Reasons for discontinuation of nevirapine-containing HAART: results from an unselected population of a large clinical cohort

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Objectives: To evaluate the frequency of and predictive factors for nevirapine-based highly active antiretroviral therapy (HAART) discontinuation.

Methods: All patients receiving nevirapine as a component of HAART at our centre were retrospectively evaluated for efficacy and tolerability. Logistic regression was used to evaluate the influence of baseline characteristics on the outcome and Kaplan–Meier (KM) estimates to evaluate time-dependent variables.

Results: Between January 1999 and June 2006, 582 patients (72% males) received 744 nevirapine-based HAART regimens. Naive patients counted for 83 of these regimens; of the remaining 661 regimens administered to experienced patients, 306 were failing virologically and 355 were undergoing simplification strategies. A once-a-day schedule was used in 136 patients. The likelihood of maintaining the nevirapine-based regimen was statistically (P < 0.0001 in both cases) influenced by the patient’s status (mean KM estimate of 812 days for virological failures, 1294 for naive patients and 1657 for treatment simplifications) and by the dosing schedule (once-daily 1315 days; twice-daily 1198 days). The most frequent reason for treatment discontinuation was resistance (17.5%) followed by reduced tolerability (16.3%), patient’s decision (14%) and treatment strategies such as structured treatment interruptions (13.8%). During 10.2% of treatments, a grade 3 or greater increase in aminotransferase levels was observed, reflecting an overall incidence rate equal to 5.3 cases per 100 person-years. This lead to treatment discontinuation in 3.9% of cases.

Conclusions: Nevirapine, especially when used in simplification strategies, enables doctors to extend the use of HAART over a long period of time. The risk of drug-induced hepatotoxicity is low, but nevirapine should be used with caution in patients co-infected with hepatitis C virus or with elevated liver function tests. As with any decision to prescribe a drug, a careful evaluation of the potential risks and benefits of using nevirapine must be made for each individual.

Keywords: adverse events, efficacy, non-nucleoside reverse transcriptase inhibitors, NNRTIs

Introduction

In 1997, nevirapine became the first non-nucleoside reverse transcriptase inhibitor (NNRTI) available for the treatment of HIV infection. Its efficacy was established both for the treatment of naive patients and in simplification strategies.1,2 It is still a widely-used antiretroviral drug and can be considered a cornerstone of highly active antiretroviral therapy (HAART) in the southern hemisphere, where it is regarded as crucial for scaling-up AIDS treatment in developing countries.3,4 The aims of the present analysis are to determine the frequency and timing of discontinuation of nevirapine-based HAART and to study factors predictive of drug discontinuation in a large, unselected population.

Patients and methods

Patients are those referred to the Antiviral Therapy Unit of a reference centre in Northern Italy, whose data are stored in an electronic
database used to manage the everyday activity of the HIV clinic. This is, therefore, an open cohort in which patients are continuously being enrolled. All events and data (i.e., CD4 cell count, HIV-RNA, haematological exams, clinical events, changes—and reasons for changes—of antiretroviral drugs, hospitalizations and deaths) are prospectively recorded in the database during routine four-monthly check-ups, unless differently required by the specific conditions of the patient. For this analysis we selected all patients treated with nevirapine-based HAART between January 1999 and June 2006. All patients gave their informed consent for the use of personal data.

The study end-point was the discontinuation of nevirapine-based HAART for any reason associated with drug intolerance, poor virological/immunological or clinical response or therapeutic strategy. The time zero for the analysis was the date on which nevirapine-based HAART was started, while the date of discontinuation was that on which nevirapine was first terminated. The reason for discontinuing nevirapine was defined as the reason for discontinuing the entire prescribed antiviral regimen. All patients failing virologically underwent virus genotyping.

Survival time was, therefore, the time elapsing between the start of therapy and the date of the last follow-up visit while on the same regimen. Patients who never discontinued nevirapine were censored at their last control.

Descriptive results are presented as means ± standard error, medians with interquartile range (IQR), and percentages with 95% confidence intervals (CI). For inferential statistics, parametric or non-parametric tests were used as appropriate. Time-dependent variables were analysed using Kaplan–Meier (KM) product-limit estimates. The log-rank test was used to assess the difference between the survival curves. We employed a multivariate logistic regression analysis to assess the relationship between baseline variables and the considered outcome. All tests were two-sided and a P value <0.05 was taken as significant. Analyses were performed using SPSS for Windows, version 13.0.

