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Low Risk of Treatment Failure after Substitution of Nevirapine for Protease Inhibitors among Human Immunodeficiency Virus–Infected Patients with Virus Suppression

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There is little information about the risk of treatment failure after a switch from human immunodeficiency virus (HIV) protease inhibitors (PIs) to nevirapine (Nvp) for patients with successful virus suppression. This study compared the 1-year risk of treatment failure for patients switching from a first PI-containing antiretroviral regimen to Nvp (Nvp group) with the risk for patients switching to second-line PIs (PI group) in the ATHENA (AIDS Therapy Evaluation, The Netherlands) study cohort (n = 2470) whose HIV-1 RNA loads were ≤500 copies/mL. Treatment failure was defined as measurement of HIV-1 RNA loads >500 twice or >10,000 copies/mL once or discontinuation of treatment for any reason. There were 446 eligible patients, 125 in the Nvp group and 321 in the PI group. The risk of treatment failure in the Nvp group, after data were adjusted for other risk factors, was 5-fold (95% confidence interval, 0.1–0.4) lower than the risk in the PI group, primarily because the discontinuation rate was lower. In patients with virus suppression, a switch to Nvp is more likely than a switch to second-line PIs to result in sustained virus suppression and maintenance of the new regimen.

Treatment of human immunodeficiency virus (HIV) type 1 infection with highly active antiretroviral therapy (HAART) that includes an HIV protease inhibitor (PI) may be associated with the need to take large quantities of capsules, stringent intake schedules, food restrictions, drug-drug interactions, and numerous adverse drug reactions [1, 2]. These factors may interfere with long-term adherence and therefore lead to premature virus rebound and the selection of resistant viral variants. Various strategies for maintenance treatment have been ineffective [3–5]. Moreover, the benefits of a switch between PIs are limited, possibly because of drug class–specific problems [6].

Nevirapine (Nvp) is a nonnucleoside reverse-transcriptase inhibitor (NNRTI) that has demonstrated potent anti-HIV efficacy when it is used in combination with 2 nucleoside reverse-transcriptase inhibitors (NRTIs) [7, 8]. Combination therapy with Nvp and 2 NRTIs is relatively simple and has few adverse effects, although potentially serious rashes and liver toxicity have been reported [8].

Patients who have been treated successfully with a PI-containing HAART regimen may benefit from the less complex Nvp treatment regimen, which should help to improve long-term adherence and the chance of sustained antiviral efficacy. This hypothesis has been the subject of a number of studies, most of which lacked a comparison arm, included few patients, or had a short follow-up period [9–12]. As a consequence, there is insufficient information regarding the effectiveness and safety of Nvp for patients with virus suppression.

To gain more insight into the consequences of substituting Nvp for PIs under everyday circumstances in the treatment of patients with virus suppression, we conducted an observational cohort analysis within the Dutch nationwide ATHENA (AIDS Therapy Evaluation, The Netherlands) study cohort of patients treated for HIV infection. This cohort has yielded detailed data on HIV treatment and treatment outcome. We determined the 1-year risk of treatment failure after a switch from PIs to Nvp,
as opposed to a switch to a second-line PI regimen, for a group of patients (the PItoN study cohort) within the ATHENA study cohort.

Subjects, Materials, and Methods

Study setting. This study was conducted within the ATHENA cohort, a nationwide observational cohort in The Netherlands. This cohort includes HIV-infected patients who are treated with ≥ 1 of the antiretroviral drugs that became available in The Netherlands in July 1996 and thereafter (i.e., all PIs, all NNRTIs, and the newer NRTIs, such as lamivudine and stavudine). The source population includes HIV-infected patients followed up at 22 hospitals that provide treatment to HIV-infected patients in The Netherlands.

