Simultaneous vs Sequential Initiation of Therapy With Indinavir, Zidovudine, and Lamivudine for HIV-1 Infection

100-Week Follow-up

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Context.—Combination antiretroviral therapy can markedly suppress human immunodeficiency virus (HIV) replication but the duration of HIV suppression varies among patients.

Objective.—To compare the antiretroviral effect of a 3-drug regimen started simultaneously or sequentially in patients with HIV infection.

Design.—A multicenter, randomized, double-blind study, modified after at least 24 weeks of blinded therapy to provide open-label 3-drug therapy with follow-up through 100 weeks.

Setting.—Four clinical research units

Patients.—Ninety-seven patients with HIV infection who had taken zidovudine for at least 6 months with serum HIV RNA level of at least 20,000 copies/mL and CD4 cell count of 0.05 to 0.40 \times 10^9/L.

Interventions.—Patients were initially randomized to receive 1 of 3 antiretroviral regimens: indinavir, 800 mg every 8 hours; zidovudine, 200 mg every 8 hours and lamivudine, 150 mg every 12 hours; or all 3 drugs. After at least 24 weeks of blinded therapy, all patients received open-label 3-drug therapy.

Main Outcome Measures.—Antiretroviral activity was assessed by changes in HIV RNA level and CD4 cell count from baseline. Data through 100 weeks were summarized.

Results.—Simultaneous initiation of indinavir, zidovudine, and lamivudine suppressed HIV RNA in 78% (25/32) of contributing patients to less than 500 copies/mL and CD4 cell count of 0.05 to 0.40 \times 10^9/L above baseline at 100 weeks. When these 3 drugs were initiated sequentially, only 30% to 45% of contributing patients (10 of 33 in the zidovudine-lamivudine group and 13 of 29 in the indinavir group, respectively) had a sustained reduction in HIV RNA to less than 500 copies/mL, and median CD4 cell count increased to 0.101 to 0.163 \times 10^9/L above baseline at 100 weeks.

Conclusions.—A 3-drug combination of indinavir, zidovudine, and lamivudine started simultaneously has durable antiretroviral activity for at least 2 years. Sequential initiation of the same 3 drugs is much less effective.
their original regimens for 24 to 52 weeks before receiving open-label 3-drug therapy with indinavir, zidovudine, and lamivudine. After changing to open-label 3-drug therapy, patients continued to be followed for 100 weeks from the time of initial randomization in an ongoing study. This provided an opportunity to compare the use of 3-drug antiretroviral therapy started simultaneously or sequentially. The magnitude and duration of HIV suppression and increase in CD4 cell count, as well as development of drug-resistance mutations, were compared between simultaneous and sequential triple-therapy groups.

**METHODS**

The study was originally designed as a randomized, double-blind comparison of 3 oral antiretroviral regimens: indinavir (Crixivan, Merck, West Point, Pa), 800 mg every 8 hours (indinavir monotherapy group); zidovudine (Retrovir, Glaxo-Wellcome, Research Triangle Park, NC), 200 mg every 8 hours, combined with lamivudine (Epivir, Glaxo-Wellcome), 150 mg every 12 hours (zidovudine/lamivudine group); or all 3 drugs together at the same doses (3-drug group). The study patients were adults with HIV infection who had taken zidovudine for at least 6 months but had not taken lamivudine or any protease inhibitor, with serum HIV RNA levels of at least 20,000 copies/mL (Amplicor HIV Monitor Test, Roche Diagnostic Systems, Branchburg, NJ) and CD4 cell counts between 0.05 and 0.40 × 10⁹/L at screening. Randomization followed a permuted block design stratified by site and CD4 cell count (either 0.050-0.250 × 10⁹/L or 0.251-0.400 × 10⁹/L). Patients were enrolled between April and December 1995.

The planned duration of the original blinded study was 52 weeks, but because of preliminary findings of superior activity of the 3-drug regimen, the study design was amended to provide open-label 3-drug therapy for all patients after at least 24 weeks of blinded, randomized therapy. The 3-drug group continued taking all 3 antiretroviral agents, while zidovudine and lamivudine were added by the indinavir monotherapy group, and indinavir was added by the zidovudine-lamivudine group. Blinding of the original treatment assignment was maintained through March 1997. After initiating open-label 3-drug therapy, patients have been monitored for 100 weeks or more from time of initial randomization (Figures 1 and 2). Results from the first 100 weeks are reported herein. The study and the amendment were approved by the internal review boards at each site, and all patients gave written informed consent.

