Superiority of Protease Inhibitors over Nonnucleoside Reverse-Transcriptase Inhibitors when Highly Active Antiretroviral Therapy Is Resumed after Treatment Interruption

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Forty-five human immunodeficiency virus (HIV)–infected patients stopped taking treatment but resumed taking it thereafter. All 11 who resumed treatment with their prior protease inhibitor (PI)–based regimen reattained an undetectable virus load, whereas this occurred for only 15 (44%) of 34 patients who resumed nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based treatment (P < .001). Distinct pharmacokinetics and resistance barriers may result in different performances for PIs and NNRTIs after treatment interruptions.

The marketing of nonnucleoside reverse-transcriptase inhibitors (NNRTIs) back in 1997 was one of the milestones in the management of HIV infection. This family of compounds has provided good antiviral activity, as well as the possibility of more-convenient regimens. Both older studies [1] and recent studies [2] that have involved drug-naive patients have confirmed that NNRTIs and protease inhibitors (PIs) have similar potency. On the other hand, many of the simplification protocols performed more recently have demonstrated that the replacement of a PI with an NNRTI may alleviate toxicities (including several aspects of lipodystrophy syndrome), facilitate compliance with treatment regimens, and improve quality of life [3]. However, the efficacy of NNRTIs in certain circumstances may not be comparable to that of PIs; this seems to be the case in drug-naive subjects with very high viral loads [4] and in some treatment–experienced individuals recruited in simplification protocols [5]. Herein, we present the results of an observational study in which NNRTI-based regimens were shown to be less effective than PI-based regimens in patients who resumed HAART after a period of treatment interruption.

We retrospectively analyzed the virologic outcome in 45 HIV-1–infected patients who voluntarily stopped taking an effective HAART regimen during 2002 at our institution (Hospital Carlos III, Madrid, Spain) and who were advised to resume therapy a few months later because of significant rebounds in the viral load and/or immunologic deterioration. Twelve patients were receiving a PI-containing regimen at the time of treatment interruption, and 33 were receiving a NNRTI-based regimen; use of all drugs was stopped at once. All patients had undetectable viral loads (HIV RNA level, <50 copies/mL) and CD4 cell counts of >500 cells/μL at the time of treatment interruption. The duration of treatment interruption was ≥3 months, and it lasted for ∼7 months in 1 individual. Additional follow-up was conducted for at least another 3 months for all patients after HAART was resumed.

A total of 11 patients resumed HAART with a PI-containing regimen. The mean HIV RNA level (±SD) before HAART resumption was 32,564 ± 19,531 copies/mL, and all patients reattained an undetectable HIV RNA level ≤6 months after resuming PI treatment. The remaining 34 subjects received an NNRTI-based, triple-drug combination regimen after viral rebound occurred during the treatment interruption. The plasma viral load returned to undetectable levels in only 15 (44%) of these subjects. The remaining 19 patients (56%) did not again achieve an undetectable viral load (P < .001, by χ² test). There was no difference in the mean viral load before treatment resumption among those for whom NNRTI-based HAART was successful (22,567 ± 17,659 copies/mL) or not successful (25,873 ± 17,674 copies/mL). The viral load at the time of HAART resumption was also comparable for recipients of PI-based HAART and recipients of NNRTI-based HAART.

In an attempt to explain the sharp difference in efficacy between PIs and NNRTIs in rescue interventions, we examined the genotypic profiles at different points in patients who resumed NNRTI-based HAART. An automatic sequencer (ABI Prism; Celera Diagnostics) was used for this purpose. Stored plasma samples from all patients were available for genotypic sequence analyses. Genotypic results, however, could be obtained for only samples from 17 individuals at month 3 after HAART discontinuation and from 13 patients at the time of treatment failure with NNRTI-based regimens. For the rest of the patients, low titers of plasma viral loads most likely pre-
<table>
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<tr>
<th>Patient</th>
<th>Prior HAART received</th>
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<th>Findings after resumption of treatment with an NNRTI–based regimen</th>
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<tr>
<td></td>
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<td>Plasma HIV RNA level, copies/mL</td>
<td>Genotype</td>
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<tr>
<td>1</td>
<td>Didanosine, nevirapine, and nef lnafavir</td>
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<td>WT</td>
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<td>Stavudine, lamivudine, and nef lnafavir</td>
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<td>184V and 211K</td>
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<td>62V, 65R, 75M, and 151M</td>
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<td>WT</td>
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<td>WT</td>
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<tr>
<td>21</td>
<td>Stavudine, lamivudine, and nevirapine</td>
<td>45,000</td>
<td>NA</td>
</tr>
</tbody>
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**NOTE.** NA, not available; PI, protease inhibitors; WT, wild type.

* New mutations. +, Prior mutations plus new mutations.
cluded the obtainment of a sufficient amount of genetic material.