According to national guidelines for HIV treatment in The Netherlands, patients are seen approximately every 3 months for regular follow-up [13]. Data for the ATHENA cohort are collected on standardized forms (retrospectively from medical records up to the time at which the patient entered the cohort and prospectively thereafter by trained research nurses and treating physicians). The resulting ATHENA database, which is updated approximately every 6 months, contains information on each patient’s sex, age, height, and weight and the hospital at which treatment is received. Start and stop dates and the dose frequency of every antiretroviral medication and prophylactic treatment administered against opportunistic infections; the primary reason why such treatments were stopped, as classified by the treating physician; the dates of onset and resolution of HIV-related diseases; CD4 cell counts; plasma HIV-1 RNA loads; and abnormal laboratory values are recorded, as are adverse events (all events that lead to a change in antiretroviral treatment and a number of prespecified adverse events, such as neuropathy, lipodystrophy, and hepatitis). Data on plasma HIV-1 RNA are from 1 of 3 different quantitative assays: Amplicor (Roche Diagnostics), NucliSens (Organon Teknika), or Quantiplex (Chiron Diagnostics). At the time of data extraction for the analysis in March 2000, data were available for 2470 patients.

PItoN study cohort. The source population for our study involved all patients in the ATHENA database who used a PI-containing first-line HAART regimen (HAART 1) during the study period. The study period was from 1 May 1997, when the compassionate-use program for Nvp became effective, through March 2000. Patients entered the PItoN study cohort when the PI component of HAART 1 was switched while the patient’s HIV-1 RNA load was ≤ 500 copies/mL. Changes in ritonavir (Rtv) formulation were not considered to be a switch, because a nationwide change to a new formulation occurred during the study period. Any other change in the PI component, including a change in dose frequency other than standard initial dose escalations, addition or removal of a PI, and change in saquinavir (Sqv) formulation, was considered to be a switch. The date of cohort entry was defined as the start date of the second-line HAART regimen (HAART 2). We excluded all patients for whom no HIV-1 RNA assessment was made within at least 3 months before the start of HAART 2 or whose treatment was interrupted for > 7 days, to ensure that virus suppression was present at the start of HAART 2.

The resulting PItoN study cohort was divided into 2 treatment groups on the basis of the inclusion of Nvp (Nvp group) or second-line PIs (PI group) in HAART 2. Switches to other NNRTIs, such as efavirenz, were not studied separately, because Nvp was the only NNRTI registered in The Netherlands at the time of this analysis. Switches to triple NRTI regimens were not studied, because the primary focus of our study was to compare a switch to Nvp with a switch between PIs.

Outcomes. The primary study end point was treatment failure within 1 year after a switch to HAART 2. Treatment failure was defined as either virologic failure or discontinuation of HAART 2 for any reason. Virologic failure was defined as a plasma HIV-1 RNA load of > 500 copies/mL on 2 consecutive measurements or a single assessment of a plasma HIV-1 RNA load of > 10,000 copies/mL. Discontinuation of HAART 2 was defined as a second treatment switch that fit the above description, discontinuation of HAART 2, or death. Notably, a switch between NRTIs was not considered to be a treatment switch.

Secondary end points included time to treatment failure, the course of CD4 cell counts, and clinical adverse events. Study follow-up was from the date of study entry until the completion of 1 year in the study, the final update of data, or treatment failure, whichever occurred first.

Covariates. Potential determinants of treatment failure and potential confounding factors included demographic factors such as age, sex, country of birth, route of HIV transmission, and Centers for Disease Control and Prevention disease classification [14] at the time of a switch. In addition, we considered treatment history before HAART 1 (patients were categorized as antiretroviral naive or antiretroviral experienced), duration of HAART 1, duration of virus suppression before the switch (defined as the last uninterrupted period in which HIV-1 RNA loads were ≤ 500 copies/mL), history of virologic rebound (defined as at least 1 measurement of an HIV-1 RNA load of > 500 copies/mL after suppression to ≤ 500 copies/mL had been achieved), CD4 cell count at the time of switch, type of antiretrovirals used in HAART 1 and 2, calendar time in study (months since start of study period), and the reason for the switch. Reasons for changes in drugs were categorized by the treating physician as intolerance, patient request, treatment failure (the latter, in the context of the ATHENA study, was defined as either increase in virus load, decrease in CD4 cell count, or disease progression), pharmacologic indication, other with specification, or unknown.

Statistical analysis. Differences in baseline characteristics in the PI and Nvp groups were tested by the Pearson χ² test or Fisher’s exact test for categorical variables. We used Student’s t test for continuous variables, unless the variables were not normally distributed, in which case we used the Mann-Whitney U test. The 1-year hazard for treatment failure was estimated by Kaplan-Meier survival analysis. Crude comparisons of the risk of treatment failure in the HAART 2 groups were made with the log-rank test and univariate Cox regression analysis.