Patients had study visits weekly for the first 4 weeks, every 2 weeks through week 16, every 4 weeks through week 52, and every 8 weeks through week 100. At baseline and at each visit, medical history was taken, a physical examination performed, and standardized laboratory tests conducted. Serum was processed, stored at −70°C, and subsequently assayed for HIV RNA (Amplicor assay). The assay lower limit of quantification was 500 HIV RNA copies/mL. Assay values were reported as numerical values greater than or equal to 500 copies/mL, “less than 500 copies/mL,” or “negative” if an amplification signal above background was not detected. Plasma samples from week 52 were assayed and for all patients (n = 47) whose serum HIV RNA value was less than 500 copies/mL, the plasma HIV RNA value was also less than 500 copies/mL. Samples with less than 500 copies/mL were assayed with an investigational ultrasensitive polymerase chain reaction assay with a consistent cutoff of detection of about 50 copies/mL of HIV RNA, as described.1,11 T-lymphocyte subgroups were quantified using flow cytometry.1

Genotypic analysis of serum viral RNA was done as described.6 Amino acid substitutions present in 50% or more of
independent molecular clones were identified. Substitutions in reverse transcriptase at positions 41, 67, 70, 215, and 219 were scored as correlates of zidovudine resistance.1,11 Substitutions in reverse transcriptase at position 184 served as a marker for lamivudine resistance.12,14 And substitutions in protease at residues 10, 20, 24, 46, 54, 71, 82, 84, and 90 were scored as correlates of indinavir resistance.9

Statistical Analysis

Virologic failure was defined as never achieving an HIV RNA level less than 500 copies/mL, or for those patients who achieved an HIV RNA level less than 500 copies/mL, the occurrence of 2 consecutive HIV RNA levels of at least 500 copies/mL. Time to virologic failure was defined as the number of weeks of therapy prior to first occurrence of 2 consecutive HIV RNA levels of at least 500 copies/mL. For patients who never had an HIV RNA level less than 500 copies/mL, virologic failure occurred at week 0. Number of days of missed doses was the sum of number of days the patient was not taking the study drug and the number of days the patient took less than the full prescribed daily dose.

The primary measure of antiretroviral drug activity was the proportion of patients with serum HIV RNA levels less than 500 copies/mL by the Amplicor assay. Proportion of patients with serum HIV RNA levels less than 50 copies/mL was also calculated; in these calculations, it was assumed that those with at least 500 RNA copies/mL by standard assay had at least 50 copies/mL.

Analyses were performed on an intention-to-treat basis. Using only observed data may overestimate the proportion of patients with an HIV RNA level below the specified level, as patients who were virologic failures may be more likely to discontinue the study. Therefore, patients discontinuing the study for therapy-related reasons (eg, increase in viral load determinations) and those with imputed values were included in all analyses. Median increase from baseline in HIV RNA levels (based on the Amplicor assay) and CD4 cell counts were calculated. Patients discontinuing the study for therapy-related reasons were considered to have RNA levels greater than or equal to 500 copies/mL at time points subsequent to their discontinuation. Median increase in CD4 cell counts was calculated for those with HIV RNA levels less than 500 copies/mL by standard assay at 100 weeks.

RESULTS

Study Patients

Ninety-seven patients with baseline median HIV RNA level of 43,190 copies/mL (range, 4,900-252,070 copies/mL) and CD4 cell count of 0.144 × 10^9/L (range, 0.035-0.480 × 10^9/L) were enrolled. Baseline characteristics were similar across the 3 original treatment groups. Patients received open-label 3-drug therapy after a median of 40 weeks of blinded, randomized therapy (range, 24-52 weeks). Of the 97 enrolled patients, 92 completed 24 weeks, 87 completed 52 weeks, and 70 completed 100 weeks of study treatment.

Reasons for early discontinuation are listed in Figure 2. Fewer patients discontinued from the group originally randomized to receive 3-drug therapy than from the other 2 groups. The most common reason for early discontinuation was increase in HIV RNA levels (16 patients); more patients randomized to the indinavir monotherapy and the zidovudine-lamivudine groups discontinued for this reason than in the 3-drug group.

Compliance, as assessed by median percentage of days on which the recommended dosage of study medications was taken, was similar among the 3 treatment groups during both open-label and blinded study periods, and exceeded 91% during both study periods (data not shown).

All therapies were generally well tolerated; 1 patient in each group discontinued study medications for a clinical or laboratory adverse event. Two deaths occurred, both in patients originally randomized to receive zidovudine and lamivudine (Figure 2). One death was due to Pneumocystis carinii pneumonia; this was the only AIDS-defining illness occurring in any group during 100 weeks of follow-up. The other death was caused by myocardial infarction.

