

3-Year Suppression of HIV Viremia with Indinavir, Zidovudine, and Lamivudine

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Background: Antiretroviral regimens containing HIV protease inhibitors suppress viremia in HIV-infected patients, but the durability of this effect is not known.

Objective: To describe the 3-year follow-up of patients randomly assigned to receive indinavir, zidovudine, and lamivudine in an ongoing clinical trial.

Design: Open-label extension of a randomized, double-blind study.

Setting: Four clinical research units.

Patients: 33 HIV-infected, zidovudine-experienced patients with serum HIV RNA levels of at least 20 000 copies/mL and CD4 counts ranging from 50 to 400 cells/mm³.

Intervention: Indinavir, zidovudine, and lamivudine.

Measurements: Safety assessments, HIV RNA levels, CD4 cell counts, and genotypic analyses.

Results: After 3 years of follow-up, 21 of 31 contributing patients (68% [95% CI, 49% to 83%]) had serum viral load levels less than 500 copies/mL. Twenty of 31 (65% [CI, 45% to 80%]) had levels less than 50 copies/mL. The median increase in CD4 count from baseline was 230 cells/mm³ (interquartile range, 150 to 316 cells/mm³). Nephrolithiasis occurred in 12 of 33 patients (36%).

Conclusion: A three-drug regimen of indinavir, zidovudine, and lamivudine suppressed viremia in two thirds of patients for at least 3 years.

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The use of antiretroviral therapy that includes an HIV protease inhibitor has markedly decreased morbidity and mortality in HIV-infected persons (1–3). In addition, antiretroviral combination therapy that includes a protease inhibitor can suppress viral load levels for up to 2 years (4–8). However, the long-term durability and toxicity of these regimens are unknown. We present results after 3 years of follow-up in patients who received three-drug therapy with indinavir, zidovudine, and lamivudine in a previously reported study (4, 5).

Methods

Study Design

The study was originally designed as a randomized, double-blind comparison of three antiretroviral regimens: indinavir (Crixivan, Merck & Co., Inc., West Point, Pennsylvania), 800 mg every 8 hours; zidovudine (Retrovir, Glaxo Wellcome, Research Triangle Park, North Carolina), 200 mg every 8 hours, with lamivudine (EpiVir, Glaxo Wellcome), 150 mg every 12 hours; and all three drugs together at the same specified doses (4, 5). Patients were encouraged to drink at least 1.5 L of fluid per day. We report on the patients who were originally assigned to re-

ceive three-drug therapy. Institutional review boards at each site approved the study and amendments, and all patients gave informed consent.

Study Participants

Eligible patients were HIV-infected adults who had received at least 6 months of zidovudine therapy but had never taken lamivudine or an HIV protease inhibitor. Patients had serum viral load levels of at least 20 000 copies/mL (Amplicor HIV Monitor Test, Roche Diagnostic Systems, Branchburg, New Jersey) and CD4 counts between 50 to 400 cells/mm³ at screening.

Assessments

Patients had study visits at least every 4 weeks through week 52 and every 8 weeks through week 156. At baseline and at each visit, a history was taken, a physical examination was performed, and standardized laboratory tests were conducted without regard to food intake. Serum was processed, stored at –70 °C, and subsequently assayed for HIV RNA by using the Amplicor and ultradirect assays (4, 5). T-lymphocyte subgroups were quantified by using flow

cytometry. Genotypic analysis of serum HIV RNA was performed as described elsewhere (5).

Individual investigators graded adverse events according to standardized guidelines. A drug-related adverse event was one that the investigator assessed as possibly, probably, or definitely related to the study therapy. Nephrolithiasis was defined as the passing of macroscopic stones or gravel or flank pain with or without associated hematuria. During follow-up, investigators assessed lipodystrophy at one time point from October to December 1998 (after approximately 2.5 to 3.5 years of treatment). Patients were considered to have lipodystrophy if they had one or more of the following features without evidence of hypercortisolism: truncal or central obesity with or without thinning of the extremities; accumulation of body fat in the abdomen, the neck (buffalo hump), the retroperitoneum, the face, or the breasts; and accumulation or redistribution of body fat in some areas that was out of proportion to other body areas.

