

A PRELIMINARY STUDY OF RITONAVIR, AN INHIBITOR OF HIV-1 PROTEASE, TO TREAT HIV-1 INFECTION

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Abstract Background. Ritonavir is a potent inhibitor in vitro of human immunodeficiency virus type 1 (HIV-1) protease, which is needed for virions to mature and become infective. We assessed the safety and efficacy of ritonavir in patients with HIV-1 infection.

Methods. We administered ritonavir orally to 62 patients in one of four dosages during a 12-week trial containing a 4-week randomized, placebo-controlled, double-blinded phase followed by an 8-week dose-blinded phase. We assessed the response with serial measurements of plasma viremia and serial CD4 cell counts.

Results. Fifty-two patients completed the 12-week trial. Diarrhea and nausea were the most common side effects, and reversible elevations in serum triglyceride and γ -glutamyltransferase levels were the most frequent laboratory abnormalities. Ritonavir had a rapid antiviral effect, with a mean maximal reduction in the number of

copies of HIV-1 RNA per milliliter of plasma that ranged from 0.86 to 1.18 log in the four dosage groups. After 12 weeks of treatment, the antiviral effect was partially maintained, with a mean reduction in plasma viremia of 0.5 log. When we used a more sensitive assay for HIV-1 RNA in a subgroup of 20 patients, we found that plasma viremia decreased by a mean of 1.7 log. This antiviral effect was partly sustained at week 12, with a mean reduction of approximately 1.1 log. The patients' CD4 cell counts rose during treatment with ritonavir (median increase, 74 and 83 cells per cubic millimeter at weeks 4 and 12, respectively).

Conclusions. The protease inhibitor ritonavir is well tolerated and has a potent antiviral effect, as shown by substantial decreases in plasma viremia and significant elevations in CD4 cell counts. Expanded clinical trials of ritonavir are warranted. (N Engl J Med 1995;333:1534-9.)

ANTIRETROVIRAL therapy directed at the reverse transcriptase of human immunodeficiency virus type 1 (HIV-1) has had limited success because of drug toxicity and the emergence of viral resistance.¹ With the recent appreciation of the continuous, high-level replication of HIV-1 in vivo,^{2,3} the limitations of current therapies are better understood, as is the urgent need for new and effective antiretroviral agents.

Ritonavir,⁴ formerly known as ABT-538, is an inhibitor of HIV-1 protease, an enzyme required for the completion of the viral life cycle. The protease cleaves the Gag and Gag-Pol polyproteins into the core proteins and viral enzymes. The inactivation of protease by mutagenesis⁵ and its inhibition by drugs⁶⁻⁸ both result in the formation of noninfectious particles. Since the structure of HIV-1 protease has been well established as a homodimer with a single active site,^{7,9,10} the enzyme is an ideal target for rationally designed inhibitors.

The design of ritonavir was based on the symmetry of the protease, and the drug was chemically modified to optimize its antiviral activity and oral pharmacokinetics.^{4,7} Ritonavir has potent activity in vitro against a variety of laboratory strains and field isolates of HIV-1.^{4,11} However, resistance to ritonavir by HIV-1 has

been described after serial passages in vitro.¹¹ Preliminary pharmacokinetic studies in humans have shown that the drug is well absorbed, reaching plasma concentrations substantially higher than the inhibitory concentration in vitro.⁴ We report the results of a phase 1-2 clinical trial designed to examine the safety and efficacy of ritonavir.

METHODS

Study Patients

Patients were screened at five sites and were enrolled if they had a viral load of 25,000 or more copies of HIV-1 RNA per milliliter of plasma, as determined by a branched-chain DNA signal-amplification assay^{12,13}; if they had a CD4 count of 50 to 500 cells per cubic millimeter; and if they had discontinued all antiviral therapy and concomitant medications except prophylaxis against *Pneumocystis carinii*. Patients were excluded if they had substantial hepatic abnormalities.