Antiretroviral Activity of Simultaneously Initiated 3-Drug Therapy: Indinavir, Zidovudine, and Lamivudine

The group originally randomized to receive simultaneously initiated 3-drug therapy continued to receive the same 3 drugs throughout 100 weeks of follow-up. In this group, the median decrease in serum HIV RNA level from baseline was 2.0 log_{10}, by week 8, which was sustained through week 100 (Figure 3). In this group, 28 (88%) of 32 contributing patients had HIV RNA levels less than 500 copies/mL at week 16, and 25 (78%) of 32 at week 100 (Figure 4, A). Similar virologic responses were shown with the investigational ultrasensitive assay; 21 (66%) of 32 contributing patients had HIV RNA levels less than 50 copies/mL at week 24, and 21 (66%) of 32 at week 100 (Figure 4, B). Median increase in CD4 cell count above baseline in this group was 0.127 × 10^9/L at week 24, 0.155 × 10^9/L at week 52, and 0.209 × 10^9/L at 100 weeks (Figure 5).

In those consistently achieving a serum viral RNA level less than 500 copies/mL, the pattern of results was variable with the investigational ultrasensitive assay, which has a consistent detection cutoff of about 50 copies/mL (data not shown). Most patients had more than 1 HIV RNA
level of at least 50 copies/mL during the period that their HIV RNA levels were consistently less than 500 copies/mL. Some had 2 or 3 consecutive HIV RNA levels of at least 50 copies/mL followed by a return to less than 50 copies/mL.

Seven of 33 patients originally randomized to receive simultaneous 3-drug therapy had HIV RNA values greater than 500 copies/mL by week 100 (Table). Four of these virologic failures occurred during the first 20 weeks of the study and 3 others occurred at 32, 40, and 100 weeks of follow-up. Review of these cases revealed that 1 patient never had a reduction of HIV RNA to less than 500 copies/mL, 1 had intestinal amebiasis 2 months prior to virologic failure, and another on 56 (25%) of 224 days prior to virologic failure. No obvious reason for virologic failure was identified in the other 3 patients, including the patient in whom therapy failed at 100 weeks. All 3 patients in whom therapy failed after week 20 had at least 1 serum RNA level less than 50 copies/mL.

**Antiretroviral Activity of Sequentially Initiated 3-Drug Therapy**

Patients randomized to the indinavir monotherapy and zidovudine-lamivudine groups crossed over to open-label 3-drug therapy (Figure 1). Results for the first 24 weeks of study were obtained while patients were on original randomized regimens. Results obtained between weeks 24 and 52 reflect patients either on their original regimen or the open-label 3-drug regimen. All crossed over to open-label 3-drug therapy by week 52.

Indinavir, Followed by Addition of Zidovudine and Lamivudine.—Over the first 24 weeks, patients received original blinded therapy. Patients randomized to the indinavir monotherapy group had a maximal median decrease in HIV RNA from baseline of 1.7 log₁₀ at week 12 and the median decrease rose to 1.0 log₁₀ below baseline at week 24 (Figure 3). In this group, 13 (43%) of 30 contributing patients had reductions in HIV RNA to less than 500 copies/mL and 9 (30%) of 30 to less than 50 copies/mL at week 24 (Figure 4). Median increase in CD4 cell count in this group was $0.111^{3}10^9/L$ over baseline at 24 weeks (Figure 5).

After patients added zidovudine-lamivudine, maximum additional median decrease in HIV RNA was 0.6 log₁₀ (data not shown). There was a 1.4-log₁₀ median decrease in HIV RNA from baseline at week 52 and at week 100 (Figure 3). Thirteen (45%) of 29 contributing patients in this group had HIV RNA levels less than 50 copies/mL at week 100, which is similar to the proportion prior to the addition.
of zidovudine-lamivudine (Figure 4, A). After adding zidovudine-lamivudine to indinavir, the median increase in CD4 cell count was \(0.127 \times 10^9/L\) above baseline at week 52 and \(0.163 \times 10^9/L\) above baseline at week 100 (Figure 5).

**Zidovudine and Lamivudine, Followed by Addition of Indinavir.**—Patients originally randomized to the 2-drug zidovudine-lamivudine combination had a maximal median decrease of HIV RNA from baseline of 1.4 \(\log_{10}\) at week 2, and the median decrease rose to 0.6 \(\log_{10}\) below baseline at week 24 (Figure 3). No patients taking zidovudine-lamivudine had HIV RNA reductions to less than 500 copies/mL at week 24 (Figure 4, A). Median increase in CD4 cell count was \(0.013 \times 10^9/L\) above baseline in this group at 24 weeks (Figure 5).

