A CONTROLLED TRIAL OF TWO NUCLEOSIDE ANALOGUES PLUS INDINAVIR IN PERSONS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND CD4 CELL COUNTS OF 200 PER CUBIC MILLIMETER OR LESS

Scott M. Hammer, M.D., Kathleen E. Squires, M.D., Michael D. Hughes, Ph.D., Janet M. Grimes, M.S., Lisa M. Demeter, M.D., Judith S. Currier, M.D., Joseph J. Eron, Jr., M.D., Judith E. Feinberg, M.D., Henry H. Balfour, Jr., M.D., Lawrence R. Deyton, M.D., Jeffrey A. Chodakewitz, M.D., and Margaret A. Fischl, M.D., for the AIDS Clinical Trials Group 320 Study Team*

ABSTRACT

Background   The efficacy and safety of adding a protease inhibitor to two nucleoside analogues to treat human immunodeficiency virus type 1 (HIV-1) infection are not clear. We compared treatment with the protease inhibitor indinavir in addition to zidovudine and lamivudine with treatment with the two nucleosides alone in HIV-infected adults previously treated with zidovudine.

Methods   A total of 1156 patients not previously treated with lamivudine or protease inhibitors were stratified according to CD4 cell count (50 or fewer vs. 51 to 200 cells per cubic millimeter) and randomly assigned to one of two daily regimens: 600 mg of zidovudine and 300 mg of lamivudine, or that regimen with 2400 mg of indinavir. Stavudine could be substituted for zidovudine. The primary end point was the time to the development of the acquired immunodeficiency syndrome (AIDS) or death.

Results   The proportion of patients whose disease progressed to AIDS or death was lower with indinavir, zidovudine (or stavudine), and lamivudine (6 percent) than with zidovudine (or stavudine) and lamivudine alone (11 percent; estimated hazard ratio, 0.50; 95 percent confidence interval, 0.33 to 0.76; P = 0.001). Mortality in the two groups was 1.4 percent and 3.1 percent, respectively (estimated hazard ratio, 0.43; 95 percent confidence interval, 0.19 to 0.99; P = 0.04). The effects of treatment were similar in both CD4 cell strata. The responses of CD4 cells and plasma HIV-1 RNA paralleled the clinical results.

Conclusions   Treatment with indinavir, zidovudine, and lamivudine as compared with zidovudine and lamivudine alone significantly slows the progression of HIV-1 disease in patients with 200 CD4 cells or fewer per cubic millimeter and prior exposure to zidovudine. (N Engl J Med 1997;337:725-33.)

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P ROGRESS in the field of antiretroviral therapy for human immunodeficiency virus type 1 (HIV-1) infection has brought the end of the zidovudine-monotherapy era,[1-3] an improved understanding of the pathogenesis of HIV-1 disease,[4-9] demonstrations of the prognostic importance of plasma HIV-1 RNA quantification,[10-17] and the availability of increasingly potent therapeutic agents. Much of this progress is linked to the introduction of the HIV-protease inhibitors, drugs that inhibit the processing of Gag and Gag–Pol polyprotein precursors and thus prevent the maturation of virions.[18-20] Trials of HIV-protease inhibitors have shown beneficial effects on CD4 cell counts and plasma HIV-1 RNA concentrations to a degree not previously described with approved reverse-transcriptase inhibitors.[21-26] The most notable findings have involved three-drug combinations that include a potent HIV-protease inhibitor and two nucleoside an-

alogues. Specifically, when patients previously exposed to zidovudine who had either 50 to 400 or 50 or fewer CD4 cells per cubic millimeter were treated with indinavir, zidovudine, and lamivudine, plasma HIV-1 RNA concentrations were suppressed to less than 500 copies per milliliter in 85 percent and 65 percent of patients, respectively.[24,25] These findings have raised the important question of the clinical efficacy and safety of a three-drug regimen containing indinavir. We addressed that issue in this study.

METHODS

Study Design and Patients

The AIDS Clinical Trials Group 320 Study was a randomized, double-blind, placebo-controlled trial that compared the three-drug regimen of indinavir (Crixivan), open-label zidovudine (Retrovir) or stavudine (Zerit), and lamivudine (Epivir) with the two-drug regimen of zidovudine (or stavudine) and lamivudine in HIV-infected patients who had no more than 200 CD4 cells per cubic millimeter and at least three months of prior zidovudine therapy. The randomization was stratified according to the CD4 cell count obtained at the time of screening (50 or fewer cells per cubic millimeter as compared with 51 to 200 cells per cubic millimeter). The study was designed to enroll 1750 patients, with 40 percent of them in the stratum with 50 or fewer CD4 cells per cubic millimeter. The primary outcome measure in the assessment of efficacy was the development of a new acquired immunodeficiency syndrome (AIDS)–defining event (except when the AIDS-defining event was the development of *Pneumocystis carinii* pneumonia, in which case both new and recurrent events were accepted as outcome measures) or death; in the assessment of safety, the outcome measure was the occurrence of adverse events (signs, symptoms, or laboratory abnormalities) defined as severe or worse according to the grading scheme of the AIDS Clinical Trials Group.[27] The secondary outcome measures studied were death and changes in CD4 cell counts and plasma HIV-1 RNA concentrations.