Study Design

The study was divided into four periods: a screening phase lasting up to 21 days; a washout phase lasting 14 days; a randomized, placebo-controlled, double-blind phase lasting 4 weeks, when the drug was administered (the "dosage phase"); and a dose-blinded phase lasting 8 weeks, when treatment was extended to all the study patients (the "extension phase"). The first patients enrolled in group 1 were randomly assigned to receive ritonavir three times a day at doses of 200 or 300 mg (total daily dose, 600 and 900 mg, respectively), or placebo. After 12 patients had been enrolled in group 1 for 14 days, enrollment into three subgroups of group 2 began. The patients in group 2 received ritonavir four times a day at doses of either 200 or 300 mg (total daily dose, 800 and 1200 mg, respectively), or placebo. At the end of the four-week dosage phase, the patients in the placebo subgroups of groups 1 and 2 were randomly assigned to one of the two drug regimens (i.e., doses of 200 or 300 mg of ritonavir) in their group for the eight-week extension phase. Patients who completed the 12-week trial were offered open-label ritonavir.

Evaluation and Follow-up

Eligible patients were assessed seven and four days before the start of the dosage period, on the day that period began, once a week dur-

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ing the dosage phase, and every two weeks during the extension phase. Additional tests of safety and efficacy were performed during these visits, as well as on days 4 and 11 after the start of the dosage period. CD4 cell counts were obtained three times before the start of the dosage period and at weeks 2, 4, 8, and 12.

Virologic Measurements

Antiretroviral activity was first assessed by measuring plasma viremia with the standard branched-chain DNA assay,^{12,13} which has a detection limit of 10,000 copies of HIV-1 RNA per milliliter. In 20 patients, plasma samples with values below the detection limit of the standard assay were subsequently tested by a modified branched-chain DNA assay with a detection limit of 400 copies of HIV-1 RNA per milliliter.²

Pharmacokinetic Studies

The study patients underwent two pharmacokinetic studies during the dosage period. The first was performed between days 4 and 11, and the second between days 22 and 29. Blood was obtained before the administration of the dose, hourly thereafter for four hours, and every two hours to complete the study, which lasted six to eight hours. Ritonavir concentrations in serum were analyzed by reverse-phase high-performance liquid chromatography.¹⁴

Statistical Analysis

Tests for differences among treatment groups in base-line characteristics were performed with Fisher's exact test for categorical variables, the Kruskal-Wallis test for base-line CD4 cell counts, and one-way analysis of variance for other continuous variables. Mean changes from base line in log plasma levels of viral RNA were compared between subgroups within groups 1 and 2 by one-way analysis of variance. Changes from base line in CD4 cell counts were compared among treatment subgroups by the Wilcoxon test. Tests for differences in response rates were performed with Fisher's exact test.

RESULTS

Base-Line Characteristics

Sixty-two patients, whose base-line characteristics are summarized in Table 1, were enrolled in the study. No statistically significant differences were found within or among treatment subgroups. Likewise, distributions of base-line CD4 cell counts did not differ significantly between treatment subgroups in either group 1 or group 2, nor did base-line levels of plasma viremia.

Treatment Period

Fifty-five patients completed the first 4 weeks of the study, and 52 patients completed the full 12 weeks. One patient who received placebo discontinued therapy on day 17 because of anxiety, tachycardia, and dyspnea. Three patients in group 1 (the group treated three times a day) who received zidovudine withdrew from the study, one on day 28 because of headache and Bell's palsy, the second by day 12 because of weakness and tachycardia, and the third on day 5 because of abdominal pain and nausea. Three patients in group 2 (the group treated four times

a day) discontinued zidovudine therapy voluntarily — two on days 7 and 16 because of dizziness, nausea, and circumoral paresthesia and one on day 11 because of acne, palpitation, and dyspnea. Two patients who initially received placebo were withdrawn from the study on days 29 and 35 because of intercurrent infections. Finally, one patient withdrew on day 14 of therapy because of an acute anxiety disorder.

