Lamivudine plus zidovudine was an effective initial therapy for HIV-1 infection


Objective
To determine the effectiveness of lamivudine and zidovudine combination therapy compared with zidovudine monotherapy in patients with HIV-1.

Design
24-week randomized, double-blind, placebo-controlled trial.

Setting
14 hospitals in Europe.

Patients
129 patients who were ≥ 18 years of age (mean age 35 y, 74% men) and were infected with HIV-1, had received minimal previous zidovudine therapy (≤ 4 weeks), had a CD4+ cell count between 100 and 400/μL, and had a Karnofsky score ≥ 70. Exclusion criteria were abnormal liver function, neutrophil count, hemoglobin level, platelet count, creatinine level, or serum amylase level; previous anti-HIV therapy other than zidovudine; history of peripheral neuropathy; or intolerance to zidovudine. Follow-up was 88%.

Intervention
Patients were allocated to zidovudine, 600 mg/d, and lamivudine, 300 mg twice daily (n = 65), or zidovudine plus lamivudine placebo (n = 64). After 24 weeks, all patients could receive lamivudine.

Main outcome measures
Change in CD4+ cell count, HIV-1 RNA viral load, and adverse and toxic events.

Main results
Analysis was by intention to treat. At 24 weeks, patients who received combination therapy had a greater mean reduction in CD4+ cells of 80 cells/μL compared with a decrease of 10 cells/μL in patients on zidovudine mono-therapy (P < 0.001). 13% of patients who received combination therapy had a CD4+ cell count below baseline compared with 57% of patients who received zidovudine monotherapy (P < 0.001). This absolute risk reduction of 44% means that 2 patients would need to be treated with combination therapy (rather than zidovudine monotherapy) for 24 weeks to prevent 1 additional patient from having a CD4+ cell count below baseline, 95% CI 2 to 4; the relative risk reduction was 77%, CI 55% to 99%.) Patients who received combination therapy had a greater mean reduction in viral load at 24 weeks than did patients who received zidovudine monotherapy (P = 0.008 by the immune capture method and P < 0.001 by the Roche method). The groups did not differ for clinical events or toxic effects, which were mild.

Conclusion
Lamivudine plus zidovudine combination therapy was well tolerated and more effective than zidovudine monotherapy in increasing CD4+ cell count and reducing viral load in patients with HIV-1.

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*Numbers calculated from data in article.

Commentary
These 2 clinical trials confirm the results of an earlier report (1) and show that the combined activity of lamivudine and lamivudine is more effective than monotherapy in reducing plasma HIV RNA and increasing CD4+ cell counts in patients with HIV infection. The authors also extend their findings to patients with a mean of 18 years of previous zidovudine therapy. In both the naive and experienced groups, the superior suppression of HIV with the combined regimen was well documented by 3 methods and further supported by increased CD4+ cell counts, decreased immune activation markers (β-2 microglobulin and neopterin), and a trend toward fewer Centers for Disease Control and Prevention category C events. A meta-analysis of 4 similar trials has confirmed these results (2). After 24 weeks, patients were allowed to receive open-label combination therapy; the results suggest that effects are maintained at 48 weeks, but the study design and number of patients do not allow for valid conclusions.

Limited effectiveness of lamivudine in the early treatment of HIV infection became evident about 4 years after (3) and led to several trials of combination therapies. Not only zidovudine and lamivudine but also zidovudine and didanosine; zidovudine and zalcitabine; and more recently 3 drug combinations, including a protease-inhibitor (4), have been reported to be superior to zidovudine monotherapy in controlled clinical trials. Such treatments are also generally well-tolerated (5). The rationale for using combinations of 2 or more drugs includes maximizing the synergistic effects of drugs and avoiding the selective pressure that favors the appearance of drug-resistant HIV mutants. More than 80% of the patients treated with combination zidovudine and lamivudine developed the 184V mutation associated with resistance to lamivudine, but this may delay the appearance of zidovudine-resistant mutants and preserve lamivudine susceptibility. Although neither study was able to show clinical effectiveness or what is more important, a meaningful survival benefit, this is hardly surprising given the relentless but very slow course of HIV infection during clinical latency. Also, a much longer observation period is needed to determine whether the antiviral effect diminishes with time. The decrease in HIV RNA that was achieved, however, is an im (Continued on page 217)