The patients, recruited from 33 AIDS Clinical Trials Units and 7 National Hemophilia Foundation sites in the United States and Puerto Rico (see the Appendix), had to be more than 16 years old and had to have laboratory documentation of HIV-1 infection, a CD4 cell count of 200 per cubic millimeter or less within the 60 days before entry into the study, at least 3 months of prior zidovudine treatment, no more than 1 week of prior lamivudine treatment, no prior treatment with protease inhibitors, a Karnofsky performance score of at least 70, and acceptable laboratory values. The study was approved by the institutional review boards of the participating institutions, and all the patients gave written informed consent.

The patients received open-label zidovudine (200 mg three times daily) and lamivudine (150 mg two times daily) and were randomly assigned to receive indinavir (800 mg) or matching placebo every eight hours. In the first version of the protocol, only patients who could tolerate zidovudine and who had had at least 6 months of prior zidovudine therapy were enrolled, and the substitution of stavudine for zidovudine was permitted in the event of drug-associated toxicity at any point after randomization or if clinical progression of HIV-1 disease occurred that did not fulfill the criteria for a protocol-defined AIDS event at or beyond 24 weeks of study. The dose of stavudine was 40 mg two times daily (or 30 mg two times daily for patients weighing less than 60 kg). A protocol modification in October 1996 reduced the required prior exposure to zidovudine to at least three months and permitted patients who could not tolerate zidovudine to enter the study with stavudine substituted for zidovudine at the time of randomization. Prophylaxis for *P. carinii* pneumonia was mandated. Pro-

phylaxis for other opportunistic infections was permitted, although the use of rifabutin was prohibited.

Patients who had verified AIDS-defining events were offered open-label indinavir therapy with the approval of the study chairs and without having their initial treatment assignments revealed. All potential AIDS-defining events were reviewed in a blinded fashion by the study chair; only those that met the criteria defined in the study protocol were included in the analysis.

Monitoring and Enrollment

The patients were followed at weeks 4, 8, and 16 and every eight weeks thereafter with a clinical assessment and routine laboratory monitoring. CD4 cell counts were determined twice at base line and at weeks 4, 8, 24, and 40. Enrollment began in January 1996. The study was reviewed twice by a data and safety monitoring board. At the second such review, on February 18, 1997, the comparison of the groups based on data on the patients randomized by January 27, 1997, showed a significant difference between groups that met the prespecified guideline for stopping the study.[28] At that time, the board recommended that the accrual of patients be terminated and the study closed.

Plasma HIV-1 RNA concentrations were determined retrospectively in appropriately stored specimens from 190 randomly selected patients. These concentrations were measured twice at base line and at weeks 4, 8, 24, and 40 (Roche Amplicor HIV-1 Monitor assay).[29]

Statistical Analysis

The times to events were compared between treatment groups by Kaplan–Meier estimates, log-rank tests, and proportional-hazards models stratified according to the CD4 cell count obtained at the time of screening (50 or fewer vs. 51 to 200 cells per cubic millimeter).[30] Changes in CD4 cell counts over time were compared in a mixed-effects regression model.[31] An analysis of covariance adjusted for the screening CD4 cell count and the AIDS Clinical Trials Unit was used to compare changes in the CD4 cell count and the HIV-1 RNA concentration at each measurement.[32] With regard to changes in HIV-1 RNA, this calculation used a regression for censored data: concentrations below the limit of quantification, 500 copies per milliliter, were censored.[33] Analyses of all the variables pertaining to efficacy were performed on an intention-to-treat basis that included data on all patients randomized and all available follow-up data (including that obtained after the discontinuation of the study treatment). In the analyses of adverse events, the treatments were compared by a chi-square test; the follow-up data were censored either when a patient began receiving open-label indinavir or 56 days after the permanent discontinuation of the study treatment, whichever came first, and were restricted to patients for whom the study treatment was dispensed. All reported P values are two-sided. P values, estimates of differences between treatments, and 95 percent confidence intervals are unadjusted for the repeated interim analyses.

RESULTS

Accrual and Characteristics of the Patients

There were 1156 patients randomized between January 29, 1996, and January 27, 1997. Of these, 439 (38 percent) had 50 CD4 cells or fewer per cubic millimeter and 717 (62 percent) had 51 to 200 CD4 cells per cubic millimeter. The base-line characteristics of the study patients (Table 1) were well balanced between treatment groups.

