A Randomized, Controlled Trial of Indinavir, Zidovudine, and Lamivudine in Adults with Advanced Human Immunodeficiency Virus Type 1 Infection and Prior Antiretroviral Therapy

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A randomized, double-blind, multicenter study of indinavir, zidovudine, and lamivudine was conducted in 320 adults with human immunodeficiency virus type 1 (HIV-1) infection, ≤50 CD4 cells/mm^3, and extensive prior zidovudine therapy. Patients received indinavir, 800 mg every 8 h; zidovudine, 200 mg every 8 h, and lamivudine, 150 mg twice daily; or all 3 drugs for 24 weeks. In an intention-to-treat analysis, proportions of patients with HIV-1 RNA <500 and <50 copies/mL, respectively, at week 24 were 56% and 45% in the indinavir-zidovudine-lamivudine group, 3% and 2% in the indinavir group, and 0% in the zidovudine-lamivudine group. Observed mean CD4 cell increases were 95, 78, and 6 cells/mm^3 in the three-, one-, and two-drug arms, respectively. Regimens were generally well tolerated. Patients with advanced HIV-1 infection benefit from triple therapy with indinavir, zidovudine, and lamivudine, although the proportion with optimal response appeared to be lower in patients with low CD4 cell counts.

Combination therapy with indinavir, zidovudine, and lamivudine slows disease progression in patients with human immunodeficiency virus (HIV) type 1 infection who have ≤200 CD4 cells/mm^3 [1]. In addition, therapy with this triple combination results in prolonged suppression of HIV replication, as measured by serum or plasma viral RNA levels, especially among subjects with >50 CD4 cells/mm^3 [2, 3]. Although some studies have included patients with ≤50 CD4 cells/mm^3, few studies have focused on this population with advanced HIV-1 infection, where chances for durable antiretroviral responses are less and chances for toxicity are great [4]. In this study, we compared the antiretroviral efficacy and safety of the combination of indinavir, zidovudine, and lamivudine with dual therapy with zidovudine plus lamivudine and with monotherapy with indinavir in zidovudine-experienced patients with ≤50 CD4 cells/mm^3.

Methods

Study design and patient selection. The study was a double-blind, randomized, 6-month study in HIV-1–seropositive patients who had an average of 2 pretreatment CD4 cell counts of ≤50 cells/mm^3. Patients, ≥18 years of age, were required to have had ≥6 months of prior zidovudine treatment and no prior treatment with protease inhibitors or lamivudine. No restrictions existed on prior use of other approved antiretroviral drugs.

Eligible patients were required to discontinue their antiretroviral therapy 2 weeks before study entry and were randomly assigned to 1 of 3 treatment regimens: indinavir, 800 mg every 8 h (Crixivan; Merck, West Point, PA); the combination of indinavir, 800 mg every 8 h, zidovudine, 200 mg every 8 h (Retrovir, Glaxo Wellcome, Research Triangle Park, NC), and lamivudine, 150 mg twice daily (Epivir; Glaxo Wellcome); or the combination of zidovudine, 200 mg every 8 h, and lamivudine, 150 mg twice daily. The regimens included appropriate matching placebos. Patients were randomized within study site by use of a permuted block design. In all, 320 patients enrolled in the study at 21 sites between August 1995 and

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Written informed consent was obtained from all patients prior to screening for this study. Human experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of this trial, and all sites received institutional review board/ethical review board approval to conduct the study.

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April 1996. After 24 weeks, all patients were eligible to continue taking open-label indinavir, 800 mg every 8 h, and other approved antiretroviral agents.

Here we present complete data pertaining to the first 24 weeks of the study, including available viral RNA and CD4 cell data at week 84 from patients randomized to the triple therapy arm. The primary measures of efficacy were the changes in serum HIV RNA levels and CD4 cell counts. In addition, we analyzed the time to progression to an AIDS-defining illness or death.

Patient monitoring. After randomization, subjects were seen at weeks 0, 2, 4, and every 4 weeks thereafter through week 24, when study medication was discontinued, and 2 weeks after the last dose of the study drug. An attempt was made to continue to follow persons who discontinued the study drug. At each visit, patients had physical examinations, and blood and urine samples were collected for safety testing, measurement of HIV RNA levels, and CD4 cell counts. All laboratory tests were performed at a central laboratory with the exception of one site, whose location prohibited the use of a central laboratory for safety testing and CD4 cell counts. Women of childbearing potential had serum pregnancy tests done at each visit; women who became pregnant were required to discontinue participation in the study. Information collected at each visit included study and concomitant therapy taken since the last visit, adverse events, and clinical events.