Risk factors for treatment failure were identified by means of univariate and subsequent multivariate Cox regression analyses. The multivariate model included all factors from the univariate analysis that were associated with treatment failure at P < .1. Time to failure was calculated from the date of PItoN cohort entry to the first date at which an HIV-1 RNA load of > 500 copies/mL was measured or to discontinuation of HAART 2, whichever oc-
Table 1. Changes from the protease inhibitor (PI) component of first-line highly active antiretroviral therapy for human immunodeficiency virus infection in patients with virus suppression.

<table>
<thead>
<tr>
<th>Group, change in treatment</th>
<th>No. (%) of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nvp group: substitution of Nvp</td>
<td>125 (28.0)</td>
</tr>
<tr>
<td>PI group:</td>
<td></td>
</tr>
<tr>
<td>Substitution of another PI</td>
<td>117 (26.2)</td>
</tr>
<tr>
<td>Cessation of 1 of 2 PIs</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Addition of 1 PI</td>
<td>99 (22.2)</td>
</tr>
<tr>
<td>Change in Sqv formulation</td>
<td>22 (4.9)</td>
</tr>
<tr>
<td>Change in dose and/or dose frequency</td>
<td>76 (17.0)</td>
</tr>
<tr>
<td>Total</td>
<td>446 (100)</td>
</tr>
</tbody>
</table>

NOTE. Nvp, nevirapine; Sqv, saquinavir.

Other characteristics associated with treatment failure were intravenous drug use as route of HIV transmission, antiretroviral treatment experience before HAART 1, inclusion of a combination of stavudine and didanosine in HAART 1 or HAART 2, and 48% of discontinuations in the Nvp and PI groups, respectively, which included 2 deaths in the Nvp group. One man with a history of cardiac disease died of heart failure at age 69; the cause of death for the other patient who died, a 41-year-old man, could not be retrieved, because neither HIV-related events nor adverse events had been reported.

Other characteristics associated with treatment failure were intravenous drug use as route of HIV transmission, antiretroviral treatment experience before HAART 1, inclusion of a combination of stavudine and didanosine in HAART 1 or HAART 2,

Table 2. Most common substitutions for the protease inhibitor component of first-line highly active antiretroviral therapy (HAART 1) for human immunodeficiency virus infection in patients with virus suppression.

<table>
<thead>
<tr>
<th>HAART 1</th>
<th>HAART 2</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sqv hgc</td>
<td>Sqv hgc/Rtv</td>
<td>53 (12)</td>
</tr>
<tr>
<td>Idv*</td>
<td>Nd</td>
<td>42 (9)</td>
</tr>
<tr>
<td>Rtv</td>
<td>Nvp</td>
<td>42 (9)</td>
</tr>
<tr>
<td>Sqv hgc/Rtv</td>
<td>Nvp</td>
<td>34 (8)</td>
</tr>
<tr>
<td>Idv</td>
<td>Nvp</td>
<td>25 (6)</td>
</tr>
<tr>
<td>Idv</td>
<td>Nfv</td>
<td>25 (6)</td>
</tr>
<tr>
<td>Rtv</td>
<td>Nfv</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Idv</td>
<td>Idv/Rtv</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Rtv</td>
<td>Sqv hgc/Rtv</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>165 (37)</td>
</tr>
</tbody>
</table>