Statistical Analysis

Antiretroviral activity was assessed by calculating 1) the proportions (with 95% CIs) of patients whose HIV RNA levels were less than 500 copies/mL (Amplicor assay) and those whose HIV RNA levels were less than 50 copies/mL (ultradirect assay) and 2) the median changes (plus interquartile ranges) from baseline in \log_{10} HIV RNA levels (Amplicor assay) and CD4 cell counts over time. Analyses were performed on an intention-to-treat basis. Patients who withdrew early from the study were considered to have had virologic failure at subsequent time points, except for two patients who withdrew for reasons that were not related to therapy and had HIV RNA levels less than 500 copies/mL at the time of withdrawal, as described elsewhere (5). Because the analyses included patients with observed values and those with imputed values, the term *contributing patients* is used. Among patients with at least two measurements, those who never achieved an HIV RNA level less than 500 copies/mL were considered to have experienced virologic failure. Those who achieved an HIV RNA level less than 500 copies/mL were considered to have experienced virologic failure if they had two consecutive measurements of HIV RNA levels that were at least 500 copies/mL but did not have subsequent re-suppression while receiving the same three-drug regimen.

Role of the Study Sponsor

Employees of the industry sponsor participated in the study as co-investigators. After designing the study with the input of the other study investigators, these employees implemented the protocol and coordinated data collection and statistical analyses. All investigators interpreted the data, determined the content of the paper, and decided whether to submit the paper for publication.

Results

Study Participants

Originally, 33 patients were randomly assigned to receive three-drug therapy with zidovudine, lamivudine, and indinavir. Median age was 40 years (range, 30 to 62 years). Thirty-one patients (94%) were men, and 2 (6%) were women; 26 (79%) were white, 2 (6%) were African American, 3 (9%) were Latin American, and 2 (6%) were members of other racial or ethnic groups. At study entry, patients had taken zidovudine for a median of 28 months (range, 6 to 92 months) and had a median baseline serum HIV RNA level of 41 900 copies/mL (range, 7550 to 219 040 copies/mL) and a median baseline CD4 count of 133 cells/mm³ (range, 35 to 433 cells/mm³). Of the 33 patients, 12 (36%) discontinued therapy within 3 years: 7 because of increased viral load levels; 2 because of need for contraindicated medications (rifampin and cytotoxic chemotherapy); and 1 each because of nausea, patient request, and investigator recommendation after resolution of urinary tract obstruction. Nine patients experienced virologic failure (6 in the first year, 0 in the second year, and 3 in the third year).

Antiretroviral Activity

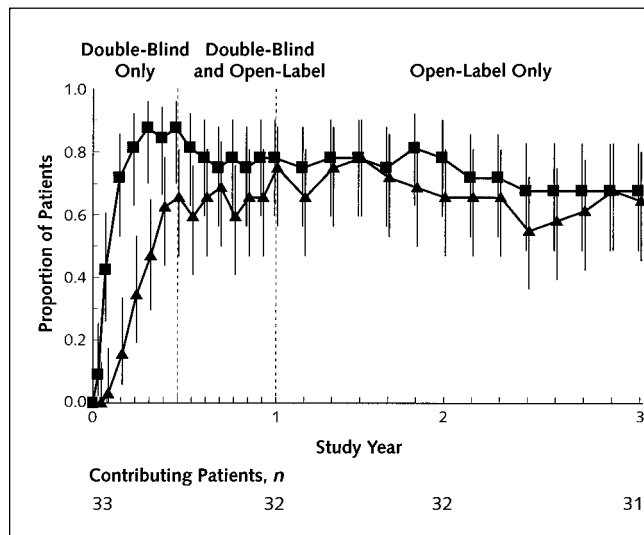
The percentages of contributing patients whose HIV RNA level decreased from baseline to less than 500 copies/mL and less than 50 copies/mL, respectively, were 78% (95% CI, 60% to 90%) and 75% (CI, 56% to 88%) at 1 year, 78% (CI, 60% to 90%) and 66% (CI, 47% to 81%) at 2 years, and 68% (CI, 49% to 83%) (21 of 31 patients) and 65% (CI, 45% to 80%) (20 of 31 patients) at 3 years (Figure 1). Patients experienced a median change in HIV RNA level from baseline of $-2.07 \log_{10}$ copies/mL (interquartile range, -2.39 to $-1.61 \log_{10}$ copies/mL) at 1 year, $-2.07 \log_{10}$ copies/mL (interquartile range, -2.40 to $-1.61 \log_{10}$ copies/mL) at 2 years, and $-1.99 \log_{10}$ copies/mL (interquartile range, -2.32 to $-1.31 \log_{10}$ copies/