Results

A total of 582 patients were included in the analysis. Their median age was 38.9 years (IQR 35–43) and 164 of them (28%) were females. At time zero, the median CD4 count was 368 cells/mm³ (IQR 221–540), HIV-RNA was 977 copies/mL (IQR <50–319 551) and ALT serum level was 43 IU (IQR 29–71). Fifty-nine percent of patients presented with baseline ALT values within the normal range (3–46 IU). Overall, 321 subjects (55.2%) were co-infected with hepatitis C virus (HCV; i.e. HCV antibody positive), but none of them had previously received HCV therapy. In the considered period of time, the selected patients received 744 nevirapine-based regimens and the total follow-up of the cohort was 1435 person-years. The nucleoside analogues (NRTIs) used with nevirapine were: lamivudine (75.1%), zidovudine (34.5%), didanosine (32.4%), stavudine (30.4%), tenofovir (14.2%), abacavir (11.2%) and emtricitabine (3.1%). Besides nevirapine + NRTIs, 40 regimens (5.4%) included a protease inhibitor. In 136 cases (18.3%) nevirapine was administered according to a once-a-day schedule with didanosine + lamivudine (60.3%), abacavir + lamivudine (16.2%) or tenofovir + lamivudine (23.5%).

Eighty-three (11.2%) HAART regimens were administered to previously naive patients, while the remaining 661 regimens were administered to pre-treated patients presenting with HIV RNA level >50 copies/mL (306 regimens, 41.1%) or a viral load below the detection limit (355 regimens, 47.7%) at commencement of nevirapine treatment. Patients in the former group were currently failing HAART (experienced patients) while the latter were undergoing simplifications strategies or switching regimens in order to manage adverse events (HAART simplification).

Treatment was not discontinued in 286 of the 744 regimens. Where the regimen was discontinued, the most common cause was the selection of NNRTI-resistant viruses (130 cases, 17.5%). The next most common reason was the presence of treatment-related adverse events (112 cases, 15.1%), most commonly allergic reactions. Skin rash counted for 28 cases, while the more serious Stevens–Johnson reaction was diagnosed in two cases. Hepatotoxicity was the cause of treatment discontinuation in 29 (3.9%) cases, with most incidences (20, 3.4%) involving a ≥grade 4 liver function test (LFT) alteration. Elevated serum ALT levels (levels ≥grade 3) were observed during 10.2% of nevirapine-based regimens, reflecting an overall incidence rate equal to 5.3 cases per 100 person-years; however, no fulminant hepatitis or deaths related to hepatic dysfunction were observed. Gastrointestinal symptoms (1.3%), metabolic alterations (1.2%) and neuropathy (1.2%) accounted for a further 28 treatment discontinuations. All other adverse events were rare (<1%) and were often linked to the NRTI backbone in the regimen.

A further 15% of the regimens were stopped either because that was what the patient wanted (72 cases, 9.7%) or because the patient was lost to follow-up (32 cases, 4.3%). Treatment discontinuation was linked to therapeutic decisions either because the regimen (especially the backbone) was simplified (67 cases, 9.0%), or because the patients entered a structured treatment interruption programme (36 cases, 4.8%). Finally, 9 patients (1.2%) died due to concomitant diseases including sepsis (two cases), acute myocardial infarction, pancreatitis, laryngeal cancer, Hodgkin lymphoma, cerebral toxoplasmosis, pneumocystosis and leucoencephalopathy (one case each).

Univariate analysis indicates that several baseline characteristics were significantly associated with discontinuation of nevirapine-based regimens (Table 1); however, in subsequent multivariate analysis only a few retained a statistically-significant prognostic value.

Being naive for antiretroviral drugs or on a simplification regimen and receiving once-daily nevirapine reduced the risk of discontinuing the ongoing regimen by at least half (OR ≤0.4).

Both these variables, when analysed as a function of time, were strongly associated with discontinuing treatment (Figure 1). The mean KM estimate for duration of HAART was 811 days (95% CI 706–916) for experienced patients, 1293 days (95% CI 1015–1572) for naive patients and 1657 days (95% CI 1516–1798) for HAART simplification patients. Similarly, KM estimates for once- and twice-daily regimens were 1315 days (95% CI 1170–1459) and 1198 days (95% CI 1086–1311), respectively.