Clinical events were defined as AIDS-defining illnesses that met specific diagnostic criteria defined in the protocol and death due to any cause. The clinical events and the supporting diagnostic information were reviewed and confirmed by a single investigator selected by Merck as a study representative. The investigator was blinded to allocation number, site, and treatment group at the time of the review.

CD4 cell count and serum HIV RNA testing. CD4 cells were measured by a central laboratory using 3-color flow cytometry for all but one international site. Values of <10 cells/mm^3 were reported as <10 cells/mm^3. For the 3 patients at one international site, testing was done at a local laboratory using 2-color flow cytometry. CD4 cell count results were made available to the patients and investigators.

Sera for HIV-1 RNA levels were processed, stored at −70°C, and assayed at a later date by a quantitative reverse transcriptase polymerase-chain reaction (PCR) assay (Amplicor HIV-1 Monitor assay; Roche Diagnostics Systems, Branchburg, NJ) at a central laboratory. The lower level of quantification for this assay was 500 RNA copies/mL. A value of "negative" was reported if no copies were detectable. If virus was detectable but the number of copies was <500 copies/mL, a value of <500 copies/mL was reported. A more sensitive investigational version of the PCR assay was performed on samples from week 24 and later visits for which the result was negative or <500 copies/mL. The investigational assay had a consistent limit of detection of ~50 RNA copies/mL. HIV RNA results were not made available to the patients or investigators during the first 24 weeks of the study.

Statistical methods. The primary measures of antiretroviral activity were the magnitude and duration of changes in serum HIV RNA and CD4 cell counts over 24 weeks, as summarized by an area-under-the-curve measurement that incorporated the baseline value and length of follow-up (AUCMB) [5, 6]. All patients with measurements at baseline and at least one on treatment were included in the analyses. HIV RNA values reported as <500 copies/mL were set equal to 500 copies/mL, and values reported as "negative" were set equal to 250 copies/mL, half of the limit of quantification. The HIV RNA values underwent a $\log_{10}$ transformation before analysis. CD4 cell counts reported as <10 cells/mm^3 were set equal to 5 cells/mm^3. The AUCMBs, which estimated the average change from baseline, were compared among the treatment groups with an analysis of variance model that included treatment group and investigative site. Mean changes and SEs, adjusted for site, and the nominal P values for the pairwise comparisons of the treatments are reported. Observed mean changes from baseline plus the 95% confidence interval (CI) at each week are displayed.

Per the protocol, the average change in CD4 cell count was the primary end point and the average change in HIV RNA level was secondary. During the time the study was conducted, changes in HIV RNA became at least as important as, if not more important than, changes in CD4 cell count, in evaluating the effectiveness of antiretroviral therapy. Thus, in evaluating the results of the study, both measures were considered to be primary from a clinical perspective. No post hoc adjustment for multiple end points was made. The protocol also specified that the 2 pairwise comparisons of the indinavir-zidovudine-lamivudine and the indinavir monotherapy groups with the zidovudine-lamivudine group were of primary interest. Per the protocol, multiplicity adjusted P values were calculated to ensure that the overall type I error for these comparisons was <.050. However, since the multiplicity adjusted P values were very similar to the nominal P values and since the monotherapy comparison is no longer of equal importance, only the nominal P values are reported here. All P values are 2-sided.

Analyses of the proportions of patients who had serum HIV RNA levels <500 copies/mL at each time point were performed on an intention-to-treat basis. Two approaches were used to handle missing data. First, a model-based analysis was done by use of the generalized estimating equation (GEE) methodology for longitudinal data [7]. Patients who discontinued therapy because of clinical or laboratory adverse experiences or because of clinical events were considered to have HIV RNA levels ≥500 copies/mL (i.e., failure) after discontinuation of therapy, regardless of RNA level. Missing values, due to a missed or mistimed visit, were assumed to be <500 copies/mL, if both the immediately preceding and succeeding HIV RNA levels were <500 copies/mL. A corresponding rule was applied if both values were ≥500 copies/mL. Other missing values, including those subsequent to discontinuation for reasons not known to be therapy related, were left as missing. The GEE methodology was then used to estimate the proportions of patients with serum HIV RNA levels <500 copies/mL by treatment group. Conceptually, GEE estimates the proportion from the available (observed and assigned) data at a time point and then adjusts this estimate based on correlations between the responses at that time point and all other points and the available data for the patients who are missing data at that time point. An autoregressive one (AR [1]) covariance structure was used so that the adjustment was influenced most by the responses closest to the time point for which response was being estimated.