Duration of Follow-up and Study Treatment

The median duration of follow-up was 38 weeks. Five percent of the patients were lost to follow-up;

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO
CD4 CELL COUNT AT THE TIME OF SCREENING.*

CHARACTERISTIC	ALL PATIENTS (N=1156)	CD4 COUNT PER CUBIC MILLIMETER	
		≤50 CELLS (N=439)	51–200 CELLS (N=717)
Male sex — no. (%)	956 (83)	365 (83)	591 (82)
Age — yr	39±9	39±8	40±9
Race or ethnic group — no. (%)			
White, non-Hispanic	598 (52)	203 (46)	395 (55)
African American	328 (28)	142 (32)	186 (26)
Hispanic	205 (18)	84 (19)	121 (17)
Asian Pacific or other	25 (2)	10 (2)	15 (2)
Injection-drug use — no. (%)	184 (16)	67 (15)	117 (16)
Hemophilia — no. (%)	36 (3)	16 (4)	20 (3)
Karnofsky score ≥90 — no. (%)	942 (81)	317 (72)	625 (87)
CD4 count — cells/mm³†	87±70	22±24	126±59
HIV-1 RNA — $\log_{10}$ copies/ml‡	5.0±0.6	5.2±0.5	4.9±0.7
Months of prior zidovudine therapy, alone or in combination — median (25th, 75th percentile)	21 (10, 42)	19 (10, 36)	22 (10, 48)

*Plus–minus values are means ±SD. Because of rounding, not all columns total 100 percent.

†Values shown are the means of two measurements obtained at least one day apart. Values obtained at screening, which had to be ≤200 cells per cubic millimeter, were not included in this calculation.

‡HIV-1 RNA was measured in a randomly selected cohort of 190 patients (75 patients with 50 CD4 cells or fewer per cubic millimeter and 115 patients with 51 to 200 CD4 cells per cubic millimeter).

the duration of follow-up and the percentage of patients lost to follow-up were similar in both treatment groups and both CD4-cell strata.

Ten patients did not have any study treatment. Of the remaining 1146 patients, 227 (20 percent) discontinued the study treatment prematurely, more than seven days before reaching a study end point. The proportion who discontinued the study treatment was higher in the group receiving zidovudine (or stavudine) and lamivudine (28 percent) than in the group receiving indinavir, zidovudine (or stavudine), and lamivudine (12 percent, P<0.001). In the stratum with 50 CD4 cells or fewer per cubic millimeter, the proportions of patients discontinuing the study treatment in the two groups were 32 percent and 16 percent, respectively (P<0.001), and in the stratum with 51 to 200 CD4 cells per cubic millimeter, these proportions were 26 percent and 9 percent (P<0.001). Only 4 percent of patients (10 of 227) discontinued the study treatment prematurely because of protocol-defined adverse events: 4 patients assigned to zidovudine (or stavudine) and lamivudine and 6 patients assigned to indinavir, zidovudine (or stavudine), and lamivudine. Among the premature discontinuations, 52 percent (117 of 227) were initiated by the patients, and for approximately half these patients the reasons given included a desire to seek open-label therapy with protease inhibitors, concern about the plasma HIV-1 RNA concen-

tration (on the basis of determinations made outside the study), or both.

Progression of Disease

Ninety-six patients (8 percent) had AIDS-defining events or died (Table 2). Sixty-three patients (11 percent) assigned to zidovudine (or stavudine) and lamivudine had disease progression, as compared with 33 patients (6 percent) assigned to indinavir, zidovudine (or stavudine), and lamivudine (P=0.001; estimated hazard ratio, 0.50; 95 percent confidence interval, 0.33 to 0.76) (Fig. 1A). There was no significant difference in the relative effects of the two treatments between the patients with 50 CD4 cells or fewer per cubic millimeter and the patients with 51 to 200 CD4 cells per cubic millimeter. Forty-four patients in the former stratum (20 percent) had AIDS-defining events or died in the group assigned to zidovudine (or stavudine) and lamivudine, as compared with 23 patients (11 percent) in the group assigned to indinavir, zidovudine (or stavudine), and lamivudine (P=0.005; estimated hazard ratio, 0.49; 95 percent confidence interval, 0.30 to 0.82) (Fig. 1B). In the stratum with 51 to 200 CD4 cells per cubic millimeter, 19 patients (5 percent) had AIDS-defining events or died in the group assigned to zidovudine (or stavudine) and lamivudine, as compared with 10 patients (3 percent) in the group assigned to indinavir, zidovudine (or stavu-

TABLE 2. RATES OF DISEASE PROGRESSION ACCORDING TO CD4 CELL COUNT
AT THE TIME OF SCREENING.