After patients added indinavir, maximum additional median decrease in HIV RNA was 1.5 \(\log_{10}\) (data not shown). There was a sustained median decrease in HIV RNA from baseline of 1.5 \(\log_{10}\) at week 52 followed by an increase to 1.3 \(\log_{10}\) below baseline at week 100 (Figure 3). In this group, 10 (30%) of 33 contributing patients had HIV RNA levels less than 500 copies/mL at week 100 (Figure 4, A). Median increases above baseline in CD4 cell counts in this group were \(0.106 \times 10^9/L\) above baseline at week 52, and \(0.101 \times 10^9/L\) at week 100 (Figure 5).

**Simultaneous vs Sequential Initiation of 3-Drug Therapy**

The HIV RNA and CD4 cell count responses were compared among the patients originally randomized to 3-drug therapy, those who added zidovudine-lamivudine to indinavir, and those who added indinavir to zidovudine-lamivudine. In this way, simultaneous initiation of indinavir, zidovudine, and lamivudine could be compared with sequential initiation of the same 3 drugs.

At 100 weeks, proportions of patients in the simultaneous 3-drug group with HIV RNA levels less than 500 (\(P = .006\)) and 50 (\(P < .05\)) copies/mL, changes in HIV RNA levels from baseline (\(P = .004\)), and changes in CD4 cell count above baseline (\(P < .05\)) were statistically significantly greater than those in either of the sequential 3-drug therapy groups. There was no difference in changes from baseline in HIV RNA level (\(P = .71\)) or CD4 cell count (\(P = .54\)) between the 2 sequential therapy groups at 100 weeks.

**Genotypic Analysis of Viral Resistance**

To better understand the reasons why simultaneous 3-drug therapy was superior to sequential therapy, detailed genotypic analysis of viral resistance markers was undertaken. Analyses were performed on specimens obtained on entry into the study and at time of crossover to open-label 3-drug therapy. Consistent with the enrollment requirement that patients had received prior zidovudine therapy, 75 (82%) of 91 patients at study entry had circulating virus with substitutions in the reverse transcriptase gene associated with zidovudine resistance. \(^8,9\) These patients were evenly distributed among the 3 study arms. Even though no patient was to have taken prior lamivudine therapy, 1 patient at study entry yielded virus with the M184 mutation responsible for lamivudine resistance, \(^12\); this patient was randomized to the indinavir monotherapy group. None of the patients at study entry had virus with substitutions in the protease gene associated with indinavir resistance. \(^9\)

Regarding the indinavir monotherapy group at the time of crossover to open-label 3-drug therapy, 22 of 28 patients yielded amplifiable viral RNA from serum. Of these, 17 (77%) had reverse transcriptase substitutions associated with zidovudine resistance, none had the substitution associated with lamivudine resistance, and 14 (64%) had substitutions associated with lamivudine resistance.
in the protease gene associated with indinavir resistance. The patient who had evidence of lamivudine resistance at study entry did not have amplifiable viral RNA from serum at time of crossover.

Of 32 patients in the original zidovudine-lamivudine group with amplifiable viral RNA from serum at time of open-label crossover, 26 (81%) had evidence of zidovudine resistance, 30 (94%) had evidence of lamivudine resistance, and none had evidence of indinavir resistance.

Genotypic analyses were also done at the time of virologic failure in the 7 patients originally randomized to simultaneous 3-drug therapy. Five patients had evidence of zidovudine resistance, all had substitutions associated with lamivudine resistance, and 5 patients had acquired substitutions associated with indinavir resistance (Table). Genetic patterns of resistance were consistent with those previously described for indinavir, zidovudine, and lamivudine.9-14

**COMMENT**

The effect of the 3-drug combination of indinavir, zidovudine, and lamivudine initiated simultaneously was a reduction in viral load in 78% of contributing patients to less than 500 copies/mL and in 66% of contributing patients to less than 50 copies/mL for 2 years. Most patients with this degree of viral load suppression at week 24 continued to have viral load suppression at week 100. At 100 weeks of follow-up, patients had a median increase in CD4 cell count of 0.209 × 10^9/L above baseline. This study has the longest follow-up to date of a combination antiretroviral regimen producing this magnitude of sustained viral load reductions, and the results imply that most patients with suppression of viral load to less than 500 copies/mL by week 24 will have continued suppression through at least 2 years of follow-up on this regimen.

