percent for patients treated with lopinavir-ritonavir (245 of 326 patients) and 63 percent for nelfinavir-treated patients (206 of 327 patients;  $P<0.001$ ) (Fig. 1A). The 95 percent confidence interval for the difference in these response rates at week 48 was 5 to 19 percent. At week 48, 67 percent of patients treated with lopinavir-ritonavir and 52 percent of nelfinavir-treated patients had fewer than 50 copies of HIV RNA per milliliter ( $P<0.001$ ) (Fig. 1B).

The primary end point for assessing the durability of the response was the time to the loss of virologic response through week 48. In this analysis, 51 patients in the lopinavir-ritonavir group did not have a persistent response, as compared with 108 patients in the nelfinavir group ( $P<0.001$  by the Cox proportional-hazards model) (Fig. 2). The Kaplan-Meier estimates of the proportion of patients with a response that persisted through week 48 were 84 percent for the lopinavir-ritonavir group and 66 percent for the nelfinavir group, corresponding to a hazard ratio of 2.0 (95 percent confidence interval, 1.5 to 2.7). The reasons for the loss of virologic response included viral rebound (which occurred in 21 patients receiving lopinavir-ritonavir and 62 patients receiving nelfinavir), failure to achieve viral suppression (22 and 38 patients, respectively), discontinuation of the regimen

**TABLE 1. SUMMARY OF BASE-LINE CHARACTERISTICS.\***

CHARACTERISTIC	LOPINAVIR-RITONAVIR PLUS LAMIVUDINE AND STAVUDINE (N=326)	NELFINAVIR PLUS LAMIVUDINE AND STAVUDINE (N=327)
Sex — no. (%)		
Male	260 (80)	264 (81)
Female	66 (20)	63 (19)
Race or ethnic group — no. (%)		
Non-Hispanic white	184 (56)	190 (58)
Non-Hispanic black	81 (25)	83 (25)
Hispanic	48 (15)	37 (11)
Asian or Pacific Islander	8 (2)	12 (4)
Native American or Alaskan	3 (1)	3 (1)
Native		
Mixed race	2 (1)	2 (1)
Age — yr		
Mean	38.4±9.7	37.3±8.9
Range	19–84	20–68
Weight — kg		
Mean	73.4±14.4	74.4±14.8
Range	38.5–136.1	42.5–149.0
HIV RNA — log <sub>10</sub> copies/ml		
Mean	4.89±0.75	4.92±0.74
Median	5.01	4.98
Range	2.60–6.82	2.79–6.84
CD4+ cell count — cells/mm <sup>3</sup>		
Mean	260±214	258±196
Median	232	232
Range	2–944	3–949

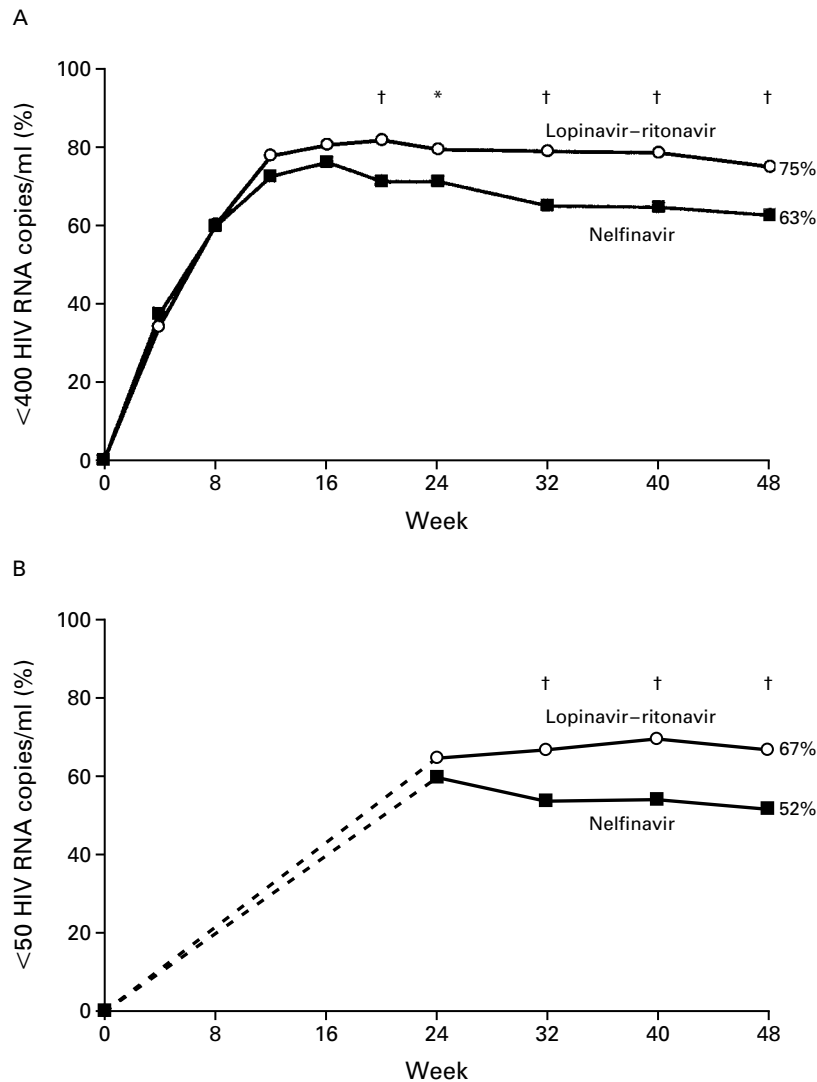
\*Plus-minus values are means ± SD.