VARIABLE	INDINAVIR, ZIDOVUDINE (OR STAVUDINE), AND LAMIVUDINE	ZIDOVUDINE (OR STAVUDINE) AND LAMIVUDINE	HAZARD RATIO (95% CONFIDENCE INTERVAL)*	P VALUE†
	no. of patients (%)			
All patients	577	579		
AIDS or death	33 (6)	63 (11)	0.50 (0.33–0.76)	0.001
Death	8 (1)	18 (3)	0.43 (0.19–0.99)	0.04
≤50 CD4 cells/mm³	219	220		
AIDS or death	23 (11)	44 (20)	0.49 (0.30–0.82)	0.005
Death	5 (2)	13 (6)	0.37 (0.13–1.04)	0.05
51–200 CD4 cells/mm³	358	359		
AIDS or death	10 (3)	19 (5)	0.51 (0.24–1.10)	0.08
Death	3 (1)	5 (1)	0.59 (0.14–2.46)	0.46

*The reference group is the group receiving zidovudine (or stavudine) and lamivudine.

†Values were calculated by the log-rank test.

dine), and lamivudine (P=0.08; estimated hazard ratio, 0.51; 95 percent confidence interval, 0.24 to 1.10) (Fig. 1C).

Overall, 26 patients died (2.2 percent) (Table 2). Eighteen patients (3.1 percent) died in the group assigned to zidovudine (or stavudine) and lamivudine, as compared with eight (1.4 percent) in the group assigned to indinavir, zidovudine (or stavudine), and lamivudine (P=0.04; estimated hazard ratio, 0.43; 95 percent confidence interval, 0.19 to 0.99). There was no significant difference in the relative effects of the two treatments between the two strata. Among the patients with 50 CD4 cells or fewer per cubic millimeter, 13 patients receiving only the two nucleoside analogues died (5.9 percent), as compared with 5 patients receiving all three drugs (2.3 percent; P=0.05; estimated hazard ratio, 0.37; 95 percent confidence interval, 0.13 to 1.04). Among the patients with 51 to 200 CD4 cells per cubic millimeter, five patients assigned to zidovudine (or stavudine) and lamivudine (1.4 percent) died, as compared with three patients assigned to indinavir, zidovudine (or stavudine), and lamivudine (0.8 percent).

A total of 109 of the 1156 patients (9.4 percent) were treated with stavudine instead of zidovudine before the development of an AIDS-defining event or death. None of the three patients who were initially assigned to stavudine had a protocol-defined end point. Among the 106 patients in whom stavudine was substituted for zidovudine after randomization, 3 (all in the two-nucleoside group) had AIDS-defining events, and none died.

AIDS-Defining Events

In all, there were 91 AIDS-defining events (including multiple events per patient). Sixty of these occurred among the patients assigned to receive zidovudine (or stavudine) and lamivudine, as compared with 31 among the patients assigned to indinavir, zidovudine (or stavudine), and lamivudine. The most common events were infections with *P. carinii*, cytomegalovirus, and *Mycobacterium avium* complex (constituting 25 percent, 20 percent, and 16 percent of events, respectively).
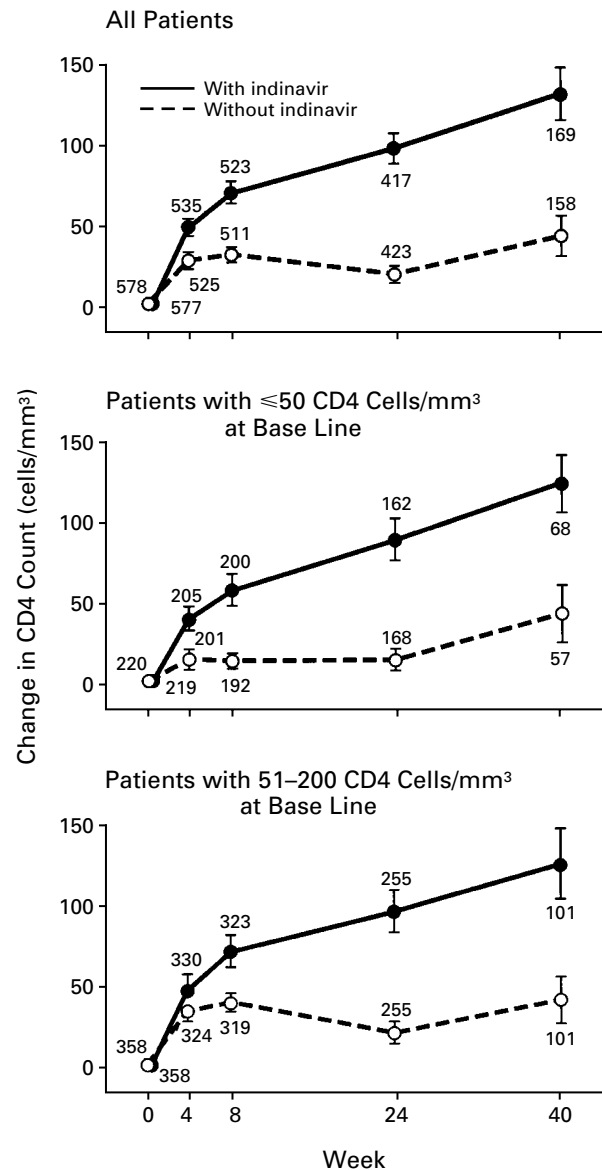
Changes in CD4 Cell Counts