A second intention-to-treat analysis was done, in which all patients who withdrew were counted as treatment failures after they discontinued therapy (referred to as withdrawal-equals-failure analysis hereafter). Missing values, due to a missed or mistimed

Table 1. Patient characteristics at baseline by treatment group.

Characteristics [a]	Indinavir-zidovudine-lamivudine (n = 108)	Indinavir (n = 107)	Zidovudine-lamivudine (n = 105)	Total (n = 320)
Sex, no. (%)				
Women	15 (14)	12 (11)	12 (11)	39 (12)
Men	93 (86)	95 (89)	93 (89)	281 (88)
Racial origin, no. (%)				
White	81 (75)	90 (84)	87 (83)	258 (81)
Black	17 (16)	9 (8)	13 (12)	39 (12)
Hispanic	8 (7)	4 (4)	3 (3)	15 (5)
Other [b]	2 (2)	4 (4)	2 (2)	8 (3)
Age (years), mean (SD)	40.0 (7.9)	37.9 (8.5)	39.5 (8.4)	39.1 (8.3)
Prior zidovudine therapy (months), mean (SD)	27.5 (19.5)	27.5 (22.3)	28.5 (20.9)	27.8 (20.9)
Prior therapy with nucleoside analogs, [c] no. (%)	92 (85)	87 (81)	93 (89)	272 (85)
Prior AIDS-defining illness, no. (%)	62 (58)	66 (62)	57 (54)	185 (58)
CD4 cells/mm^3 [d]				
Mean (SD)	19.1 (15.0)	18.3 (12.5)	17.8 (13.5)	18.4 (13.6)
Median	15.0	17.0	14.0	15.0
Range	5.0–63.0	5.0–66.0	5.0–57.0	5.0–66.0
Serum HIV RNA, no.	107	106	98	311
Log_{10} copies/mL				
Mean (SD)	4.83 (0.51)	4.93 (0.55)	4.85 (0.46)	4.87 (0.51)
Median	4.89	4.97	4.98	4.96
Range	3.04–6.08	3.29–6.25	3.60–5.77	3.04–6.25
Copies/mL				
Geometric mean	68,151	85,010	70,742	74,353
Median	76,900	94,030	94,430	90,790
Range	1090–1,204,720	1900–1,775,030	4020–590,280	1090–1,775,030

[a] SD, standard deviation; HIV, human immunodeficiency virus.
[b] Includes Asian, Asian/White, Asian Indian, South American, Nicaraguan, and other.
[c] Didanosine, zalcitabine, and stavudine.
[d] Values reported as <10 cells/mm^3 were coded as 5 cells/mm^3.

visit, were left as missing, if both the immediately preceding and succeeding HIV RNA levels were <500 copies/mL; otherwise they were assumed to be ⩾500 copies/mL. The proportion of subjects with HIV RNA <500 copies/mL at each time point was estimated by dividing the number of patients with HIV RNA <500 copies/mL by the number of patients with available (observed and assigned) data. The observed proportions of patients with HIV RNA <500 copies/mL, based on all observed data regardless of whether the patients were on study therapy at the time of the measurements, were also calculated. For all 3 analyses, 95% CIs were calculated.

The same approaches to analysis were used for the proportion of patients with <50 HIV RNA copies/mL with one exception. Since data from the more sensitive assay were available at only one time point during the double-blind portion of the study, the model-based analysis could not be done for the week-24 data. In these analyses, it was assumed that samples with ⩾500 copies/mL by the standard assay had ⩾50 copies/mL by the more sensitive assay.

An intention-to-treat analysis of the changes in CD4 cells at week 84 was done by carrying forward the last observation for subjects who discontinued therapy because of either clinical or laboratory adverse experiences or clinical events. Changes from baseline were then estimated by use of a generalization of analysis of covariance that allows for correlation and nonconstant variability in longitudinal data. An AR (1) covariance structure was used, and the model was fitted to the data by use of the method of restricted maximum likelihood. Baseline CD4 cell count, investigative site, treatment, week, and treatment by week interaction were included in the model.

The distribution of the time to the first clinical event was compared pairwise between the treatment groups by use of the log-rank test stratified by investigative site. An estimate of the relative risk of disease progression was obtained from the Cox proportional hazards model with treatment and site as covariates.