Safety and Tolerance

Adverse events during the placebo-controlled phase of the study and the eight-week extension phase are summarized in Table 2. During the dosage phase, diarrhea and headache were the most common adverse events reported by patients receiving either placebo or zidovudine. Altered taste sensations, circumoral paresthesia, and peripheral paresthesia were more common among the study-drug recipients. During the eight-week extension phase, nearly all patients reported adverse events. Diarrhea was the most common, followed by nausea, headache, and weakness. Circumoral paresthesia was reported more frequently in group 2 than in group 1, particularly by the patients receiving the 1200-mg daily dose of zidovudine. These adverse signs and symptoms were generally minor and reversible.

During the dosage phase, the administration of zidovudine was associated with at least a doubling of the serum triglyceride concentration in 25 patients, as compared with 4 patients receiving placebo who had such elevations. Seven drug recipients had triglyceride concentrations exceeding 1000 mg per deciliter (11.3 mmol per liter), but no clinical consequences of the hypertriglyceridemia were reported. Doubling of serum aminotransferase concentrations was equally common in both the zidovudine and the placebo groups. A doubling or an even greater increase in the serum γ -glutamyltransferase concentration was observed in 10 drug-treated patients, as compared with none of the patients in the placebo group. An elevation in liver enzymes by a factor

Table 1. Base-Line Characteristics of the Study Patients.

VARIABLE	GROUP 1 (3 DOSES/DAY)			GROUP 2 (4 DOSES/DAY)		
	PLACEBO	RITONAVIR, 200 mg	RITONAVIR, 300 mg	PLACEBO	RITONAVIR, 200 mg	RITONAVIR, 300 mg
No. of patients	10	11	10	11	10	10
Male sex — no. (%)	10 (100)	11 (100)	10 (100)	10 (91)	9 (90)	10 (100)
White race — no. (%)	9 (90)	10 (91)	8 (80)	10 (91)	8 (80)	10 (100)
Mean age — yr	38	41	39	36	43	39
Mean weight — kg	75	71	77	81	78	74
Diagnosis of AIDS — no. of patients (%) [*]	8 (80)	9 (82)	8 (80)	7 (64)	9 (90)	8 (80)
Prior antiretroviral treatment — no. of patients (%)	8 (80)	5 (45)	10 (100)	6 (55)	8 (80)	4 (40)
Median CD4 count — cells/mm ³	108	104	257	162	159	155
Mean log copies of HIV-1 RNA/ml of plasma	5.23	5.21	4.87	4.86	4.92	5.04

*AIDS denotes acquired immunodeficiency syndrome.

greater than 5 occurred in only one patient, who was receiving 1200 mg of ritonavir daily. Neither the treated patients nor those receiving placebo had significant reductions in total white-cell counts, hemoglobin concentrations, or platelet counts.

In all, three patients withdrew from the study voluntarily because of adverse events that appeared to result directly from ritonavir treatment. One discontinued treatment because of nausea and abdominal pain, and the other two withdrew because of dizziness, nausea, and circumoral paresthesia.

Pharmacokinetics

The results of the two pharmacokinetic studies are shown in Table 3. Peak serum concentrations of ritonavir were reached within two to four hours of the administration of the dose and did not differ significantly between the first and the second study. The maximal concentration at all dose levels exceeded 2.1 mg per milliliter, the 95 percent inhibitory concentration predicted when allowance was made for the binding of ritonavir to plasma proteins.^{4,11,14} However, the trough

concentrations of ritonavir measured at the end of the second study in the patients in group 1 fell slightly below this level. Similarly, determinations of the area under the curve for time and ritonavir concentration were consistently lower in the second study in all four treatment subgroups, although the differences were not statistically significant.

Antiviral Response

Figure 1A summarizes the mean changes in the plasma viral load in the treated patients and the placebo recipients during the dosage phase. Statistically significant decreases in plasma viremia ($P < 0.001$) were found in all four treatment subgroups (receiving from 600 to 1200 mg daily), whereas no significant changes were noted in the placebo recipients. A maximal antiviral effect consisting of a decrease of 0.86 to 1.18 log per milliliter in the plasma concentration of viral RNA was seen by day 15. At four weeks, the ritonavir-treated patients had, on average, a reduction in plasma viremia of 0.83 log, whereas the mean viral load remained essentially unchanged in the placebo group.

