Indinavir plus zidovudine and lamivudine reduced the progression to AIDS in patients with previous zidovudine therapy


**Objective**
To compare the efficacy and safety of indinavir plus zidovudine and lamivudine with zidovudine and lamivudine in patients with HIV infection who have had previous zidovudine therapy.

**Design**
Randomized, double-blind, placebo-controlled trial with a median follow-up of 38 weeks.

**Setting**
33 AIDS Clinical Trials Units and 7 National Hemophilia Foundation Sites in the United States and Puerto Rico.

**Patients**
1156 patients (mean age 39 y, 83% men) who had HIV infection. Inclusion criteria were ≤ 200 CD4+ cells/mm³, ≥ 3 months of previous zidovudine treatment (median 21 mo), no previous treatment with protease inhibitors, ≤ 1 week of previous lamivudine treatment, and acceptable laboratory values. Follow-up was 95%.

**Intervention**
577 patients were allocated to indinavir, 800 mg every 8 hours; zidovudine, 200 mg 3 times daily; and lamivudine, 150 mg twice daily. 579 patients were allocated to the same dose of zidovudine and lamivudine and to a matching placebo. Stavudine could be substituted for zidovudine for toxicity or disease progression (n = 109).

**Main outcome measures**
The primary outcome measure for efficacy was the development of a new AIDS-defining event or death. The primary outcome measure for safety was the occurrence of grade 3 or 4 adverse events.

**Main results**
Analysis was by intention to treat. Fewer patients who received indinavir plus zidovudine and lamivudine had AIDS-defining events or died than did patients who received zidovudine and lamivudine (P = 0.001) (Table). 21% of patients receiving indinavir plus zidovudine and lamivudine had grade 3 or 4 adverse events compared with 18% of patients receiving zidovudine and lamivudine (P = 0.17).

**Conclusion**
The combination of indinavir, zidovudine, and lamivudine resulted in fewer deaths and AIDS-defining events than zidovudine and lamivudine alone in patients with HIV infection who had previous zidovudine therapy.

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**Indinavir plus zidovudine and lamivudine (3 drugs) vs zidovudine plus lamivudine**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>3 drugs</th>
<th>Zidovudine plus lamivudine</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EER</td>
<td>CER</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AIDS or death</td>
<td>6%</td>
<td>11%</td>
<td>47%</td>
<td>5%</td>
<td>20</td>
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<tr>
<td></td>
<td>(21 to 65)</td>
<td>(12 to 30)</td>
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</tbody>
</table>

*Abbreviations defined in Glossary; RRR, ARR, NNT, and CI calculated from data in article.*

Both studies were done using viral load assays with limits of detection of 500 copies/mL. Gallick and colleagues also used an assay with a lower limit of 50 copies/mL. Newer assays permit detection levels as low as 25 copies/mL. It is not clear how many patients would have had demonstrable viral loads if these more sensitive assays were available.

Although the most recently published guidelines for antiretroviral therapy from the International AIDS Society–USA panel give clinicians the option of initiating therapy with a protease inhibitor (2), the 2 studies reviewed here provide strong evidence of the beneficial effect of the routine use of protease inhibitors. These agents may well be partially responsible for the first-ever decrease in deaths from AIDS seen in the United States in 1996 (3).

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**References**