Fisher's exact test was used to compare treatment groups with respect to the proportions of patients who discontinued the study, who had adverse experiences, and who had clinically significant laboratory abnormalities. A clinically significant laboratory abnormality was considered present if a value exceeded the predefined criteria or an abnormality present at baseline became worse.

The planned sample size for this study was 150 patients per group. With this sample size and assuming an SD of 75 cells/mm^3, there would have been 80% power to detect a difference of 27 cells/mm^3 in the average change from baseline over 24 weeks in CD4 cell counts between indinavir alone or in combination with zidovudine plus lamivudine and zidovudine plus lamivudine by use of a 2-tailed test at the 2.5% significance level.

Results

Patient characteristics. In total, 320 HIV-1–infected subjects were enrolled in the study. The baseline patient characteristics are presented in table 1. The 3 treatment groups were comparable at baseline. Most subjects were men (88%) and white (81%). Mean age was 39 years. The mean CD4 cell count for all patients was 18 cells/mm^3. The mean serum HIV-1 RNA level was 4.87 log_{10} copies/mL. Nine patients did not have baseline viral RNA measurements, 1 each in the indinavir and

indinavir-zidovudine-lamivudine groups and 7 in the zidovudine-lamivudine group.

All patients were zidovudine-experienced, with a mean exposure of 27.8 months, and 85% had previously received at least one other nucleoside analogue: didanosine, 57%; zalcitabine, 51%; or stavudine, 35%. In addition, 5% received nevirapine and 1% delavirdine.

More than half the patients (58%) had at least one previous AIDS-defining illness. The most common illness, experienced by 28% of the patients, was *Pneumocystis carinii* pneumonia.

Patient follow-up. Overall, 69 (22%) patients discontinued their participation in the study prior to completing 24 weeks: 15 (14%) in the indinavir-zidovudine-lamivudine group, 20 (19%) in the indinavir group, and 34 (32%) in the zidovudine-lamivudine group. The proportion of patients who discontinued study treatment was significantly lower in the indinavir-zidovudine-lamivudine and the indinavir groups than in the zidovudine-lamivudine group ($P = .002$ and .027, respectively). The difference between the indinavir-zidovudine-lamivudine group and the indinavir group in the proportion of patients who discontinued was not significant ($P = .361$). Only 20 (6%) patients discontinued because of a clinical or laboratory adverse event: 6 in the indinavir-zidovudine-lamivudine group, 5 in the indinavir group, and 9 in the zidovudine-lamivudine group. Other reasons for discontinuation were clinical event (3 patients), patient withdrawal (37), lost to follow-up (5), other (3), and protocol deviation (1).

Changes in viral RNA. Figure 1 displays the observed mean changes in HIV RNA from baseline through week 24. Patients in the indinavir-zidovudine-lamivudine group had the greatest mean decrease from baseline through week 24. At week 24, the mean decreases were 1.93, 0.36, and 0.25 $\log_{10}$ copies/mL for the indinavir-zidovudine-lamivudine, indinavir monotherapy, and zidovudine-lamivudine groups, respectively. The adjusted mean decrease ($\pm$SE) over the 24-week period (as measured by AUCMB) was 1.52 ($\pm$0.07), 0.52 ($\pm$0.07), and 0.37 ($\pm$0.07) $\log_{10}$ copies/mL in the indinavir-zidovudine-lamivudine, indinavir, and zidovudine-lamivudine groups, respectively. The decrease in the indinavir-zidovudine-lamivudine group was significantly greater ($P < .001$) than in the indinavir and zidovudine-lamivudine groups. The average decreases over 24 weeks were similar for the indinavir and zidovudine-lamivudine groups ($P = .132$).

Figure 2*A* displays the proportion of patients with serum HIV-1 RNA levels <500 copies/mL, as estimated by the model-based analysis (see Methods). The estimated proportions of patients with HIV RNA levels <500 copies/mL at week 24 were 60%, 3%, and 0% for the indinavir-zidovudine-lamivudine, indinavir monotherapy, and zidovudine-lamivudine groups, respectively. In the withdrawal-equals-failure analysis, the proportions of patients with HIV RNA levels <500 copies/mL at week 24 were 56% (60/108), 3% (3/107), and 0% (0/105), respectively. For comparison, based only on observed data, the proportions of patients with HIV RNA levels <500 copies/mL were 66% (60/91), 4% (3/85), and 0% (0/68), respectively, at week 24. Figure 2*B* displays the results of the 3 methods of analysis for the indinavir-zidovudine-lamivudine group.