The virologic responses in all the ritonavir-treated patients during the 12-week period are shown in Figure 1B. In this analysis, the 12-week data on the patients initially assigned to receive ritonavir and the 8-week ritonavir-treatment data on the patients assigned to the placebo group were combined. Again, mean peak antiviral activity consisting of a reduction in the plasma concentration of viral RNA of about 1.0 log was observed in all the treatment groups after two weeks of therapy. Subsequently, the viral load increased steadily in each group. However, at the end of 12 weeks, a persistent reduction of 0.50 log in the viral load was maintained at all dose levels.

Given that 38 percent of the patients who completed 12 weeks of ritonavir therapy had plasma viral loads below the lower limit of detection of the standard branched-chain DNA assay (data not shown), the antiviral effect shown in Figure 1B clearly underestimates the actual activity of the drug. To address this issue, samples of plasma from the subgroup of 20 patients treated at the Aaron Diamond AIDS Research Center were analyzed further with a sensitive assay that had a detection limit of 400 copies of HIV-1 RNA per milliliter. The results, summarized in Figure 1C, show that a maximal reduction in plasma viremia of about 1.7 log was reached in two to three weeks. With regard to the durability of the antiviral response, the group receiving 600 mg of ritonavir daily fared poorest, with only one of seven patients maintaining a reduction in plasma HIV-1 RNA of more than 0.5 log, whereas four of the five patients receiving 900 mg of drug daily maintained responses at this level. Similarly, three of the four patients in group 2 studied at each dose level had persistent antiviral responses (greater than 0.5 log). Overall, a mean reduction of about 1.1 log was maintained at week 12.

Despite rebounds in viremia in the majority of the study patients, the plasma viral loads of 12 patients

Table 2. Adverse Events in the Study Patients.*

ADVERSE EVENT	PATIENTS RECEIVING PLACEBO, 1ST 4 WK (N = 21)	PATIENTS TREATED WITH RITONAVIR	
		1ST 4 WK (N = 41)	ALL 12 WK† (N = 60)
		number (percent)	
Signs and symptoms			
Any reported	18 (86)	39 (95)	59 (98)
Diarrhea	5 (24)	19 (46)	37 (62)
Altered taste sensation	1 (5)	6 (15)	9 (15)
Nausea	3 (14)	10 (24)	18 (30)
Vomiting	0	5 (12)	9 (15)
Anorexia	1 (5)	2 (5)	3 (5)
Asthenia	1 (5)	4 (10)	10 (17)
Dizziness	1 (5)	4 (10)	7 (12)
Paresthesia			
Circumoral	0	6 (15)	9 (15)
Peripheral	0	3 (7)	3 (5)
Rash	2 (10)	8 (20)	13 (22)
Headache	6 (29)	11 (27)	17 (28)
Fever	5 (24)	3 (7)	10 (17)
Flatulence	1 (5)	2 (5)	2 (3)
Dyspepsia	4 (19)	3 (7)	9 (15)
Abdominal pain	3 (14)	4 (10)	6 (10)
Laboratory values			
AST (>200% increase)	4 (19)	5 (12)	11 (18)
ALT (>200% increase)	6 (29)	6 (15)	8 (13)
GGT (>200% increase)	0	10 (24)‡	18 (30)
Triglycerides (>200% increase)	4 (19)	25 (61)§	39 (65)
Cholesterol (>200% increase)	0	0	5 (8)
Uric acid (>50% increase)	0	4 (10)	4 (7)
White cells (>50% reduction)	0	0	2 (3)
ANC (>50% reduction)	1 (5)	2 (5)	6 (10)
Hemoglobin (reduction by >3 g/dl [1.9 mmol/liter])	0	0	2 (3)
Platelets (>50% reduction)	0	0	0

*Since similar patterns of adverse events were observed in the six subgroups (four treated with ritonavir and two receiving placebo), the incidence of adverse events was summarized according to the study-drug assignment. AST denotes aspartate aminotransferase, ALT alanine aminotransferase, GGT γ -glutamyltransferase, and ANC absolute neutrophil count.