The durable antiretroviral effect associated with simultaneous initiation of the 3-drug regimen likely results from the ability of the combination to suppress emergence of drug-resistant HIV variants. Most patients initiating simultaneous 3-drug therapy not only had reductions in HIV RNA below 500 copies/mL, but also below 50 copies/mL. It has been shown that a greater therapy-induced reduction of viral load corresponds with a more durable antiretroviral response.15,16 It is important to note, however, that it was common to find isolated serum viral RNA levels of at least 50 copies/mL even in those patients who consistently achieved a serum viral RNA level less than 500 copies/mL.

In contrast to initiating the 3 drugs simultaneously, when sequential 3-drug combination therapy was used, either adding indinavir to regimens of patients already taking zidovudine and lamivudine, or adding zidovudine and lamivudine for those already taking indinavir, an inferior antiretroviral effect was seen with only 30% to 45% of patients having sustained reductions in viral load levels to less than 500 copies/mL at 100 weeks. The marked sustained antiretroviral response seen in the original 3-drug group was likely due to the fact that none of the patients had prior use of lamivudine or any protease inhibitor, and when the study began, the drugs were begun simultaneously.

In the current study, detailed genotypic analysis of viral resistance helped explain the mechanism of failure of sequential antiretroviral therapy. Of the group originally randomized to zidovudine-lamivudine, no patient experienced a sustained decrease in HIV RNA to less than 500 copies/mL, and by the time of open-label crossover, 94% of patients had developed virus with the reverse transcriptase substitution at position 184 associated with lamivudine resistance.17,18 When this group added indinavir to zidovudine-lamivudine, the proportion of patients with HIV RNA levels reduced to less than 500 copies/mL at week 100 was similar to that observed in the indinavir monotherapy group prior to crossover. Similarly, of the group originally treated with indinavir monotherapy, at the time of crossover to open-label 3-drug therapy, 64% of patients had selected for virus with substitutions associated with indinavir resistance. Consequently, sequential addition of zidovudine and lamivudine to this group occurred in the presence of considerable indinavir resistance.

The practice of adding antiretroviral agents sequentially after an initial antiretroviral regimen fails is similar to using monotherapy. Monotherapy, even with a potent agent, is commonly associated with subsequent virologic failure due to emergence of drug-resistant virus.19-22 In contrast, simultaneously adding at least 2 new potent antiretroviral agents inhibits HIV replication more effectively and thereby inhibits emergence of drug-resistant mutant viruses, increasing the likelihood that antiretroviral effect is maintained.

Use of sequential monotherapy with antiretroviral agents has occurred commonly in clinical practice as a consequence of the sequential approval of drugs for clinical use. Lamivudine was approved by the US Food and Drug Administration in December 1995, and ritonavir and indinavir were approved in March 1996. Clinicians with limited therapeutic options often added the drugs sequentially as they became available. In their retrospective chart review, Deeks et al found that for most patients in whom combination antiretroviral therapy failed, a protease inhibitor had been added to their regimen without changing other antiretroviral drugs.

In the patient subset for whom a new nucleoside analogue together with a protease inhibitor were simultaneously added, about 80% had reductions in HIV RNA levels to less than 500 copies/mL at 24 weeks,23 similar to our findings. The use of sequential antiretroviral therapy has likely played a major part in causing drug failure in community settings.

The simultaneous initiation of indinavir, zidovudine, and lamivudine was associated with an initial rapid increase in CD4 cell count over the first 4 to 12 weeks of therapy. After the initial rise, CD4 cell count then continued to increase steadily for at least 2 years. The CD4 response in the sequential 3-drug groups was inferior to that seen with the simultaneous 3-drug group. Several groups have noted not only increases in CD4 cell numbers, but also associated returns in immunologic function with other potent antiretroviral therapy regimens over the first year of therapy.24-26 In persons with diagnoses of autoimmune disease or cancer who have received intensive chemotherapy or radiation therapy, CD4 cell counts recover slowly and may take 3 years or more for normal levels to be attained.27-30 Further study is required to determine the level of immunologic restoration that is ultimately possible with potent antiretroviral therapy administered over the course of years.

There is evidence that patients with more advanced HIV disease than in those in our study (ie, higher viral load or lower CD4 cell count at baseline) may have less consistent responses to 3-drug antiretroviral regimens, with fewer patients having sustained viral load suppression.29,31,32 Patient populations with more advanced HIV disease may require more intensive antiretroviral therapy. Studies of 4-drug combinations using combinations of protease inhibitors and other agents are in progress. Results from the current study support the concept that antiretroviral treatment initiated by patients in earlier stages of HIV disease may have a greater likelihood of sustained beneficial virologic effects. Recent reports of the isolation of replication-competent HIV from lymphocytes of patients taking antiretroviral therapy with prolonged viral suppression...
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References