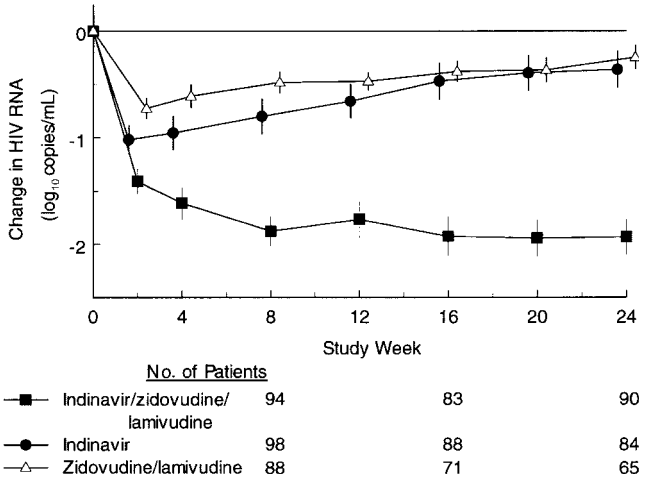

Figure 1. Mean changes from baseline in serum human immunodeficiency virus (HIV) RNA levels based on observed data for patients with $\leq$50 CD4 cells/mm^3 at baseline. Bars are 95% confidence intervals.

A more sensitive investigational assay was also used to measure HIV RNA at week 24. In the withdrawal-equals-failure analysis, the proportions of patients with serum viral RNA values <50 copies/mL were 45% (48/106) in the indinavir-zidovudine-lamivudine group, 2% (2/107) in the indinavir group, and 0% (0/105) in the zidovudine-lamivudine group. The corresponding observed proportions were 54% (48/89) in the indinavir-zidovudine-lamivudine group, 2% (2/85) in the indinavir group, and 0% (0/68) in the zidovudine-lamivudine group.

HIV RNA measurements were available at week 84 for 64 patients randomized to receive indinavir-zidovudine-lamivudine. Table 2 shows the proportions of patients with serum HIV RNA levels <500 copies/mL and <50 copies/mL by the 3 methods of analysis.

Changes in CD4 cells. Figure 3 displays the observed mean changes from baseline in CD4 cells by treatment group. At week 24, patients experienced mean increases of 95, 78, and 6 cells/mm^3 in the indinavir-zidovudine-lamivudine, indinavir, and zidovudine-lamivudine groups, respectively. The adjusted mean increases ($\pm$SE) in CD4 cells through week 24 (as measured by the AUCMB) for the respective groups were 61.3 $\pm$ 4.5, 59.9 $\pm$ 4.6, and 6.8 $\pm$ 4.6 cells/mm^3. The increases in the indinavir-zidovudine-lamivudine and indinavir groups were significantly greater ($P < .001$) than in the zidovudine-lamivudine group. The difference between the indinavir-zidovudine-lamivudine and indinavir groups was not significant ($P = .812$). In an analysis of data available for 67 patients through week 84, the observed mean increase in CD4 cells was 201 $\pm$ 14.4 cells/mm^3 for subjects randomized to receive indinavir-zidovudine-

lamivudine. In an intention-to-treat analysis, the estimated mean change was 159 ± 8.3 cells/mm^3.

Progression to clinical events. Thirty-six patients (11%) experienced ⩾1 confirmed clinical event: 11 in the indinavir-zidovudine-lamivudine group, 10 in the indinavir group, and 15 in the zidovudine-lamivudine group. Two patients in the indinavir group and 3 in the zidovudine-lamivudine group had a second confirmed event at a later date. The most common primary events were *Pneumocystis carinii* pneumonia (9 patients) and cytomegalovirus retinitis (5 patients). There were no significant differences between the treatment groups in the time to progression to an AIDS-defining illness or death. The estimated hazard ratio comparing indinavir-zidovudine-lamivudine with zidovudine-lamivudine was 0.70 (95% CI, 0.32–1.53); for comparison of indinavir with zidovudine-lamivudine, it was 0.62 (95% CI, 0.28–1.40).

Five of the 11 patients in the indinavir-zidovudine-lamivudine group who experienced a clinical event did so during the first 2 weeks of the study. During the first 8 weeks, 7 patients in each of the indinavir-zidovudine-lamivudine and zidovudine-lamivudine groups and 4 patients in the indinavir group had clinical events.