†Includes all events occurring during the four-week dosing phase among the patients randomly assigned to ritonavir treatment and all events occurring during the eight-week extension phase.

‡ $P = 0.012$ for the comparison with the placebo group.

§ $P = 0.003$ for the comparison with the placebo group.

Table 3. Measurements of Ritonavir Obtained in Two Pharmacokinetic Studies, Conducted between Days 4 and 11 and Days 22 and 29 of the Four-Week Dosing Period.*

VARIABLE	GROUP 1 (3 DOSES/DAY)				GROUP 2 (4 DOSES/DAY)			
	200 mg		300 mg		200 mg		300 mg	
	1st Study	2nd Study	1st Study	2nd Study	1st Study	2nd Study	1st Study	2nd Study
Time to maximal concentration — hr	2.6±1.0 (11)	2.4±1.4 (10)	3.2±1.4 (10)	3.1±1.5 (9)	2.0±2.2 (9)	3.8±1.8 (9)	3.6±2.1 (9)	3.6±1.9 (8)
Maximal concentration — µg/ml	6.7±3.6 (11)	5.3±2.9 (10)	8.7±3.7 (10)	6.2±3.5 (9)	5.0±3.1 (9)	4.2±2.5 (9)	9.0±9.5 (9)	7.8±5.9 (8)
Trough concentration — µg/ml	2.5±1.9 (11)	1.4±0.9 (10)	3.6±2.1 (10)	1.9±1.6 (9)	3.1±2.8 (9)	2.3±1.5 (9)	3.7±4.0 (9)	4.4±4.6 (8)
Area under the curve per dose interval — µg/hr/ml†	35.1±19.5 (11)	24.4±12.7 (10)	49.9±21.8 (10)	35.6±22.2 (9)	23.6±18.1 (9)	18.3±11.1 (9)	37.9±41.9 (9)	36.9±29.5 (8)

*Plus-minus values are means ±SD. Numbers in parentheses are the numbers of patients studied.

†Refers to the mean area under the time-concentration curve for the interval between two successive doses.

were kept below 10,000 copies of HIV-1 RNA per milliliter for 12 weeks or more. For example, as Figure 1D shows, two of the four patients receiving 1200 mg of ritonavir daily maintained reductions in plasma viremia of 2 log or higher for more than eight months. In fact, neither patient had plasma viremia detectable by the sensitive branched-chain DNA assay after 100 days of treatment, and cultures of peripheral-blood mononuclear cells (5×10^6) from each patient became negative for infectious HIV-1 after three to six months of therapy (data not shown).

Immunologic Effects

The immunologic sequelae of the antiviral effect of ritonavir are shown in Figure 2A. The patients in the dosage subgroups of group 1 had median increases of 114 and 90 CD4 cells per cubic millimeter — a significant difference from the decrease in the patients receiving placebo. In group 2 the increase was less pronounced, with median increases of 25 and 63 cells per cubic millimeter in the dosage subgroups, although the increases were significant as compared with the results in the placebo recipients, who had a median decline of 20 cells per cubic millimeter. Overall, the median increase in CD4 cells with ritonavir was 74 cells per cubic millimeter at four weeks.

As Figure 2B shows, the median increases in the CD4 cell count at 12 weeks in the groups receiving 600, 800, 900, and 1200 mg of ritonavir per day were 137, 60, 140, and 59 cells per cubic millimeter, respectively, and the median increase overall was 83 cells per cubic millimeter. A prominent increase in the CD8 lymphocyte count was also observed (data not shown). In general, the increase in the CD4 lymphocyte count in each patient was maintained as long as the antiviral effect was sustained. For example, the two patients whose viral loads were reduced to undetectable levels for prolonged periods also had sustained increases in their CD4 cell counts (Fig. 1D).