**TABLE 2. REASONS FOR STUDY DISCONTINUATION AT OR BEFORE WEEK 48.**

REASON	LOPINAVIR-RITONAVIR PLUS LAMIVUDINE AND STAVUDINE (N=326)	NELFINAVIR PLUS LAMIVUDINE AND STAVUDINE (N=327)
	no. (%)	
Death	5 (1.5)	3 (0.9)
Study drug-related adverse event	11 (3.4)	12 (3.7)
Other adverse event or HIV-related event	5 (1.5)	2 (0.6)
Loss to follow-up	13 (4.0)	16 (4.9)
Personal or other reasons	14 (4.3)	10 (3.1)
Noncompliance	7 (2.1)	6 (1.8)
Patient required prohibited medication	1 (0.3)	0
Virologic failure*	2 (0.6)	30 (9.2)
Total†	56 (17.2)	77 (23.5)

\* $P<0.001$  for the comparison between the treatment groups. All the patients who discontinued the study with an investigator-specified reason of virologic failure had reached a protocol-defined end point.

†Two patients in each group indicated more than one reason for discontinuation.



**Figure 1.** Percentage of Patients with Plasma Human Immunodeficiency Virus (HIV) RNA Levels of Fewer Than 400 Copies per Milliliter (Panel A) and Fewer Than 50 Copies per Milliliter (Panel B). All the patients who received a study drug are included (326 in the lopinavir-ritonavir group and 327 in the nelfinavir group). The asterisk denotes  $P < 0.05$  and the daggers  $P < 0.001$  for the comparison between the treatment groups. The dashed portions of the curves represent the period before testing at fewer than 50 copies per milliliter was begun.

because of study drug-related adverse events (7 and 5 patients), and the addition of antiretroviral agents not allowed in the protocol (1 and 3 patients).