Increased CD4 cell counts that persisted above base-line values were seen in both treatment groups, with superior responses in the group receiving indinavir. At weeks 4, 8, 24, and 40, the mean CD4 cell count in the patients assigned to zidovudine (or stavudine) and lamivudine increased by 27, 30, 18, and 40 cells per cubic millimeter, respectively. The corresponding mean increases in the patients assigned to indinavir, zidovudine (or stavudine), and lamivudine were 46, 65, 91, and 121 cells per cubic millimeter (Fig. 2A). Thus, the change at week 4 was greater by 19 cells per cubic millimeter (P<0.001) in the group that received indinavir, and the difference increased with time (P<0.001), to 36, 73, and 82 cells per cubic millimeter at weeks 8, 24, and 40, respectively.

The responses of the CD4 cell count to treatment are shown in Figures 2B and 2C. In the group receiving zidovudine (or stavudine) and lamivudine, the early increases from base line — those at weeks 4 and 8 — were smaller in the stratum with 50 CD4 cells or fewer per cubic millimeter than in the stratum with 51 to 200 CD4 cells per cubic millimeter. However, the changes from base line in the longer term — those at weeks 24 and 40 — were similar in the two strata. Exploratory analyses of the CD4 cell counts in the two treatment groups when the data were censored at the times patients changed from the treatment to which they were initially assigned showed increases from base line that were similar to those in the intention-to-treat analyses at weeks 4,
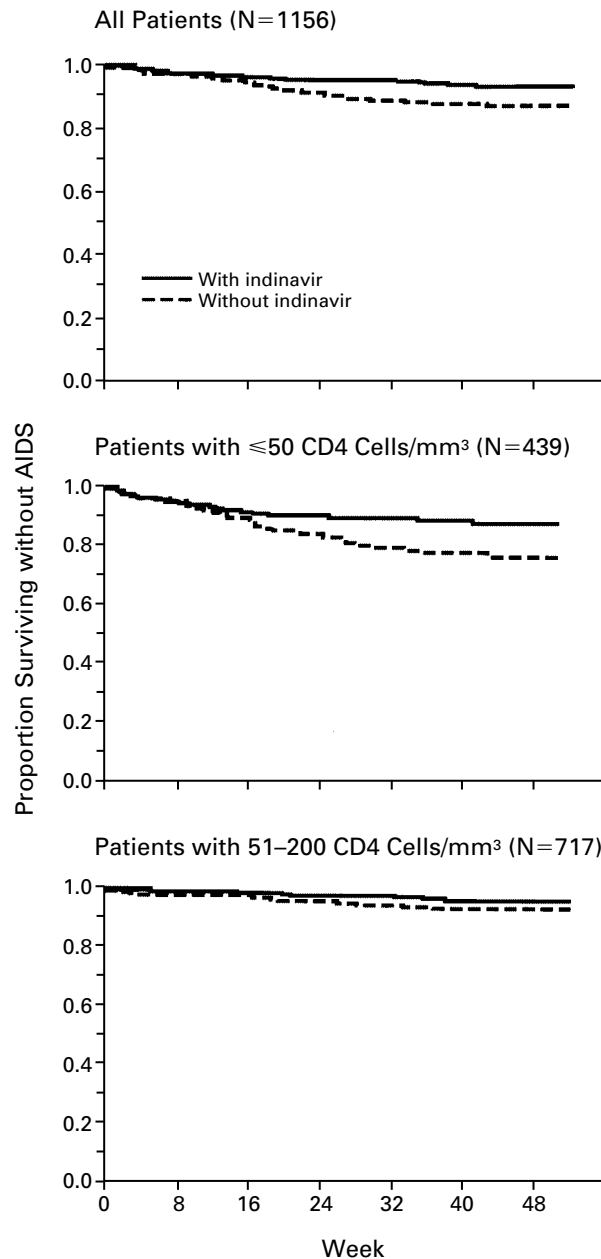
Figure 1. Kaplan–Meier Estimates of the Proportion of Patients Who Did Not Reach the Primary Study End Point of AIDS or Death.

Figure 2. Mean Changes from Base Line in the CD4 Cell Count. The number of patients who could be evaluated at each time point is shown. Bars indicate 95 percent confidence intervals.