mL) at 3 years (Figure 2). The median increase in CD4 counts from baseline was 155 cells/mm³ (interquartile range, 95 to 230 cells/mm³) at 1 year, 209 cells/mm³ (interquartile range, 117 to 339 cells/mm³) at 2 years, and 230 cells/mm³ (interquartile range, 150 to 316 cells/mm³) at 3 years (Figure 2).

Genotypic Analysis of Viral Resistance

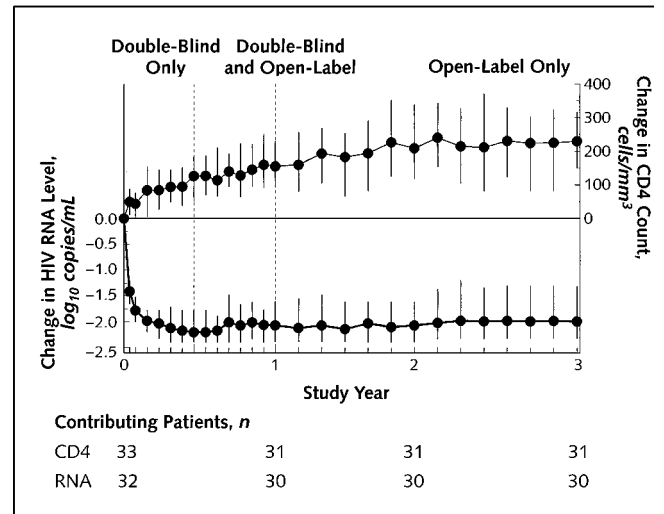
For the nine patients who experienced virologic failure by year 3, results of genotypic analyses performed at baseline and at the time of virologic failure were similar to the results of the 2-year analysis (5). Briefly, six patients had preexisting zidovudine resistance, as evidenced by the presence of the reverse transcriptase T215Y substitution combined with M41L (four patients), K70R (one patient), or D67N/K70R/K219Q (one patient). One patient developed zidovudine resistance (M41L), and all nine developed lamivudine resistance (M184V). Five patients acquired protease substitutions that were previously associated with indinavir resistance (9): M46L/V82A (four patients) and L90M (one patient). In two additional patients, evidence of new protease substitutions (L10V or L63P/S/A) appeared during treatment; however, the significance of sub-

Figure 1. Proportion of patients with serum HIV RNA levels less than 500 copies/mL and less than 50 copies/mL during 3 years of treatment with indinavir, zidovudine, and lamivudine.



Squares represent proportions with levels less than 500 copies/mL; triangles represent proportions with levels less than 50 copies/mL; error bars represent 95% CIs.

Figure 2. Median changes in serum HIV RNA level and CD4 cell count from baseline during 3 years of treatment with indinavir, zidovudine, and lamivudine.



Error bars represent the 25th and 75th percentiles.

stitutions at these two naturally occurring polymorphic sites is unclear.