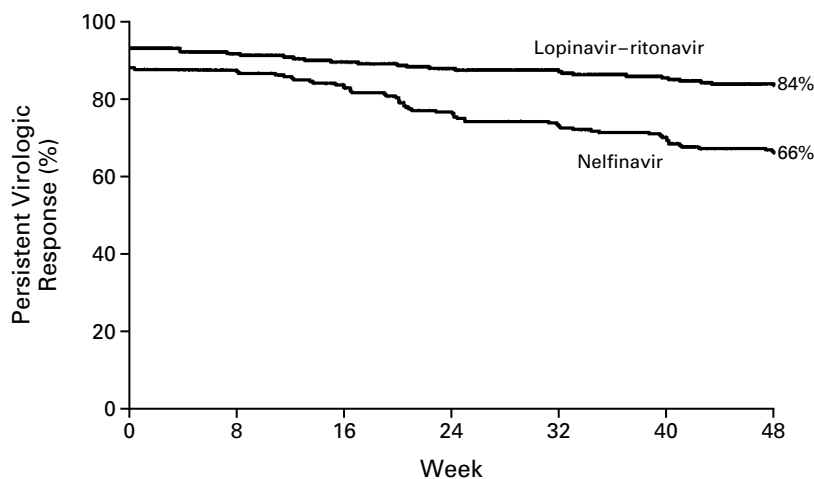
**Immunologic Changes**

Significant mean increases from base line in the CD4+ cell count were observed at all visits for each treatment group. Among 517 patients with CD4+ cell counts at both base line and week 48, similar mean increases from base line to week 48 were ob-

served in the lopinavir-ritonavir group and the nelfinavir group (207 and 195 cells per cubic millimeter, respectively).

**Adverse Events**

The most common adverse events of at least moderate severity and with a possible, probable, or unknown relation to protease inhibitor occurred with similar frequency in the two treatment groups (Table 3). Diarrhea was the most common adverse event in



No. AT RISK						
Lopinavir-ritonavir	297	283	274	269	262	250
Nelfinavir	285	270	244	231	216	204

**Figure 2.** Kaplan-Meier Analysis of the Time to the Loss of Virologic Response through Week 48.  $P < 0.001$  for the comparison between the treatment groups, based on the Cox proportional-hazards model.

both treatment groups. Diarrhea and nausea each resulted in the interruption or discontinuation of study drugs in less than 2 percent of patients in both treatment groups. Adverse events consistent with the presence of lipodystrophy or lipoatrophy were reported in 5 percent of patients receiving lopinavir-ritonavir and 6 percent of those receiving nelfinavir. Five patients receiving lopinavir-ritonavir and three receiving nelfinavir died. Four deaths were caused by HIV-associated opportunistic infections or cancers, one by pneumonia, one by coronary artery disease, and one by lactic acidosis. These four deaths were considered unrelated to the study medications. One death due to pancreatitis was considered possibly related to lopinavir-ritonavir; the patient also had lactic acidosis. New acquired immunodeficiency syndrome (AIDS)-defining events (Centers for Disease Control and Prevention class C<sup>15</sup>) were reported in 2 percent of patients in each treatment group.

**Laboratory Abnormalities**

Laboratory measurements were performed without regard to fasting. Grade 3 or 4 elevations in total cholesterol and in triglycerides were more common in patients receiving lopinavir-ritonavir than in those receiving nelfinavir, although the difference was not statistically significant for total cholesterol (Table 3). The mean increases from base line to week 48 in total

cholesterol were 53 mg per deciliter (1.37 mmol per liter) in patients treated with lopinavir-ritonavir and 48 mg per deciliter (1.24 mmol per liter) in those treated with nelfinavir ( $P = 0.17$  for the comparison between the groups). The mean increases in triglycerides from base line to week 48 were 125 mg per deciliter (1.4 mmol per liter) in patients receiving lopinavir-ritonavir and 47 mg per deciliter (0.5 mmol per liter) in those receiving nelfinavir ( $P < 0.001$  for the comparison between the groups). No patient discontinued the study because of elevated lipid or aminotransferase levels.

**Viral Resistance**

Fifty-eight patients treated with lopinavir-ritonavir and 102 treated with nelfinavir had at least 400 copies of HIV RNA per milliliter at week 24, 32, 40, or 48. Samples from 37 of the 58 patients receiving lopinavir-ritonavir and 76 of the 102 receiving nelfinavir could be amplified for resistance testing. None of the samples from the 37 patients treated with lopinavir-ritonavir and 25 of 76 samples from those treated with nelfinavir (33 percent) had evidence of genotypic resistance in HIV protease ( $P < 0.001$ ). The absence of resistance to lopinavir in patients treated with lopinavir-ritonavir was confirmed by phenotypic analysis, with all isolates demonstrating wild-type susceptibility. For the 25 nelfinavir-treated subjects