NOTE. hgc, hard gelatin capsule; Idv, indinavir; Nfv, nelfinavir; Nvp, nevirapine; Rtv, ritonavir; Sqv, saquinavir.
* Change in dose frequency.
Table 3. Characteristics and changes in treatment for the 446 patients included in the protease inhibitor (PI)–to–nevirapine (Nvp) study cohort within the ATHENA (AIDS Therapy Evaluation, The Netherlands) study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th></th>
<th></th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nvp group (n = 125)</td>
<td>PI group (n = 321)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median years (IQR)</td>
<td>40 (35–48)</td>
<td>39 (33–46)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>110 (88.0)</td>
<td>264 (82.0)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15 (12.0)</td>
<td>57 (17.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>83 (66.9)</td>
<td>233 (73.7)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>41 (33.1)</td>
<td>83 (26.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route of HIV transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>80 (67.8)</td>
<td>204 (67.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>3 (2.5)</td>
<td>20 (6.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>35 (27.9)</td>
<td>79 (26.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC classification^c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>30 (24.0)</td>
<td>78 (24.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>A or B</td>
<td>95 (76.0)</td>
<td>243 (75.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretroviral naive at the start of HAART 1</td>
<td>&lt;.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>97 (77.6)</td>
<td>189 (58.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28 (22.4)</td>
<td>132 (41.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of HAART 1, median weeks (IQR)</td>
<td>66 (38–92)</td>
<td>64 (30–87)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Duration of virus suppression,^d median weeks (IQR)</td>
<td>47 (21–82)</td>
<td>37 (15–66)</td>
<td>.008</td>
<td></td>
</tr>
<tr>
<td>Prior virologic failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (14.7)</td>
<td>61 (22.4)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>99 (85.3)</td>
<td>211 (77.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count at switch, median cells/mL (IQR)</td>
<td>440 (300–600)</td>
<td>420 (300–600)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Change in NRTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (25.6)</td>
<td>36 (11.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>93 (74.4)</td>
<td>285 (88.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calendar time in study, median months (IQR)</td>
<td>20 (16–23)</td>
<td>14 (10–18)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Reason for change from HAART 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intolerance</td>
<td>62 (49.6)</td>
<td>89 (27.7)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Patient request</td>
<td>38 (30.4)</td>
<td>66 (20.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacologic indication</td>
<td>3 (2.4)</td>
<td>36 (11.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Treatment failure^e</td>
<td>3 (2.4)</td>
<td>15 (4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other with specification^f</td>
<td>11 (8.8)</td>
<td>83 (25.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (6.4)</td>
<td>32 (10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs received before switch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nfv</td>
<td>5 (4.0)</td>
<td>6 (1.9)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Idv</td>
<td>25 (20.0)</td>
<td>104 (32.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sqv hgc</td>
<td>10 (8.0)</td>
<td>77 (24.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sqv sgc</td>
<td>2 (1.6)</td>
<td>2 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rtv</td>
<td>42 (33.6)</td>
<td>66 (20.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idv/Rtv</td>
<td>6 (4.8)</td>
<td>2 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sqv hgc/Nfv</td>
<td>1 (0.8)</td>
<td>14 (4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sqv sgc/Nfv</td>
<td>0</td>
<td>10 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sqv hgc/Rtv</td>
<td>34 (27.2)</td>
<td>38 (11.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTIs received before switch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zdv/3TC</td>
<td>60 (48.0)</td>
<td>151 (47.0)</td>
<td>.042</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. (Continued.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th></th>
<th></th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nvp group (n = 125)</td>
<td>PI group (n = 321)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T/3TC</td>
<td>44 (35.2)</td>
<td>117 (36.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T</td>
<td>10 (8.0)</td>
<td>9 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zdvd/ddl</td>
<td>2 (1.6)</td>
<td>14 (4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T/ddl</td>
<td>2 (1.6)</td>
<td>12 (3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.4)</td>
<td>15 (4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4 (3.2)</td>
<td>3 (0.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. CDC, Centers for Disease Control and Prevention; ddI, didanosine; d4T, stavudine; HAART 1, first-line highly active antiretroviral therapy; hgc, hard gelatin capsule; HIV, human immunodeficiency virus; Idv, indinavir; IQR, interquartile range; MSM, men having sex with men; Nfv, nelfinavir; NRTI, nucleoside reverse-transcriptase inhibitor; NS, not significant; Rtv, ritonavir; sgc, soft gelatin capsule; Sqv, saquinavir; Zdv, zidovudine; 3TC, lamivudine.

^a The Pearson \( \chi^2 \) test or Fisher’s exact test was used to compare categorical variables, and the Mann-Whitney \( U \) test was used for continuous variables. \( P > .05 \) was considered to be NS.

^b PI group consisted of patients receiving Nfv (22%), Idv (20%), Sqv hgc (4%), Sqv sgc (3%), Rtv (3%), Idv/Rtv (9%), Sqv hgc/Nfv (1%), Sqv/Nfv (7%), Sqv hgc/Rtv (30%), Sqv sgc/Rtv (1%), or another PI (2%).