The as-treated analysis included all patients still on treatment and undergoing four-monthly check-ups. Over 60 months of follow-up, the proportion of subjects with HIV-RNA <400 copies/mL, in the as-treated analysis, was always superior to 90% (range 90.6% to 96.7%) for HAART simplification patients and was between 79.4% and 96.6% for naive patients and between 50.9% and 61.9% for experienced patients.
Current guidelines for the treatment of HIV-infected adults recommend nevirapine as an alternative choice for the treatment of naive patients. In this study we evaluated the reasons for discontinuing nevirapine-based regimens using a regimen termination end-point that strictly reflected standard clinical practice. Not surprisingly, patients’ previous therapeutic experiences markedly influenced their risk for discontinuing the nevirapine-based regimen. In some cases discontinuation rates were extremely low, and, according to KM estimates, 50% of patients who started a nevirapine-based regimen to simplify an existing, effective regimen were still on nevirapine after more than 5 years. The same proportion of naive patients were still receiving nevirapine after almost 3 years.

A distinctive result of this study is that the once-daily nevirapine dosing schedule performed at least as well as the usual twice-daily schedule. Previously published data have indicated that a once-daily schedule was less well tolerated than twice-daily administration. It should be noted, however, that in the authors’ practice, patients are usually switched from a twice-daily to a once-daily schedule after a minimum of 2 months of therapy, which may have limited the occurrence of adverse events related to higher drug concentrations.

In contrast with other studies we also observed an overall low incidence (5.3 cases per 100 person-years) of hepatotoxicity. Nevirapine-associated hepatotoxicity is unevenly distributed over time, however, and the much longer follow-up time in our study may explain this difference. It should also be noted that the uncontrolled, observational nature of this study might have introduced selection biases into the cohort, however, the large number of treated patients should limit the effects of such a bias.

Nevirapine, especially when used in simplification strategies, enables doctors to extend the use of HAART over a long period.

### Table 1. Baseline characteristics distribution and association with occurrence of nevirapine-based HAART cessation irrespective of the cause leading to treatment cessation/change

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nevirapine discontinuation</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (95% CI)</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Female sex</td>
<td>109 (28.8)</td>
<td>1.2 (0.8–1.6)</td>
<td>0.428</td>
</tr>
<tr>
<td>Calendar year (&lt;2003)</td>
<td>253 (75.5)</td>
<td>1.0 (0.9–1.1)</td>
<td>0.930</td>
</tr>
<tr>
<td>HCV antibody positive</td>
<td>227 (60.1)</td>
<td>1.5 (1.1–2.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Risk factor for HIV</td>
<td></td>
<td>0.860</td>
<td></td>
</tr>
<tr>
<td>intravenous drug use</td>
<td>265 (56.7)</td>
<td>0.79 (0.4–1.7)</td>
<td>0.569</td>
</tr>
<tr>
<td>heterosexual</td>
<td>171 (36.6)</td>
<td>0.99 (0.5–2.2)</td>
<td>0.994</td>
</tr>
<tr>
<td>homosexual</td>
<td>31 (6.6)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CD4, cells/mm³</td>
<td>360 ± 13</td>
<td>&lt;0.0001</td>
<td>1.0 (0.99–1.01)</td>
</tr>
<tr>
<td>Age, years</td>
<td>38.9 ± 0.4</td>
<td>0.014</td>
<td>0.9 (0.95–0.99)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>68.2 ± 3.8</td>
<td>0.004</td>
<td>1.01 (1–1.07)</td>
</tr>
<tr>
<td>Patient status</td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
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<td>naive</td>
<td>48 (12.7)</td>
<td>0.2 (0.1–0.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>simplification</td>
<td>106 (28.0)</td>
<td>0.4 (0.2–0.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>experienced</td>
<td>224 (59.3)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nevirapine once-daily dosing</td>
<td>42 (11.1)</td>
<td>0.4 (0.3–0.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Discussion**

Current guidelines for the treatment of HIV-infected adults recommend nevirapine as an alternative choice for the treatment of naive patients. In this study we evaluated the reasons for discontinuing nevirapine-based regimens using a regimen termination end-point that strictly reflected standard clinical practice. Not surprisingly, patients’ previous therapeutic experiences markedly influenced their risk for discontinuing the nevirapine-based regimen. In some cases discontinuation rates were extremely low, and, according to KM estimates, 50% of patients who started a nevirapine-based regimen to simplify an existing, effective regimen were still on nevirapine after more than 5 years. The same proportion of naive patients were still receiving nevirapine after almost 3 years.

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Transparency declarations

None to declare.

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