**TABLE 3.** MOST COMMON ADVERSE EVENTS AND GRADE 3 OR 4 LABORATORY ABNORMALITIES.\*

EVENT OR ABNORMALITY	LOPINAVIR- RITONAVIR PLUS LAMIVUDINE AND STAVUDINE (N=326)	NELFINAVIR PLUS LAMIVUDINE AND STAVUDINE (N=327)
	no. (%)	
Abdominal pain	13 (4.0)	10 (3.1)
Asthenia	13 (4.0)	11 (3.4)
Headache	8 (2.5)	6 (1.8)
Digestive problems		
Diarrhea	51 (15.6)	56 (17.1)
Dyspepsia†	7 (2.1)	1 (0.3)
Nausea	22 (6.7)	15 (4.6)
Vomiting	8 (2.5)	8 (2.4)
Laboratory abnormalities‡		
Aspartate aminotransferase or alanine aminotransferase >5 times upper limit of normal	14 (4.5)	17 (5.2)
Total cholesterol >300 mg/dl	28 (9.0)	16 (4.9)
Triglycerides >750 mg/dl§	29 (9.3)	4 (1.3)

\*Events listed are of at least moderate severity and of probable, possible, or unknown relation to protease inhibitor. To convert the value for total cholesterol to millimoles per liter, multiply by 0.02586; to convert the value for triglycerides to millimoles per liter, multiply by 0.01129.

† $P < 0.05$  for the comparison between treatment groups.

‡Percentages are based on patients for whom post–base-line values were available (312 treated with lopinavir–ritonavir and 318 treated with nelfinavir).

§ $P < 0.001$  for the comparison between treatment groups.

with resistance, none of the 24 available corresponding base-line isolates demonstrated resistance. Among the samples from week 24 through week 48, resistance to lamivudine was less frequent in patients receiving lopinavir–ritonavir than in those receiving nelfinavir (41 percent vs. 82 percent,  $P < 0.001$ ). There was no statistically significant difference between the treatment groups in adherence or exposure to viral replication (mean HIV RNA at base line or time of genotyping, mean days of treatment with 400 or more copies of HIV RNA per milliliter) among patients with genotypic data.

#### Adherence

Overall rates of adherence to the active protease-inhibitor regimens were similar in the treatment groups, with 86 percent of patients treated with lopinavir–ritonavir and 83 percent of those treated with nelfinavir having overall adherence above 90 percent. Adherence was strongly associated with treatment response, with 89 percent of all those with a response at week 48 (fewer than 400 copies of HIV RNA per

milliliter) having overall adherence rates above 90 percent, as compared with 61 percent of those without a response at week 48 ( $P < 0.001$ ).

#### DISCUSSION

Protease-inhibitor therapy can greatly reduce HIV-related morbidity and mortality.<sup>1-4</sup> Protease inhibitors are highly active in vitro, but their activity in vivo is limited by rapid clearance, resulting in trough levels that are only one to six times above the  $EC_{50}$  of wild-type virus.<sup>8,9,16</sup> Variability among patients in drug concentrations, particularly trough levels,<sup>17,18</sup> and imperfect adherence also reduce the effectiveness of the antiviral therapy. In order to achieve maximal drug levels, protease inhibitors must be given often and at high doses, potentially compromising tolerability and adherence.<sup>19,20</sup> Low trough levels of protease inhibitors significantly increase the risk of clinical failure and virologic resistance.<sup>21,22</sup> More potent protease inhibitors with trough concentrations substantially above the  $EC_{50}$  of wild-type virus would be expected to lower rates of viral resistance and improve overall efficacy, provided there is no increased toxicity.

Pharmacologic enhancement of protease inhibitors with ritonavir has been widely employed and has been shown to result in substantial increases in drug concentrations.<sup>23-26</sup> However, with the exception of lopinavir–ritonavir, systematic dose-ranging and prospective, randomized, controlled trials have generally not been conducted for these regimens. In this study, lopinavir–ritonavir showed greater efficacy than nelfinavir, according to analyses of the proportion of patients with fewer than 400 or fewer than 50 copies of HIV RNA per milliliter at week 48 and the proportion of patients with a virologic response that persisted through 48 weeks. This improvement was achieved with similar rates of adherence and low rates of study drug–related withdrawals in both treatment groups. The overall response rates observed in the lopinavir–ritonavir group compared favorably with those observed in other randomized clinical trials of highly active antiretroviral therapy.<sup>27-30</sup> The response seen in the nelfinavir group was similar to that previously reported for this drug.<sup>31-33</sup> Differences in the frequency of administration of nelfinavir and lopinavir–ritonavir are unlikely to have contributed to the difference in response rates, since the adherence rates were similar in both treatment groups. Furthermore, previous clinical trials comparing nelfinavir given either twice daily or three times daily have shown no significant differences in response rates.<sup>32,33</sup> These observations suggest that the superior response seen in the patients treated with lopinavir–ritonavir reflected improved antiviral activity and not differences in dosage or adherence.