8, and 24 (data not shown). At week 40, the difference between the two treatment groups was smaller in the intention-to-treat analysis than in the censored analysis (difference in mean change, 82 vs. 115 cells per cubic millimeter), suggesting that the difference may have been reduced by the greater proportion of subjects who changed treatment in the group receiving zidovudine (or stavudine) and lamivudine.

Changes in Plasma HIV-1 RNA Concentrations

The responses of the plasma HIV-1 RNA concentrations to treatment were studied in 190 randomly selected patients. There were persistent decreases from the base-line values in both treatment groups, with significantly better responses in the group whose treatment included indinavir ($P<0.001$ in an area-under-the-curve analysis). At weeks 4, 8, 24, and 40, the mean decreases in plasma HIV-1 RNA

in the group receiving zidovudine (or stavudine) and lamivudine were 0.9, 0.6, 0.6, and 1.0 $\log_{10}$ copies per milliliter, respectively. The corresponding decreases in the group receiving indinavir, zidovudine (or stavudine), and lamivudine were 1.8, 2.3, 2.8, and 2.1 $\log_{10}$ copies per milliliter (Fig. 3A). The changes from base line were significantly greater at each time point in the group treated with indinavir ($P<0.001$ at weeks 4, 8, and 24; $P=0.007$ at week 40). At week 24, the proportion of patients with plasma HIV-1 RNA concentrations of less than 500 copies per milliliter was 9 percent in the two-nucleoside group, as compared with 60 percent in the group treated with indinavir.

The plasma HIV-1 RNA responses according to the CD4 cell count are shown in Figures 3B and 3C. In the patients with 50 CD4 cells or fewer per cubic millimeter, the decreases in plasma HIV-1 RNA appeared to be smaller than those in the patients with 51 to 200 CD4 cells per cubic millimeter. However, conclusions about stratum-specific plasma HIV-1 RNA responses need to be made cautiously because of the small numbers of patients followed through week 40.

Adverse Events

The proportion of patients with signs and symptoms that were severe (grade 3) or worse (grade 4) in the group receiving zidovudine (or stavudine) and lamivudine was 18 percent, as compared with 21 percent in the group receiving indinavir, zidovudine (or stavudine), and lamivudine ($P=0.17$). The most common symptoms were nonspecific discomfort, malaise, fever, headache, and nausea and vomiting, with no difference in the reporting of symptoms between treatment groups.

The proportion of patients with severe laboratory abnormalities or worse in the group receiving zidovudine (or stavudine) and lamivudine was 26 percent, as compared with 21 percent in the group receiving indinavir, zidovudine (or stavudine), and lamivudine ($P=0.06$). This difference primarily reflected a difference between the groups in the incidence of neutropenia (15 percent and 5 percent, respectively; $P<0.001$). In contrast, the proportion of patients with hyperbilirubinemia was 1 percent in the two-nucleoside group, as compared with 6 percent in the group treated with indinavir ($P<0.001$), a finding compatible with the known elevation of indirect bilirubin associated with the use of indinavir. Two percent of the patients in each treatment group had hyperglycemia.

Five patients receiving zidovudine (or stavudine) and lamivudine (1 percent) had episodes of renal colic or nephrolithiasis (irrespective of grade), as compared with 21 patients receiving indinavir, zidovudine (or stavudine), and lamivudine (4 percent, $P=0.001$). Three of the five patients in the two-
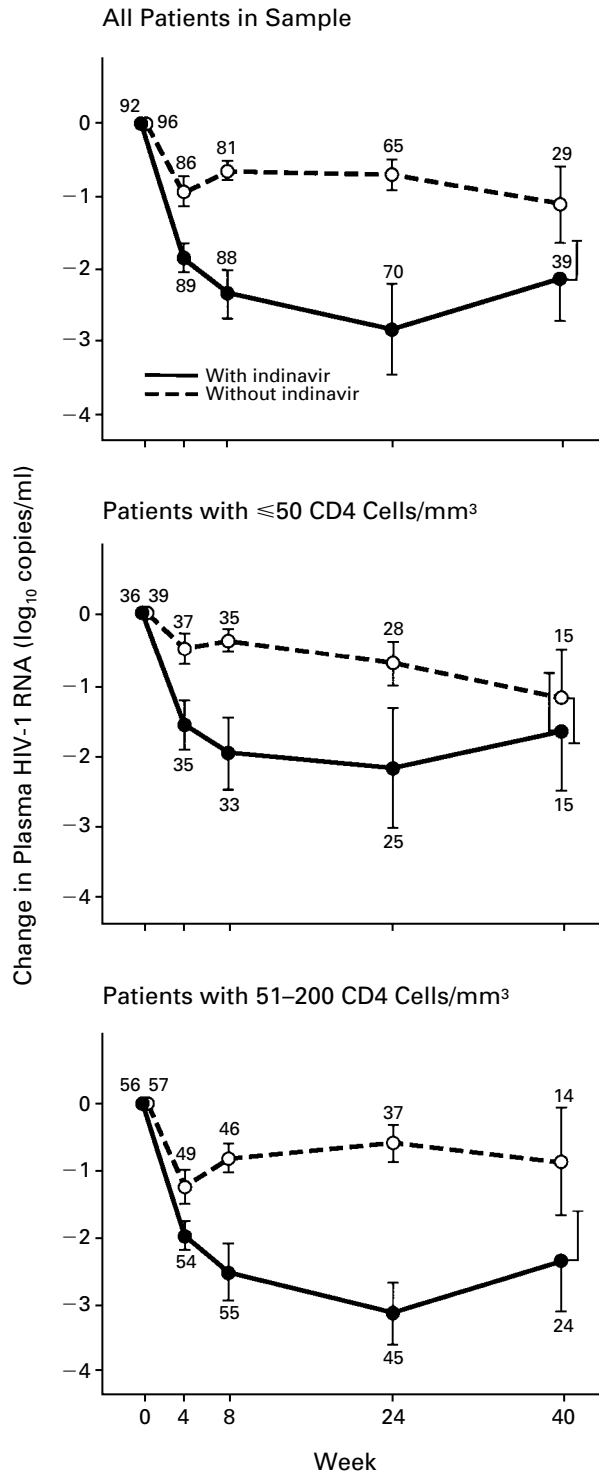
Figure 3. Mean Change from Base Line in the Plasma HIV-1 RNA Concentration.

