this mutation in a large HIV-infected population. We performed protease sequence analysis with use of an automated sequence analyzer (ABI Prism 3100; Applied Biosystems) on HIV-RNA from samples of plasma obtained from 952 HIV-positive individuals. All patients were undergoing regular follow-up at clinical centers widely distributed across Spain, and drug resistance testing had been requested for all. A total of 813 plasma samples were obtained from subjects exposed to antiretroviral drugs, of whom 737 had virological failure after treatment with regimens that included nelfinavir and/or indinavir. Only 139 plasma samples were obtained from antiretroviral-naive individuals, for whom resistance testing had been requested before the initiation of therapy, as recommended in Spanish national guidelines for resistance testing [7].

Overall, HIV with changes at codon 88 was identified in 39 (4.8%) of 813 previously treated patients, although HIV with the N88S mutation was detected in 11 (1.3%); N88D was detected in 28 (3.4%) of subjects. In all instances, N88D or N88S mutant virus was detected only in subjects previously exposed to nelfinavir and/or indinavir: N88D in 20 (3.4%) of 737 exposed subjects and N88S in 11 (1.5%) of 737. HIV with changes at position 88 was detected in none of the antiretroviral-naive individuals.

Our data support the conclusion that changes at position 88 in the HIV protease gene should be considered resistance mutations, because they do not appear in the absence of previous drug exposure. Moreover, selection for the N88S/D/S mutant genotype seems to require previous therapy with the protease inhibitors nelfinavir and/or indinavir, because treatment with other drugs from this class does not select for this change. Finally, the N88D/S mutation seems to occur in the viral genome at very low rate, because HIV strains with the mutation are only detected in a few subjects who have virological failure after treatment with protease inhibitor–containing regimens. This observation is in accordance with reports that viruses with changes at codon 88 have a lower level of fitness than do wild-type strains [3]. If the virulence of HIV strains is related to their fitness, then selection for HIV with the N88S mutation might be exploited, from a therapeutic perspective. Moreover, if hypersensitivity to any compounds used in rescue therapy plays a role, drugs such as atazanavir—which preferentially selects for the N88S mutation—could be preferred as first-line therapy to increase the effectiveness of rescue interventions with amprenavir.

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References


Metabolic Acidosis in HIV-Infected Patients

Sir—We read with interest the recent article by Boubaker et al. [1], which described patients with hyperlactatemia who were receiving antiretroviral therapy in the Swiss HIV Cohort Study. Dr. Boubaker and colleagues found that 73 (8.3%) of 880 patients in a cross-sectional study had an elevated lactate level and that only 1 patient developed severe lactic acidosis. Lactic acidosis is a metabolic acidosis (pH level, <7.37) with an anion gap of >16 mM. Therefore, we would like to report the preliminary results from a retrospective cohort study that evaluated 100 patients to determine the incidence of metabolic acidosis (pH level, <7.37) with an anion gap of >16 mM.

The study involved a randomized sample of 100 HIV-infected patients who were followed at the Hôpital Saint-André, a university hospital in Bordeaux, France. Antiretroviral-naive patients were given dual nucleoside-analogue therapy as the first line of treatment. They were followed every 3 months for a 48-month period that ended on 1 June 2000. The clinical and biological data that were obtained and recorded were as follows: age; sex; HIV-transmission group; hepatitis B and C serological status; associated morbidity (e.g., renal or cardiac failure or alcohol consumption); antiretroviral therapy received; type of antiretrovirals received; clinical events, HIV RNA load; CD4+ T lymphocyte count; Na+, Cl−, and HCO3− levels; anion gap; and creatinine, aspartate aminotransferase, amylase, lipase, and creatine phosphokinase levels.

The median age of the patients was 37 years, and 74% were male. The HIV-transmission groups and the percentage of patients in each group were as follows: injection drug users, 40%; men who have
Table 1. Findings from laboratory examinations of 100 HIV-infected patients who were receiving dual nucleoside-analogue therapy, according to month of follow-up.

<table>
<thead>
<tr>
<th>Finding</th>
<th>No. of patients, by month of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
</tr>
<tr>
<td>HCO₃⁻ level &lt;24 mM</td>
<td>1</td>
</tr>
<tr>
<td>Anion gap &gt;16 mM</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine level &gt;124 μM</td>
<td>0</td>
</tr>
<tr>
<td>Amylase level &gt;390 IU/L</td>
<td>1</td>
</tr>
<tr>
<td>Lipase level &gt;190 IU/L</td>
<td>4</td>
</tr>
<tr>
<td>AST level &gt;40 IU/L</td>
<td>16</td>
</tr>
<tr>
<td>CPK level &gt;195 IU/L</td>
<td>4</td>
</tr>
</tbody>
</table>

**NOTE.** AST, aspartate aminotransferase; CPK, creatine phosphokinase; month 0, the month when dual nucleoside-analogue therapy was initiated.

be more likely to occur in the presence of such cofactors as renal or hepatic failure, treatment for associated conditions, or general disease. The high prevalence of hyperlactatemia and the low incidence of lactic acidosis do not support the need for a systematic survey of lactate levels in the usual surveillance of HIV-infected patients who are receiving nucleoside-analogue therapy. Nevertheless, urgent biological investigations are warranted in patients who show even mild clinical signs that suggest hyperlactatemia premonitory of lactic acidosis. Furthermore, additional studies are needed to determine the potential risk factors for lactic acidosis in HIV-infected patients who receive nucleoside-analogue therapy.

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References