Additional important considerations in antiretrovi-

ral therapy are the risks and consequences of treatment failure. Significantly more patients had viral rebound and discontinued treatment because of virologic failure in the nelfinavir group than in the lopinavir-ritonavir group. In addition, the consequences of detectable viral load differed in the two treatment groups, in that patients with 400 or more copies of HIV RNA per milliliter were significantly more likely to have protease-inhibitor resistance in the nelfinavir group than in the lopinavir-ritonavir group (33 percent vs. 0 percent). The higher rate of resistance to lamivudine and the development of HIV-protease mutations in nelfinavir-treated patients may also undermine the response to subsequent treatment regimens.<sup>34</sup>

The double-blind, placebo-controlled design of this study may have resulted in a smaller difference in dropout rates between the groups than in other recent studies of antiretroviral therapy<sup>30</sup> and minimized the potential for bias in the reporting of adverse events. Both regimens were well tolerated, with 3.4 percent of patients receiving lopinavir-ritonavir and 3.7 percent of nelfinavir-treated patients discontinuing the study because of study drug-related adverse events. Diarrhea and nausea were the most common adverse events. Laboratory abnormalities were also infrequent, although the incidence of grade 3 or 4 triglyceride elevations was greater in the lopinavir-ritonavir group. These results must be interpreted with caution, since specimens were obtained without regard to fasting. Grade 3 or 4 triglyceride elevations were not associated with acute clinical events. However, longer follow-up will be necessary to determine the clinical significance of elevations in lipid levels, especially as they relate to cardiovascular morbidity and mortality. The incidence of lipodystrophy or lipotrophy was low and was similar in the two treatment groups. However, because these changes can take longer than 48 weeks to develop, the relative long-term rates remain unknown.

Successful antiviral therapy requires adequate drug potency, good tolerability, and a high barrier to resistance. Pharmacologic improvements in the administration of protease inhibitors are likely to provide more sustained clinical benefit. When antiretroviral therapy is selected for patients not previously treated with antiretroviral drugs, the balance among antiretroviral activity, immunologic recovery, and short- and long-term toxicity must be determined for each patient individually. The findings from this trial show the benefits of therapy with lopinavir-ritonavir, as demonstrated by its superior antiviral activity in comparison with that of nelfinavir and its continued tolerability and high barrier to resistance. These characteristics suggest an important role for lopinavir-ritonavir as an initial protease inhibitor-based treatment for HIV infection.

Supported by Abbott Laboratories. Dr. Walmsley and Dr. Arribas have served as paid consultants to advisory boards for Abbott Laboratories within the past two years.

*We are indebted to J. Moseley, K. Real, A. Potthoff, D. Kempf, P. Cernobous, K. Sheehan, G. Yang, G. Jones, K. Dale, K. Gu, M. Opperman, E. Bauer, and J. Feinberg for providing important assistance in the conduct of this study.*