For this analysis, 190 patients were randomly selected and their HIV-1 RNA concentrations were studied. The number of patients who could be evaluated at each time point is shown. Bars indicate 95 percent confidence intervals.

nucleoside group in whom renal colic or nephrolithiasis developed had that condition after discontinuing the study treatment and starting open-label indinavir treatment.

Five new diagnoses of diabetes mellitus were recorded: two in the two-nucleoside group and three in the group treated with indinavir.

DISCUSSION

This study showed the clinical superiority of the three-drug regimen containing indinavir over the two-nucleoside combination in patients previously treated with zidovudine who had CD4 cell counts of 200 per cubic millimeter or less. The proportion of patients whose disease progressed to AIDS or death was reduced from 11 percent to 6 percent by the three-drug combination, a 50 percent reduction ($P = 0.001$). The hazard ratios in the study patients as a whole (0.50), those with CD4 cell counts of 50 per cubic millimeter or less (0.49), and those with counts of 51 to 200 per cubic millimeter (0.51) were very similar, suggesting that the effect of treatment was similar across the study population, although the possibility of differential effects cannot be ruled out. Mortality, low in both groups, was reduced from 3.1 percent to 1.4 percent with the three-drug regimen ($P = 0.04$). Thus, there was evidence of a reduction in mortality that was consistent with the reduced risk of progression to the primary outcome measure of AIDS or death.

The rate of loss to follow-up in this study was low (5 percent), and the overall rate of premature discontinuation of treatment was moderate (20 percent). Seventy-nine percent of the 96 AIDS-defining events or deaths occurred while the patients were receiving the study treatment or within seven days of its discontinuation. Although rates of withdrawal from treatment differed between the two study groups, the tendency for patients who withdrew prematurely from the two-nucleoside group to seek treatment with protease inhibitors would tend to narrow the differences between the groups in rates of disease progression and therefore should not affect the conclusions of the study. Conversely, when a study is terminated early because a stopping guideline is used, differences between the treatment groups tend to be overestimated because of random variation.[34] However, it is impossible to determine the relative magnitude of these effects.

These findings confirm on the basis of clinical end points the results of earlier trials of the combination of indinavir, zidovudine, and lamivudine in patients previously treated with zidovudine, trials that showed that the three-drug combination produces superior responses in plasma HIV-1 RNA concentrations and CD4 cell counts.[24,25] The suppression of plasma HIV-1 RNA to unquantifiable levels in the majority of subjects with this drug combination is accompa-

nied by greater suppression of HIV-1 RNA expression in lymphoid tissue[35] and may prevent the emergence of resistance — factors that may add to the clinical benefit now established for this regimen. Our study also found superior responses of CD4 cells and plasma HIV-1 RNA with the three-drug regimen.