DISCUSSION

This study assessed the safety, pharmacokinetics, and efficacy of ritonavir, a novel inhibitor of HIV-1 protease. Generally, the drug was well tolerated, and severe

adverse events were rare. The major adverse symptoms attributed to ritonavir were diarrhea, nausea, and headache. Ritonavir therapy was also associated with alterations in taste and circumoral paresthesia, particularly when the drug was given at higher doses. The most common laboratory abnormalities associated with the therapy were reversible elevations in serum triglyceride and aminotransferase concentrations. No hematologic toxicity attributable to the drug was detected.

Ritonavir was well absorbed, reaching peak concentrations within two to four hours of the administration of the dose. Although trough concentrations were generally lower at the end of the dosage period (as measured in the second pharmacokinetic study) than during an earlier phase (as measured in the first study), values for the area under the curve and the maximal concentration did not differ significantly between the two studies. The decline in the trough concentration of ritonavir with time suggests the possibility of altered drug absorption; altered binding of the drug to protein, perhaps attributable to changes in lipid levels; or an increase in drug metabolism. The fact that the area under the curve and the maximal concentration of drug did not change with time does not support increased drug metabolism as the primary explanation for the declining trough concentration.

As compared with placebo, ritonavir produced marked reductions in plasma HIV-1 levels. The initial antiviral effect observed in the first few weeks of treatment was similar at all dose levels, achieving a reduction of about 1.7 log in plasma viremia (Fig. 1C). These findings suggest that the potency of ritonavir is similar to that described^{3,15} for MK-639, and to the combined antiviral effect of zidovudine and lamivudine.¹⁶ In contrast, the potency of saquinavir⁶ is substantially lower. Similarly, the acute antiviral activity of zidovudine^{13,16} or didanosine¹⁷ monotherapy resulted in a reduction in plasma viremia of only 0.7 log or less, whereas nevirapine lowered the plasma viral load by 1.0 to 1.5 log.³ Therefore, on the basis of these comparisons, ritonavir clearly emerges as one of the most potent antiretroviral agents developed to date.

The antiviral effect of ritonavir, however, was only partly sustained after 12 weeks of therapy. For the en-