Mortality. Four patients died during the study: none in the indinavir-zidovudine-lamivudine group, 3 in the indinavir monotherapy group, and 1 in the zidovudine-lamivudine group. Of the 4 patients who died, 2 died 4–8 weeks after discontinuation of the study drug.

Safety. For each treatment group, the overall occurrence of adverse events and discontinuations due to adverse events were similar. The only clinical adverse event that occurred significantly more frequently in both indinavir groups than in the zidovudine-lamivudine group was upper respiratory infection. Ten (9.3%) patients in the indinavir monotherapy group and 4 (3.7%) in the indinavir-zidovudine-lamivudine group had adverse experiences associated with nephrolithiasis, compared with 3 (2.9%) in the zidovudine-lamivudine group. Only 1 patient (in the indinavir group) discontinued the study because of nephrolithiasis. The differences in the incidence of nephrolithiasis between the treatment groups were not significant.

Table 2. Week 84 serum human immunodeficiency virus (HIV) RNA levels for patients initially randomized to indinavir-zidovudine-lamivudine.

	<500 copies/mL		<50 copies/mL	
Analysis	*n*/*N* (%)	95% CI	*n*/*N* (%)	95% CI
Observed data	48/64 (75%)	(62%–85%)	37/63 (59%)	(46%–71%)
Model based	— (52%)	(42%–62%)	— (41%)	(32%–51%)
Withdrawal = failure	48/107 (45%)	(35%–55%)	37/106 (35%)	(26%–45%)

NOTE. One patient with HIV RNA <500 copies/mL did not have more sensitive assay done and is not included in <50 copies/mL analysis. *n*, no. of patients with HIV RNA <500 (50) copies/mL; *N*, no. of patients with measurements for observed data analysis; withdrawal = failure also includes patients who withdrew. CI, confidence interval.

Table 3 shows the proportion of patients in each treatment group with laboratory abnormalities for which there were significant differences. Total bilirubin levels of ⩾2.5 mg/dL and elevated triglycerides >750 mg/dL were more common in the indinavir treatment groups than in the zidovudine-lamivudine group. Decreased hemoglobin (<10 g/L) and neutrophil levels (<1000 and <500 cells/μL) were more common in the zidovudine-lamivudine group than in the indinavir treatment groups.

Discussion

This study is one of the first to focus on the use of triple therapy in patients with advanced HIV infection, as evidenced by ⩽50 CD4 cells/mm^3 (mean, 18) and extensive prior antiretroviral therapy. Even in this difficult-to-treat patient population, indinavir-zidovudine-lamivudine resulted in the suppression of serum HIV-1 RNA levels to <500 copies/mL in the majority of patients over a 24-week period.

The suppression of HIV-1 RNA levels for the indinavir-zidovudine-lamivudine group was both substantial and durable. More than 50% of patients had serum HIV-1 RNA levels decline to <500 copies/mL by week 8. In an analysis using ob-

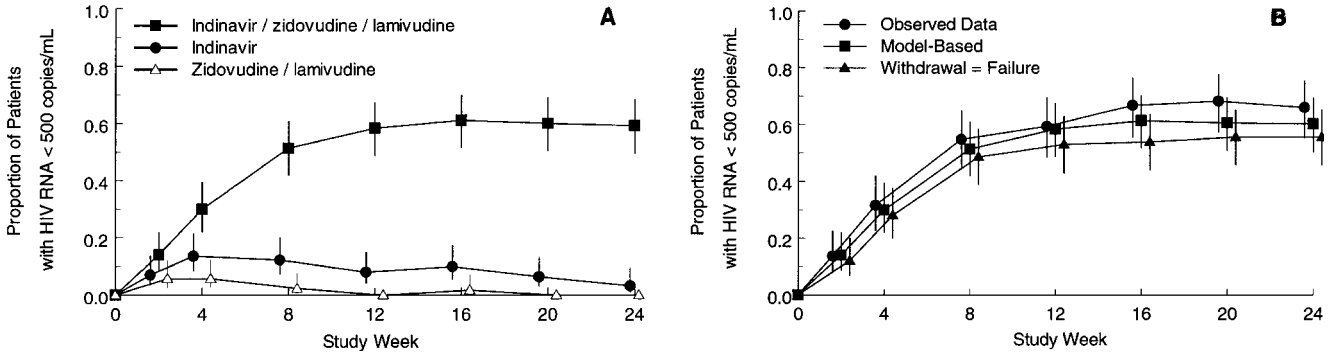

Figure 2. Proportion of patients with serum human immunodeficiency virus (HIV) RNA <500 copies/mL. *A,* Model-based estimates for 3 treatment groups. *B,* Results based on observed data, model-based analysis, and withdrawal-equals-failure analysis for subjects in indinavir-zidovudine-lamivudine group. Bars are 95% confidence intervals.

served data at week 24, 66% of the patients with HIV-1 RNA measurements had levels <500 copies/mL and 54% had levels <50 copies/mL. In a model-based intention-to-treat analysis, the estimated proportion of patients with HIV-1 RNA levels <500 copies/mL after 24 weeks was 60%. Extended follow-up of this cohort through week 60 and at week 84 suggests that this degree of HIV RNA suppression has been maintained [8].