## APPENDIX

The following investigators participated in Study M98-863: A.M. Allworth, Royal Brisbane Hospital, Herston, Queensland, Australia; E.L. Altice, Yale University School of Medicine, New Haven, Conn.; K. Arasteh, EPIMED, Berlin, Germany; A.D. Badley, Ottawa Hospital, Ottawa, Ont., Canada; C. Barros, Hospital de Mostoles, Madrid; J. Beal, Associates in Medical and Mental Health, Tulsa, Okla.; J.D. Brand, North Texas Center for AIDS and Clinical Research, Dallas; W. Cameron, Ottawa Hospital, Ottawa, Ont., Canada; P.J. Cimocho, Orange County Center for Special Immunology, Fountain Valley, Calif.; B. Clotet Sala, Hospital Universitari Germans Trias I Pujol, Barcelona, Spain; C.J. Cohen, Community Research Initiative of New England, Boston; T.P. Cooley, Boston Medical Center, Boston; J.-F. Delfraissy, Centre Hospitalier Universitaire de Kremlin-Bicêtre, Kremlin-Bicêtre, France; G. Faetkenheuer, Klinik I für Innere Medizin der Universität zu Köln, Cologne, Germany; C.E. Farthing, AIDS Healthcare Foundation-Research Center, Los Angeles; J. Feinberg, University of Cincinnati Medical Center, Cincinnati; M.A. Fischl, University of Miami School of Medicine, Miami; M. Fisher, Elton John Centre, Brighton General Hospital, Brighton, United Kingdom; M. Flepp, University Hospital Zurich, Zurich, Switzerland; J. Gallant, Johns Hopkins University School of Medicine, Baltimore; J.C. Gathe, Therapeutic Concepts, Houston; J. Gerstoft, Rigshospitalet, Copenhagen, Denmark; M. Goldman, Wishard Memorial Hospital, Indianapolis; J.M. Gonzalez-Lahoz, Hospital Carlos III, Madrid; E.M. Graziano, University of Wisconsin Hospital and Clinics, Madison; S. Green, Hampton Roads Medical Specialists, Hampton, Va.; H.A. Grossman, St. Luke's-Roosevelt Hospital, New York; D.W. Haas, Vanderbilt University Medical Center, Nashville; E.F. Haas, Associates in Medical and Mental Health, Tulsa, Okla.; S.P. Hauptman, Thomas Jefferson University, Philadelphia; C.B. Hicks, Duke University Medical Center, Durham, N.C.; A. Horban, AIDS Diagnostics and Therapy Center, Warsaw, Poland; J.M. Horton, Carolinas Medical Center, Charlotte, N.C.; N.E. Hyslop, Jr., Tulane University Medical Center, New Orleans; R.C. Kalayjian, MetroHealth Medical Center, Cleveland; P.H. Kazanjian, University of Michigan Health System, Ann Arbor; J. Kostman, Philadelphia FIGHT, Philadelphia; H.W. Lampiris, San Francisco Veterans Affairs Medical Center, San Francisco; F. LaPlante, Clinique Médical du Quartier Latin, Montreal; J.L. Lennox, Emory University School of Medicine, Atlanta; R. Luskin-Hawk, Lakeshore Infectious Diseases, Chicago; S. Mallal, Royal Perth Hospital, Perth, Australia; L. Mathiesen, Hvidovre University Hospital, Hvidovre, Denmark; J. Silva de Mendonca, Hospital do Servidor Público Estadual de São Paulo, São Paulo, Brazil; P. Miao, Sherman Oaks, Calif.; D. Mildvan, Beth Israel Medical Center, New York; S. Miller, Bedford Gardens, South Africa; J.S.G. Montaner, St. Paul's Hospital, University of British Columbia, Vancouver, B.C., Canada; Y. Mouton, Hôpital Guy Chatiliez, Tourcoing, France; R.A. Myers, Jr., Phoenix Body Positive, Phoenix, Ariz.; A.T. Pavia, University of Utah, Salt Lake City; C. Pedersen, Odense University Hospital, Odense, Denmark; G. Pierone, Jr., Vero Beach, Calif.; R.B. Pollard, University of Texas Medical Branch, Galveston; A. Pozniak, St. Stephens Centre/Chelsea and Westminster Hospital, London; A.R. Rachlis, Sunnybrook Health Science Centre, Toronto; E.S. Rhamé, Abbott Northwestern Hospital, Clinic 42, Minneapolis; R. Rubio, Hospital 12 de Octubre, Madrid; A.G. Saimot, Hôpital Bichat-Claude Bernard, Paris; J.H. Sampson, Research and Education Group, Portland, Oreg.; I. Sanne, Wits Health Consortium-Infectious Disease Clinical Trial Unit, Johannesburg, South Africa; J.L. Santana, San Juan AIDS Program Clinical Research, San Juan, Puerto Rico; D. Seekins, Saint Joseph's Baptist Comprehensive Research, Tampa, Fla.; G.E. Sepulveda, Immunology Clinic, Ponce University Hospital, Ponce, Puerto Rico; D. Sereni, Hôpital Saint-Louis, Paris; S. Sharma, Comprehensive Care Center, Ft. Lauderdale, Fla.; R.D. Sherer, Jr., Cook County Hospital, Chicago; L.G. Smith, Saint Michael's Medical Center, Newark, N.J.; K.E. Squires, University of Alabama, Birmingham; S. Staszewski, Klinikum der Johann-Wolfgang von Goethe Universität, Frankfurt, Germany; R.T. Steigbigel, State University of New York-Stony Brook, Stony Brook; C.R. Steinhart, Steinhart Medical Association, Miami; A. Stoehr, Allgemeines Krankenhaus St. Georg, Hamburg, Germany; R. Stryker, Pacific Oaks Research, Beverly Hills, Calif;