^c HIV disease stages are from the CDC classification [14].

^d Virus suppression was defined as an HIV-1 RNA load of \( \leq 500 \) copies/mL.

^e Treatment failure during virus suppression was defined as a decrease in CD4 cell count, clinical progression, and/or detection of HIV-1 RNA with an ultrasensitive HIV-1 RNA assay.

^f "Other" includes convenience (7% and 12% in the Nvp and PI groups, respectively), protocol directed (2% and 9%, respectively), and other changes (0% and 4%, respectively).

shorter duration of virus suppression before switch, absence of a change in NRTIs, and switch later in calendar time. In addition, the use of Rtv or a combination of Rtv and Sqv in HAART 1 was associated with fewer failures of the subsequent treatment regimen. Many factors were not equally distributed across the Nvp and PI groups at baseline. After adjustment for all of these factors, including the reason for HAART 1 switch, in a multivariate analysis, substitution of Nvp for PIs, relative to other changes in the PI component, was associated with a lower risk of treatment failure (adjusted RR, 0.3; 95% CI, 0.1–0.5) (table 4). When the outcomes were restricted to virologic failure and a switch because of intolerance, with right-censoring of the other switches, the results were similar to those obtained using the primary outcome (table 4). Separation of virologic failure and treatment switches showed that differences between the Nvp and PI groups mainly were attributable to treatment discontinuation, because the risk of virologic failure in the 2 groups did not differ significantly in the multivariate analysis. Stratification for NRTI experience before HAART 1 showed that the favorable effect of Nvp was more pronounced among antiretroviral-naive patients. The adjusted RRs for treatment failure were relatively constant when we compared data for the Nvp group to data for individual types of switch (i.e., change to another PI, continuation of 1 of 2 PIs, addition of 1 PI, change of Sqv formulation, and change of dose and/or frequency), ranging from 0.1 (95% CI, 0.03–0.2) to 0.3 (95% CI, 0.1–0.6).
Adverse effects. Adverse events that occurred before the switch to HAART 2 were reported for 91 patients (73%) in the Nvp group and 207 patients (65%) in the PI group (P = .094). Forty-three (47%) and 96 (46%) of the patients in the Nvp and PI groups, respectively, did not experience resolution of these events or died within the follow-up period. For 19 patients (21%) in the Nvp group and 38 patients (18%) in the PI group, some events resolved. In total, 29 patients (32%) in the Nvp group and 73 patients (35%) in the PI group had complete resolution of all events. Lipodystrophy (diagnosed by the treating physician) was the most frequent new adverse event to occur after a switch, occurring in 16 (13%) and 35 (11%) patients in the Nvp and PI groups, respectively. Only 2 patients (2%) in the Nvp group and 5 patients (2%) in the PI group experienced dermatologic adverse effects. There were no reports of toxic (non-viral) hepatitis or severe rash in patients receiving Nvp that resulted in discontinuation of Nvp.

Immunologic results. CD4 cell counts continued to increase in both groups after the start of HAART 2 (figure 2). No statistically significant difference in CD4 cell counts was observed between the Nvp and PI groups at any time point (P = .088; GLM for repeated measurements).

Discussion

In this study, substitution of Nvp for PIs during virus suppression, under everyday circumstances, was 3-fold more likely to result in sustained virus suppression and maintenance of the new treatment regimen than substitution of an alternative PI or PI

Table 4. Relative risk (RR) of treatment failure within 1 year after a change in the protease inhibitor (PI) component of first-line highly active antiretroviral therapy (HAART 1) for human immunodeficiency virus (HIV) infection in patients with virus suppression in the ATHENA (AIDS Therapy Evaluation, The Netherlands) Study.