An early decrease in serum HIV-1 RNA was also observed in the indinavir and zidovudine-lamivudine groups but was not sustained. The average change from baseline for serum viral RNA was significantly greater for the indinavir-zidovudine-lamivudine group, compared with the other 2 groups. The average change from baseline for the indinavir group, however, was not significantly different from that for the zidovudine-lamivudine group.

Elevations in CD4 cell counts were demonstrated in both indinavir treatment groups. These elevations persisted throughout the study period. The maximum effect in the zidovudine-lamivudine group was seen early and was both minimal and transient. The average change from baseline in CD4 cells was significantly greater for each of the indinavir treatment groups, compared with the zidovudine-lamivudine group. However, there was not a significant difference between the indinavir-zidovudine-lamivudine group and the indinavir group with regard to CD4 cell changes.

These results demonstrate that persons with advanced AIDS can have substantial responses to indinavir-zidovudine-lamivudine therapy. Patients receiving this 3-drug combination received 2 potent antiretroviral agents that had not been used previously in their treatment regimen.

Patients receiving indinavir alone had an early 1 log decline in serum HIV-1 RNA, which began to diminish by week 8. Despite this unsustained serum HIV-1 RNA response, persistent increases in CD4 cells were observed. The reasons for the discordance between sustained CD4 cell increases and transient serum HIV-1 RNA responses in the indinavir monotherapy group are unclear, but similar discordances have also been observed by others [9]. These results confirm the observation that persons receiving an indinavir treatment regimen maintain substantial increases in CD4 cells even after loss of initial viral RNA response.

Clinical progression, defined as the first occurrence of an AIDS-defining illness or death, occurred in 11% of patients during the 24 weeks of the study. The differences among the treatment groups in time to progression were not significant, but the study was not powered to detect differences in clinical efficacy. Thus, this study cannot directly demonstrate that the antiretroviral effect provides clinical benefit, although this was shown in a large clinical end-point study using the same regimen [1].

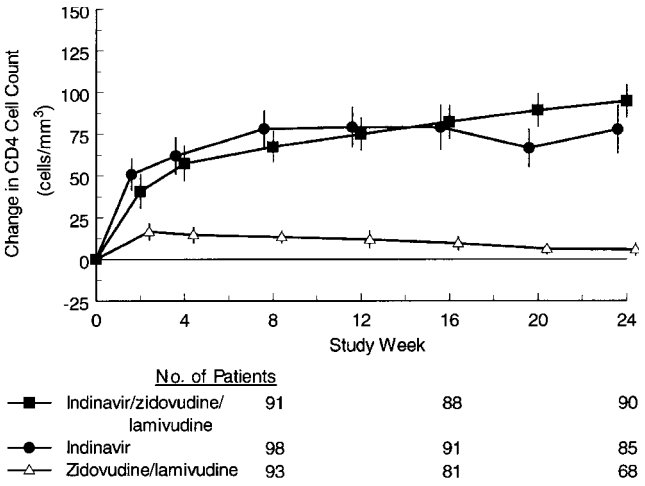

Figure 3. Mean changes from baseline in CD4 cell count based on observed data for patients with ≤50 CD4 cells/mm^3 at baseline. Bars are 95% confidence intervals.

The adverse events observed in this study were similar to those observed in other indinavir studies, with the exception of elevated triglycerides [1, 2, 10–12]. In this study, elevated triglycerides were observed more often in the indinavir groups. It is possible that persons with advanced HIV infection who are on multiple concomitant medications are more susceptible to this complication. Zidovudine-associated hematologic toxicity (anemia, neutropenia) was diminished in the 3-drug group, perhaps because of better control of underlying HIV infection.

Twenty-two percent of subjects discontinued the study prior to completing 24 weeks. The study began enrolling patients in August 1995 prior to approval and widespread availability of indinavir and lamivudine. As these drugs became available, the

Table 3. Laboratory abnormalities.