D.E. Sweet, University of Kansas School of Medicine, Wichita; K.T. Tashima, Miriam Hospital, Providence, R.I.; A. Theisen, Universitätsklinik Klinik für Gastroenterologie, Dusseldorf, Germany; R. Thomas, Clinique Médicale l'Actuel, Montreal; J.A. Thommes, Pacific Oaks Research, Beverly Hills, Calif.; M.A. Thompson, AIDS Clinical Research Consortium of Atlanta, Atlanta; A. Timmermann, Hospital Heliopolis, São Paulo, Brazil; P. Viciana, Hospital Universitario Virgen del Rocío, Seville, Spain; D. Vittecoq, Hôpital Paul Brousse, Villejuif, France; J.N. Weber, St. Mary's Hospital Medical School, London; D.L. Weitner, Hamburg, Germany; I.P. van der Westhuizen, Cape Town, South Africa; D.A. Wheeler, Infectious Diseases Physicians, Annandale, Va.; D.P. Wright, Central Texas Medical Foundation, Austin; B.G. Yangco, Infectious Diseases Research Institute, Tampa, Fla.

## REFERENCES

1. Selik RM, Karon JM, Ward JW. Effect of the human immunodeficiency virus epidemic on mortality from opportunistic infections in the United States in 1993. *J Infect Dis* 1997;176:632-6.
2. Hogg RS, O'Shaughnessy MV, Gataric N, et al. Decline in deaths from AIDS due to new antiretrovirals. *Lancet* 1997;349:1294.
3. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;338:853-60.
4. Murphy SL. Deaths: final data for 1998. National vital statistics report. Vol. 48. No. 11. Hyattsville, Md.: National Center for Health Statistics, 2000:1-105. (DHHS publication no. (PHS) 0-0487)
5. Wit FW, van Leeuwen R, Weverling GJ, et al. Outcome and predictors of failure of highly active antiretroviral therapy: one-year follow-up of a cohort of human immunodeficiency virus type 1-infected persons. *J Infect Dis* 1999;179:790-8.
6. Fatkenheuer G, Theisen A, Rockstroh J, et al. Virological treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected patients. *AIDS* 1997;11:F113-F116.
7. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study: Swiss HIV Cohort Study. *Lancet* 1999;353:863-8.
8. Barry M, Gibbons S, Back D, Mulcahy F. Protease inhibitors in patients with HIV disease: clinically important pharmacokinetic considerations. *Clin Pharmacokinet* 1997;32:194-209.
9. Condra JH, Petropoulos CJ, Ziermann R, Schleif WA, Shivaprakash M, Emimi EA. Drug resistance and predicted virologic responses to human immunodeficiency virus type 1 protease inhibitor therapy. *J Infect Dis* 2000;182:758-65.
10. Sham HL, Kempf DJ, Molla A, et al. ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease. *Antimicrob Agents Chemother* 1998;42:3218-24.
11. Bertz R, Renz C, Foit C, et al. Steady-state pharmacokinetics of Kaletra (lopinavir/ritonavir 400/100 mg BID) in HIV-infected subjects when taken with food. In: Proceedings of the Second International Workshop on Clinical Pharmacology of HIV Therapy, Noordwijk, the Netherlands, April 2-4, 2001:3.1. abstract.
12. Murphy RL, Brun S, Hicks C, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48-week results. *AIDS* 2001;15:F1-F9.
13. Atkinson B, Isaacson J, Knowles M, Mazabel E, Patick AK. Correlation between human immunodeficiency virus genotypic resistance and virologic response in patients receiving nelfinavir monotherapy or nelfinavir with lamivudine and zidovudine. *J Infect Dis* 2000;182:420-7.
14. Hirsch MS, Brun-Vezinet F, D'Aquila RT, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA panel. *JAMA* 2000;283:2417-26.
15. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep* 1992;41:(RR-17):1-19.