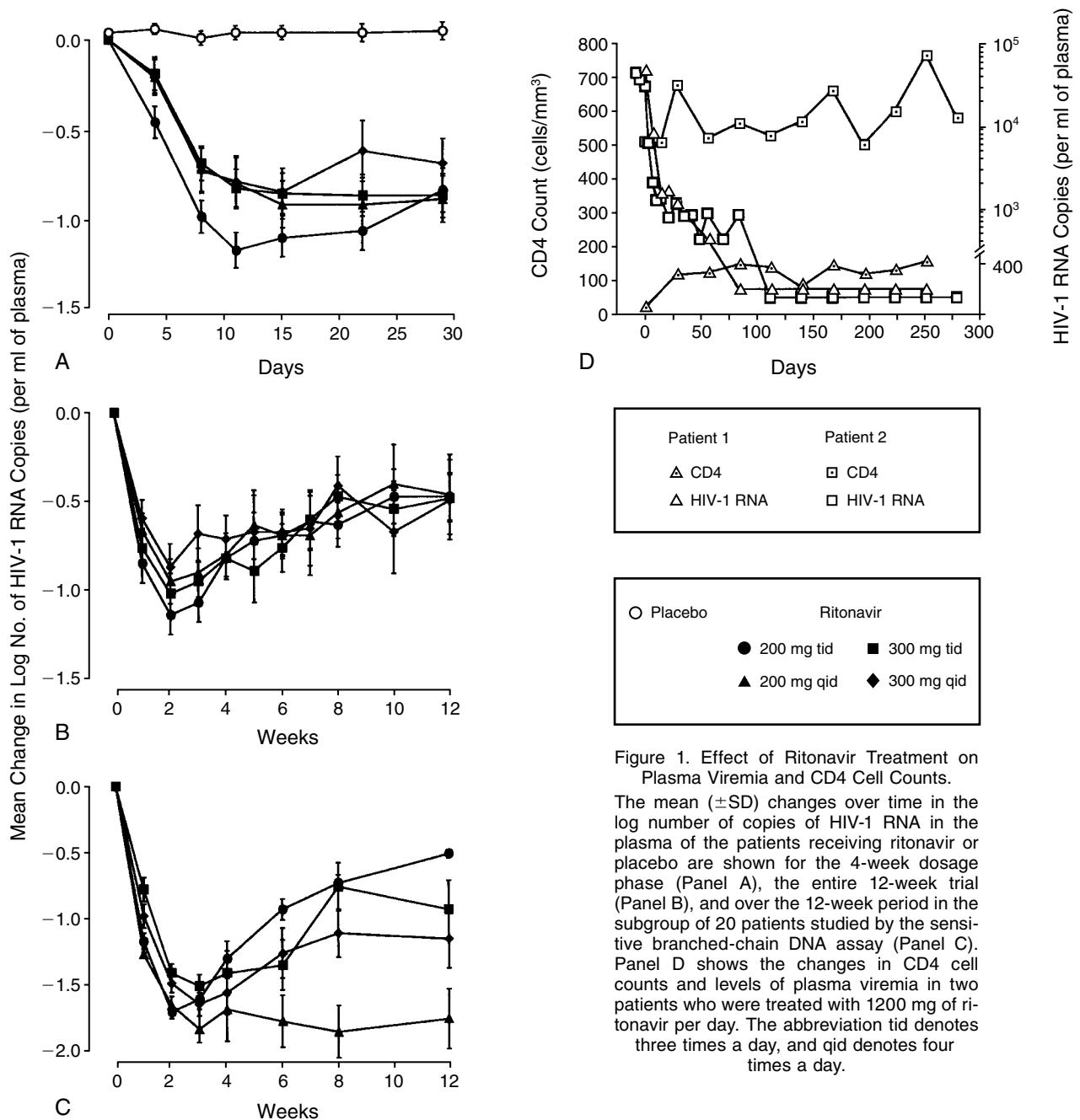


Figure 1. Effect of Ritonavir Treatment on Plasma Viremia and CD4 Cell Counts.

The mean (\pm SD) changes over time in the log number of copies of HIV-1 RNA in the plasma of the patients receiving ritonavir or placebo are shown for the 4-week dosage phase (Panel A), the entire 12-week trial (Panel B), and over the 12-week period in the subgroup of 20 patients studied by the sensitive branched-chain DNA assay (Panel C). Panel D shows the changes in CD4 cell counts and levels of plasma viremia in two patients who were treated with 1200 mg of ritonavir per day. The abbreviation tid denotes three times a day, and qid denotes four times a day.

tire study cohort, the durability of this effect was similar in each treatment subgroup (Fig. 1B). A high degree of variability among subjects in the area under the time-concentration curve, perhaps resulting from incomplete compliance with the frequent dosing in this study, may account in part for the similar virologic outcomes. However, in the subgroup of 20 patients who had more extensive virologic analysis, the antiviral effect was better sustained at daily doses of 800 mg or higher (Fig. 1C), with a mean reduction in plasma viremia of about 1.0 to 1.8 log at week 12.

Overall, the durability of the antiviral effect of ritonavir appears to be similar to that of zidovudine and lamivudine combined.¹⁶ The partial loss of antiviral ac-

tivity found with ritonavir may be attributable to decreased trough concentrations of drug with time. In addition, the emergence of drug-resistant HIV-1 is a likely explanation, since resistant strains of the virus have been selected in vitro in the presence of the drug.¹¹ Moreover, preliminary studies have found phenotypic resistance to ritonavir, as well as specific changes in genotype (for example, mutations to alanine at position 82, valine at position 54, arginine at position 24, isoleucine at position 46, and valine at position 71 of the protease gene) in isolates of HIV-1 obtained from patients whose levels of plasma viremia were returning toward the values measured before ritonavir therapy (unpublished data).