Laboratory abnormality	Indinavir-zidovudine-lamivudine (n = 108)	Indinavir (n = 107)	Zidovudine-lamivudine (n = 105)
Hemoglobin <10 g/L	14/108 (13.0)	12/106 (11.3)	29/105 (27.6)[a,b]
Neutrophils <1000 cells/mL	25/107 (23.4)	12/106 (11.3)[c]	60/105 (57.1)[a,b]
Neutrophils <500 cells/mL	4/107 (3.7)	0/106 (0.0)	19/105 (18.1)[a,b]
Total serum bilirubin ≥2.5 mg/dL	20/108 (18.5)	8/106 (7.5)[c]	0/105 (0.0)[a,b]
Triglycerides >750 mg/dL	7/108 (6.5)	13/106 (12.3)	0/105 (0.0)[b,c]

NOTE. N, total no. of patients in treatment group. Data are no. of patients with abnormality/no. of patients with laboratory test (%).

[a] Significantly different from indinavir-zidovudine-lamivudine ($P \leq .01$) by Fisher's exact test.

[b] Significantly different from indinavir ($P \leq .01$) by Fisher's exact test.

[c] Significantly different from indinavir-zidovudine-lamivudine ($P \leq .05$) by Fisher's exact test.

proportion of patients who discontinued the study increased. In addition, although patients and investigators did not have access to the HIV-1 RNA results, which were considered experimental at the start of the study, they did have access to all other laboratory results, including CD4 cell counts.

The overall results should not be affected by the dropout rate, since significantly more subjects dropped from the zidovudine-lamivudine group, the arm that showed the least efficacy, than from the indinavir groups. However, dropouts from the study result in missing data that can make study results difficult to interpret. This is particularly apparent in presenting the proportion of patients with HIV RNA of <500 copies/mL, where missing data may disproportionately decrease the denominator leading to an artifactually high proportion. In order to address these issues, we used a model-based approach using GEE methodology for longitudinal data to estimate this proportion [7]. Patients who discontinued study participation because of adverse experiences or clinical events were counted as failures at subsequent time points. The proportion of patients with suppression of RNA was estimated from the available data and then adjusted based on the correlations between these data and the available data for patients who discontinued for other reasons or who missed a scheduled visit. This allows for an intention-to-treat analysis, since data for all randomized patients are used. In this study, the model-based approach resulted in an estimated proportion of 60% of patients receiving triple combination therapy having HIV RNA <500 copies/mL at week 24, whereas the observed proportion was 66%. The issue of dealing with missing data is important in presenting data from clinical trials, and this model-based approach may provide an alternative approach for presenting such information.

This study extends the favorable results of combination therapy with indinavir-zidovudine-lamivudine to persons with advanced AIDS and shows that such persons can tolerate and benefit from this 3-drug combination therapy. The results also support the concept of earlier versus later therapy, since the overall benefits, with respect to numbers of patients obtaining and maintaining undetectable HIV RNA levels, were muted when compared with a similar trial in patients with earlier disease [2, 3]. In treating HIV-infected persons, the best results are obtained when several potent new drugs are started together relatively early in the course of infection. These data, along with other recent studies, show that, with potent combination therapy, many HIV-infected persons can expect to achieve long-term suppression of serum viral RNA. The challenge we now face is maintaining viral suppression with regimens that are generally well tolerated and easy to use.

Protocol 039 Study Group Members

We gratefully acknowledge the following investigators and their staff who participated in this study and contributed to the information presented: Ellen Yetzer (Pacific Oaks Research, CA), Kelly Henning (Thomas Jefferson University, Philadelphia), Ann Collier (University of Washington, Seattle), Paul Sax (Brigham and Women's Hospital, Boston), Stephen Boswell (Fenway Community Health Center, MA), James Kahn (University of California, San Francisco), Thomas Merigan, (Stanford University, CA), Donna Mildvan (Beth Israel Medical Center, New York), Robert Murphy (Northwestern University, Chicago), Kent Sepkowitz (Memorial Sloan-Kettering Cancer Center, New York), Melanie Thompson (AIDS Research Consortium of Atlanta), Daniel Vittecoq (Hopital Paul Brousse, Villejuif, France), Willy Rozenbaum (Hopital Rothschild, Paris, France), Stephen Adelstein (Royal Prince Alfred Hospital, Campertown, Australia), and Christos Tsoukas (Montreal General Hospital).

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