Adverse Events

Four patients experienced a serious drug-related adverse event related to nephrolithiasis. Two of these patients experienced urinary tract obstruction, and one withdrew from the study 2 months after the adverse event resolved. Two of these patients also had other serious drug-related adverse events (pain and abdominal pain). In total, 12 of 33 patients (36%) had at least one episode of clinical nephrolithiasis during 3 years of treatment and 7 of 33 patients (21%) had more than one episode. Initial episodes of nephrolithiasis occurred from 24 weeks to 3 years of treatment. A total of 64.6 person-years of follow-up occurred before the first episode of nephrolithiasis or before censoring at 3 years. Therefore, the incidence of nephrolithiasis was 1.86 per 10 person-years of follow-up.

Of the 21 patients in active follow-up, 4 (19%) fulfilled the clinical definition of lipodystrophy. When random, nonfasting specimens obtained throughout the study were used, serum triglyceride levels greater than 8.47 mmol/L (750 mg/dL) were documented at least once in 8 of 33 patients (24%) and levels greater than 13.55 mmol/L (1200 mg/dL) were documented in 2 of 33 patients (6%). Serum glucose levels greater than 13.88 mmol/L (250 mg/dL) occurred at least once in 1 of 33 patients (3%). Total

serum cholesterol level was measured retrospectively in frozen samples obtained after 0.5, 1, 2, and 3 years of follow-up. Seven of 30 patients (23%) had total serum cholesterol levels of at least 6.21 mmol/L (240 mg/dL), and 1 of 30 patients (3%) had a level of at least 7.76 mmol/L (300 mg/dL) at least once.

Discussion

Evidence shows that it will be difficult to eradicate HIV infection because of a long-lived, latently HIV-infected cell population (10–12). Therefore, antiretroviral regimens that provide potent, durable suppression of HIV replication are critical for preventing progression of HIV disease. We show that in an intention-to-treat analysis, 68% of zidovudine-experienced patients who received the three-drug regimen of indinavir, zidovudine, and lamivudine achieved viral load levels less than 500 copies/mL and 65% achieved viral load levels less than 50 copies/mL after 3 years of follow-up. Over the same period, the median increase in CD4 counts from baseline was greater than 200 cells/mm³. This represents the longest prospectively followed cohort of HIV-infected patients receiving a potent antiretroviral regimen.

Of 12 patients who discontinued treatment over 3 years, 9 had documented virologic failure and 3 withdrew from the study with viral load levels less than 500 copies/mL. We found evidence of lamivudine-resistant virus in 9 patients and protease substitutions that correlated with indinavir resistance in 5 patients who experienced virologic breakthrough. The reasons for virologic failure during the first year of treatment were thought to include poor adherence, malabsorption, and others (5). It is possible that decreased adherence over time or evolution of resistance caused by low-grade virologic replication resulted in later virologic breakthrough in patients who experienced failure after the first year of treatment.

In this cohort, 36% of patients had at least one episode of nephrolithiasis (according to a broad clinical definition) during 3 years of follow-up. This is a higher incidence of nephrolithiasis than the 9.3% rate reported elsewhere (13) and indicates the potential for ongoing risk with continued treatment. By performing a cross-sectional assessment, we found that 19% of patients in our cohort fulfilled a broad clinical case definition of lipodystrophy. Other studies have reported prevalence rates as high as 83% (14). Although associations between lipodystrophy and protease inhibitors (14) or nucleoside analogue reverse

transcriptase inhibitors (15) have been made, the causality and mechanism have not been established.

In summary, we showed that two thirds of HIV-infected patients who took the three-drug combination of indinavir, zidovudine, and lamivudine experienced potent virologic suppression for 3 years. Current guidelines for the treatment of HIV infection recommend a regimen of a protease inhibitor or a non-nucleoside analogue reverse transcriptase inhibitor in combination with two nucleoside analogues (16, 17). Although our 3-year findings support these guidelines and provide evidence of a durable virologic response in most patients, better-tolerated regimens with higher rates of sustained virologic suppression are clearly needed.

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