Table 1 summarizes the main virologic features of the study population at different points. Seven of 8 patients who retained undetectable viral loads while receiving an NNRTI-based regimen harbored wild-type viruses at the time of viral rebound during the treatment interruption. Of note, the single subject (patient 13) infected with drug-resistant virus who regained an undetectable viral load after treatment resumption (with didanosine, abacavir, and nevirapine) had a low plasma viral load when HAART was reintroduced, and the nucleoside-associated mutations (NAMs) present should minimally impact abacavir and didanosine activities.

Conversely, 8 of 9 patients for whom the NNRTI-based rescue regimen failed harbored drug-resistant virus 3 months after HAART discontinuation. Three of these patients (patients 6, 15, and 16) had virus that carried multiple NAMs, and another 2 (patients 4 and 17) had virus that carried Q151M, a multi-nucleoside-resistant genotype. In another 2 subjects (patients 3 and 18), the presence of M184V may have additionally contributed to HAART failure. Interestingly, the presence of K103N during treatment discontinuation was recognized in only 1 subject (patient 5), who thereafter experienced treatment failure with an NNRTI-based rescue intervention. Finally, at the time of failure with the resumed NNRTI-based regimen, all patients showed NNRTI-associated resistance mutations (table 1).

NNRTI-based regimens have often been considered more convenient but potentially less potent than PI-based combinations, particularly when PI-based regimens are boosted with ritonavir. The genetic barrier for resistance is much higher for PIs than for NNRTIs [6, 7]. Besides, it might be argued that targeting 2 different viral enzymes (protease and reverse transcriptase) may accomplish the goal of blocking HIV replication more efficiently [8]. The greater antiviral potency of PIs over NNRTIs could also explain the better immune recovery seen in subjects who receive PIs, compared with those who receive NNRTIs [9].

In patients with high viral loads and/or low CD4 cell counts, the ability of NNRTIs to cause complete viral suppression seems to be less than that of PIs [10]. Both lower intrinsic antiviral potency and rapid selection of resistance might account for this observation. The fact that 1 single nucleotide substitution (TAT to TGT for Y181C mutation or AAA to AAC for K103N) is required for production of high-level NNRTI resistance is the basis of this phenomenon.

On the other hand, the pharmacokinetics of NNRTIs may facilitate the rapid selection of resistance mutants in some circumstances [11]. When a regimen that contains NNRTIs is stopped, most of the other compounds are cleared in <48 h, but the long half-life of NNRTIs yields to persistent detectable levels in plasma for as long as 14–21 days [12, 13]. In this situation, the pressure for selecting NNRTI resistance mutations is pushed. If the subjects resume HAART later with an NNRTI-based regimen, it should not be surprising to observe a rapid emergence of NNRTI-associated resistance mutants [14].

The relative weakness of NNRTIs may also become manifest in treatment-experienced patients who have undetectable viral loads while receiving PI-based regimens. For instance, in the NEFA trial [15], which involved a simplification protocol, the risk of virological failure was much higher in subjects who had been exposed to suboptimal therapy with 1 or 2 nucleoside analogues in the past. These subjects often carried viruses with NRTI-associated resistant viruses. Although the higher potency of PIs had protected these patients from viral escape, the weaker genetic barrier of NNRTIs failed to do so. Although failures with NNRTI rechallenges in our study could be associated with preexisting NRTI-associated resistance mutations, we can not exclude the possibility that minority populations of NNRTI-resistant viruses may have been selected after discontinuation of a successful NNRTI-based regimen. The presence of minority NNRTI-resistant quasi species has been underlined recently as cause of treatment failure after an NNRTI rechallenge [16]. However, because administration of NNRTI-based combinations in our study also led to treatment failure in a few subjects who had received only PIs (patients 3, 6, and 7), our results do not indicate an important role for these minority quasi species as causes of failure in NNRTI-based regimens. In fact, 10 of 12 subjects who had previous exposure to PIs did not retain undetectable viral loads with receipt of NNRTIs; almost all of these patients harbored NAMs. In contrast, all patients but one (patient 14) showing wild-type viruses at the time of viral rebound during the HAART interruption attained undetectable viral loads while receiving NNRTIs.

In summary, interruption of HAART may be deleterious when patients are beyond their first-line therapy, especially if NNRTI are part of the combination. The best chances for regaining complete viral suppression are obtained using potent regimens, and PI-based regimens seem to fit this consideration better than do NNRTI-based regimens, given the higher genetic barrier for resistance in PI-based regimens. NNRTI-based combinations should be used cautiously in the face of active viral replication, especially in subjects who have previously been exposed to nucleoside analogues, given their weaker barrier for resistance. In this situation, resistance testing may be helpful for choosing the best candidates for NNRTI-based therapies, who, ideally, should be persons without HIV containing reverse-transcriptase resistance mutations.

**Acknowledgments**

**Financial support.** Fundacion Investigacion y Educacion en SIDA and Red de Investigacion en SIDA.

**Potential conflicts of interest.** All authors: no conflicts.
References