Although the antiviral effect of ritonavir is lost in a

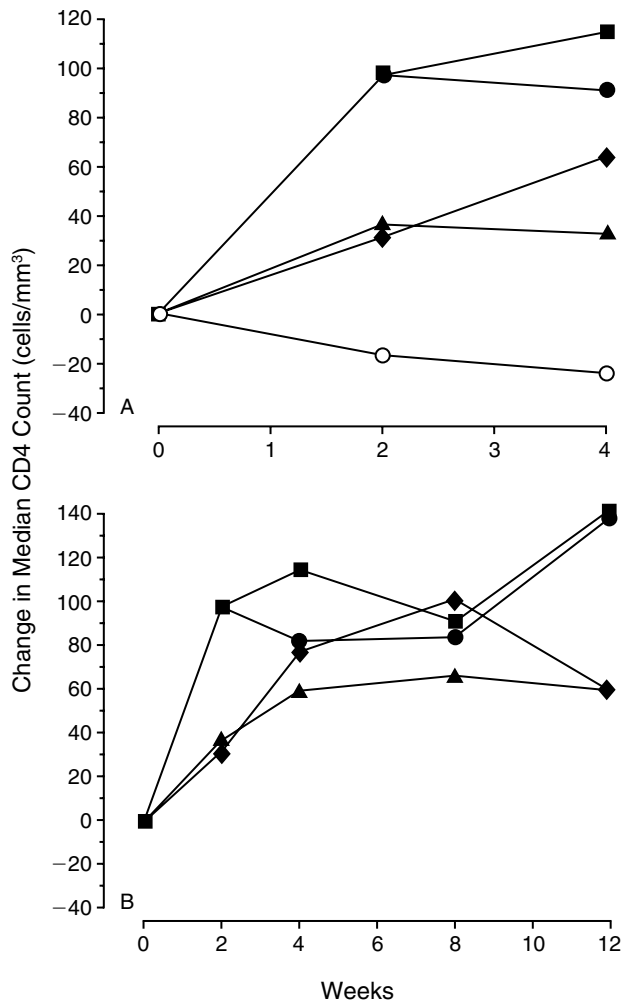


Figure 2. Changes in Median CD4 Cell Counts during the Dosing Phase (Panel A) and the Entire 12-Week Study Period (Panel B) in the Patients Treated with 200 (●) or 300 (■) mg Three Times a Day, 200 (▲) or 300 (◆) mg Four Times a Day, or Placebo (○).

majority of subjects, impressive antiviral activity has been maintained in a few. In the two patients whose cell counts and viral loads are shown in Figure 1D, for example, not only is HIV-1 RNA undetectable in plasma, but infectious virus also cannot be cultured from the blood. These cases, though strictly anecdotal, serve to emphasize the potent and apparently unprecedented antiviral activity of ritonavir, as well as to provide a sense of the antiviral potential of the drug, if this activity could be combined with that of another potent agent.

Equally encouraging is the marked increase in CD4 cell counts in the patients treated with ritonavir. In this study, therapy resulted in a sustained increase in the median CD4 cell count of nearly 100 cells per cubic millimeter after 12 weeks of therapy (Fig. 2B) — to our knowledge, more than has been achieved previously with any single antiretroviral agent. In each case, the elevation in the CD4 count was maintained as long as the antiviral effect was sustained. This increase appeared to result from a decreased rate of CD4 cell de-

struction associated with the concurrent decrease in HIV-1 replication, suggesting that much CD4 lymphocyte depletion in vivo is the direct or indirect consequence of the continuous, high-level replication of virus.² However, important questions remain about the functional import of the increase in CD4 counts. Future studies should investigate the immunologic repertoire of the repopulating lymphocytes, as well as the mechanisms of their regeneration.

In conclusion, ritonavir appears to be a safe and effective antiretroviral agent. Its novel mechanism of action and its apparent lack of overlapping toxicity with existing treatments for AIDS make it an ideal candidate for combination therapy with inhibitors of HIV-1 reverse transcriptase. The challenge now is to determine how best to incorporate this drug into the current antiretroviral armamentarium.

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