We chose the combination of zidovudine and lamivudine as the control treatment because of the unique interactions between these two agents with respect to mutations conferring resistance, the results of phase 2 trials, the tolerance associated with the regimen, and its widespread use in clinical practice.[36-40] The clinical benefit of lamivudine when that drug is added to previously available nucleoside analogues to treat patients with 25 to 250 CD4 cells per cubic millimeter was recently confirmed in the CAESAR trial, in which the risk of AIDS or death was reduced by approximately 50 percent.[41] In the control group in our study, there was a relatively low rate of disease progression, as well as a moderate increase in the CD4 cell count and a decline in plasma HIV-1 RNA; these persisted throughout the study, even though it is now recognized that simply adding lamivudine to a preexisting regimen is not a standard clinical approach. The strength of the control group in this study is also an important difference between this study and previously reported studies of other HIV-protease inhibitors that have assessed clinical end points.[42,43] In the Abbott M94-247 trial, ritonavir or placebo was added to stable prior nucleoside-analogue therapy or no therapy.[42] In the Hoffmann–La Roche NV14256 trial, a regimen of saquinavir plus zalcitabine was compared with zalcitabine monotherapy.[43] In the context of these other trials, our study makes it clear that more potent therapies, now represented by three-drug regimens containing a protease inhibitor, are preferable in patients with advanced disease. The durability of the clinical benefit conferred by indinavir as part of a three-drug regimen has not been fully defined, however.

Improving the use of the currently approved agents to treat HIV-1 infection, and the promising drugs on the clinical horizon,[44-46] in the management of HIV-1 disease remains a challenge.[47] However, this study supports the view that employing well-tolerated regimens of increasing potency will translate into greater clinical benefits for patients with HIV-1 infection.

APPENDIX

The following institutions and investigators participated in the AIDS Clinical Trials Group 320 Study: *University of North Carolina* — T. Lane and J. Horton; *University of Cincinnati* — D. Neumann and B. Letcher; *University of Puerto Rico* — G. Vazquez, M. Cruz-Ortiz, and I. Lopes; *University of Minnesota* — C. Kumekawa, R. Schut, and S. Swindells; *Washington University* — P. Tebas, W. Powderly, and A. Slack; *Ohio State University College of Medicine* — M. Para, R. Fass, and J. Neidig; *Northwestern University* — J. Pulvirenti and J. Pottage, Jr.; *University of Alabama and Emory University* — J. Lennox and K. Tamburello; *New York University Medical Center and Bellevue Hospital* — R. Gulick, J. Dowling, and M. Laverty; *University of Miami* — E. Scerpella and A. Rodriguez; *University of Texas at Galveston* — R. Pollard, S. Hausrath, and M. Pickthall; *Case Western Reserve University* — B. Gripshover, H. Valdez, and M. Chance; *Howard University* — R. Delapenha, J. McNeil, and Y. Butler; *Harvard University and Boston Medical Center* — L. Jackson-Pope and T. Cooley; *University of Rochester* — R. Hewitt and C. Greisberger; *University of California, Los Angeles* — R. Mitsuyasu, M. Guerrero, and P. Miller; *Indiana University Hospital* — K. Fife, H. Nixon, and D. Heise; *Meharry Medical College and Vanderbilt University Medical Center* — M.A. South, D. Haas, and S. Raffanti; *Duke University* — C. Hicks, P. Robinson, and K. Shipp; *University of California, San Diego* — C. Fegan, T.-C. Meng, and S. Little; *Johns Hopkins University* — R. Becker, M. Higgins, L. Apuzzo, and J.B. Jackson; *Mount Sinai Medical Center* — P. Gerits, H. Mendoza, and D. Mildvan; *University of Pennsylvania* — R.R. MacGregor, I. Matozzo, and E. McCann; *University of Southern California* — M. Dube and C. Olsen; *University of Colorado* — D. Kuritzkes, B. Putnam, and D. Torre; *Tulane University and Louisiana State University* — J. Lertora, R. Clark, and M. Beilke; *University of Hawaii* — S. Souza, M. Millard, and L. Oshita; *Stanford University* — T. Merigan, Jr., J. Fessel, and D. Israelski; *Memorial Sloan-Kettering Cancer Center* — M. Giordano, P. Ristau, and M. Granville; *University of Washington, Seattle* — A. Collier, R. Vasquez, B. Royer, and R. Coombs; *New York University Medical Center and Bellevue Hospital (pediatric site)* — W. Borkowsky, S. Chandwani, and M. Minter; *Columbus Children's Hospital* — M. Brady, J. Hunkler, and C. Callaway; *Medical University of South Carolina* — G. Johnson and E. Matters; *National Hemophilia Foundation* — T. Coates, T. Hofstra, W.-Y. Wong, E. Eyster, S. Seremetis, C. Kessler, S. Stabler, W. Hanna, C. Leissenger, J. Gill, P. Timmons, W.K. Hoots, and M. Cantini; *Division of AIDS, National Institute of Allergy and Infectious Diseases* — J. Ioannidis and A. Martinez; *Statistical and Data Management Center* — K. Kazial; *Harvard School of Public Health* — S.-H. Liou; *Community Constituency Group* — H. Chang; *Bristol-Myers Squibb* — J. Skovronski and L. Dunkle; *Merck and Co.* — A. Meibohm.

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