16. Flexner C. HIV-protease inhibitors. *N Engl J Med* 1998;338:1281-92.
17. Acosta EP, Henry K, Baken L, Page LM, Fletcher CV. Indinavir concentrations and antiviral effect. *Pharmacotherapy* 1999;19:708-12.
18. Langmann P, Zilly M, Weissbrich B, et al. Therapeutic drug monitoring of saquinavir in patients during protease inhibitor therapy with saquinavir alone or in combination with zidovudine or zalcitabine. *Eur J Med Res* 2000;5:59-62.
19. Andrews L, Friedland G. Progress in HIV therapeutics and the challenges of adherence to antiretroviral therapy. *Infect Dis Clin North Am* 2000;14:901-28.
20. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000;133:21-30. [Erratum, *Ann Intern Med* 2002;136:253.]
21. Molla A, Korniyeva M, Gao Q, et al. Ordered accumulation of mutations in HIV protease confers resistance to ritonavir. *Nat Med* 1996;2:760-6.
22. Durant J, Clevenbergh P, Garraffo R, et al. Importance of protease inhibitor plasma levels in HIV-infected patients treated with genotypic-guided therapy: pharmacological data from the Viradapt Study. *AIDS* 2000;14:1333-9.
23. Kempf DJ, Marsh KC, Kumar G, et al. Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. *Antimicrob Agents Chemother* 1997;41:654-60.
24. Hsu A, Granneman GR, Cao Q, et al. Pharmacokinetic interactions between two human immunodeficiency virus inhibitors, ritonavir and saquinavir. *Clin Pharmacol Ther* 1998;63:453-64.
25. van Heeswijk RP, Veldkamp AI, Hoetelmans RM, et al. The steady-state plasma pharmacokinetics of indinavir alone and in combination with a low dose of ritonavir in twice daily dosing regimens in HIV-1-infected individuals. *AIDS* 1999;13:F95-F99.
26. Hsu A, Granneman GR, Cao G, et al. Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. *Antimicrob Agents Chemother* 1998;42:2784-91.
27. Squires K, Johnson V, Katlama C, et al. The Atlantic Study: a randomized open-label study to evaluate the efficacy and safety of three triple-combination therapies aimed at different HIV targets in antiretroviral naïve HIV-1 infected patients. In: Program and abstracts of the XIII International AIDS Conference, Durban, South Africa, July 9-14, 2000:43. abstract.
28. Podzamceer D, Ferrer E, Consiglio E, et al. A randomized open multicenter trial comparing nelfinavir or nevirapine in HIV-infected naïve patients (the Combine Study). In: Programs and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, September 17-20, 2000. Washington, D.C.: American Society for Microbiology, 2000:293. abstract.
29. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naïve HIV infected adults: a randomized equivalence trial. *JAMA* 2001;285:1155-63. [Erratum, *JAMA* 2001;285:2858.]
30. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999;341:1865-73.
31. Bardsley-Elliott A, Plosker GL. Nelfinavir: an update on its use in HIV infection. *Drugs* 2000;59:581-620.
32. Saag M, Tebas P, Senson M, et al. Randomized, double-blind comparison of two nelfinavir doses plus nucleosides in HIV-infected patients (Agouron study 511). *AIDS* 2001;15:1971-8.
33. Nelfinavir. La Jolla, Calif.: Agouron Pharmaceuticals, January 25, 2001 (package insert).
34. Condra J, Holder W, Schleif A, et al. Genetic correlates of virologic response to an indinavir-containing salvage regimen in patients with nelfinavir failure. *Antiviral Ther* 1999;4:Suppl:44.

Copyright © 2002 Massachusetts Medical Society.