<table>
<thead>
<tr>
<th>Comparison(s)</th>
<th>Crude</th>
<th>Adjusted a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nvp group vs. PI group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.2 (0.1–0.3)</td>
<td>0.2 (0.1–0.4)</td>
</tr>
<tr>
<td>Antiretroviral-experienced patients</td>
<td>0.4 (0.2–0.8)</td>
<td>0.3 (0.1–0.96)</td>
</tr>
<tr>
<td>Antiretroviral-naive patients</td>
<td>0.1 (0.1–0.3)</td>
<td>0.1 (0.1–0.3)</td>
</tr>
<tr>
<td>Outcome of HAART 2 b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic failure or treatment switch due to intolerance</td>
<td>0.2 (0.1–0.4)</td>
<td>0.3 (0.1–0.6)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>0.4 (0.2–1.2)</td>
<td>0.8 (0.2–3.0)</td>
</tr>
<tr>
<td>Treatment switch for any reason</td>
<td>0.2 (0.1–0.3)</td>
<td>0.2 (0.1–0.3)</td>
</tr>
<tr>
<td>Type of treatment switch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nvp vs. another type of PI</td>
<td>0.2 (0.1–0.4)</td>
<td>0.3 (0.1–0.6)</td>
</tr>
<tr>
<td>Nvp vs. cessation of 1 of 2 PIs</td>
<td>0.1 (0.04–0.3)</td>
<td>ND</td>
</tr>
<tr>
<td>Nvp vs. addition of 1 PI</td>
<td>0.2 (0.1–0.3)</td>
<td>0.1 (0.03–0.2)</td>
</tr>
<tr>
<td>Nvp vs. change in Sqv formulation</td>
<td>0.2 (0.1–0.4)</td>
<td>0.1 (0.02–0.4)</td>
</tr>
<tr>
<td>Nvp vs. change in PI dose frequency</td>
<td>0.2 (0.1–0.4)</td>
<td>0.1 (0.05–0.4)</td>
</tr>
<tr>
<td>Most common switches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sqv hgc to Sqv hgc/Rtv</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Change in lvd dose frequency</td>
<td>1.2 (0.7–2.1)</td>
<td>0.9 (0.4–2.0)</td>
</tr>
<tr>
<td>Rtv to Nvp</td>
<td>0.1 (0.05–0.4)</td>
<td>0.2 (0.1–0.6)</td>
</tr>
<tr>
<td>Sqv hgc/Rtv to Nvp</td>
<td>0.2 (0.1–0.6)</td>
<td>0.4 (0.1–1.5)</td>
</tr>
<tr>
<td>Idv to Nvp</td>
<td>0.3 (0.1–0.8)</td>
<td>0.3 (0.1–0.98)</td>
</tr>
<tr>
<td>Idv to Nfv</td>
<td>0.8 (0.4–1.7)</td>
<td>0.7 (0.3–1.7)</td>
</tr>
<tr>
<td>Rtv to Nfv</td>
<td>0.4 (0.2–1.03)</td>
<td>0.4 (0.1–1.2)</td>
</tr>
<tr>
<td>Idv to Idv/Rtv</td>
<td>2.2 (1.2–4.1)</td>
<td>3.6 (1.6–8.2)</td>
</tr>
<tr>
<td>Rtv to Sqv hgc/Rtv</td>
<td>1.9 (1.00–3.7)</td>
<td>2.4 (1.03–5.6)</td>
</tr>
<tr>
<td>Other</td>
<td>0.9 (0.6–1.5)</td>
<td>1.2 (0.6–2.4)</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; hgc, hard gelatin capsule; lvd, indinavir; ND, not done because of insufficient data; Nfv, nelfinavir; NRTI, nucleoside reverse-transcriptase inhibitor; Nvp, nevirapine; Rtv, ritonavir; Sqv, saquinavir.

a Analysis was adjusted for route of HIV transmission, type of PIs included in HAART 1, inclusion of NRTIs in HAART 1 and HAART 2, duration of virus suppression before HAART 2, change in NRTIs (yes or no), duration of HAART 1 before switch, and reason for switch and was either adjusted or stratified for treatment experience before start of HAART 1.

b Calculated with right-censoring of alternative outcome(s).

c Adjusted for all variables listed in footnote a, except type of PIs included in HAART 1.
combination. This was found after data were adjusted for the imbalance in other determinants of treatment failure (i.e., route of HIV transmission, type of antiretrovirals used in HAART 1 and HAART 2, concomitant changes of NRTIs, duration of virus suppression before switch, calendar time of switch, and reasons for switch). The differences were most pronounced among persons who were fully antiretroviral naive before administration of the first PI, and differences were mainly attributable to the occurrence of fewer treatment discontinuations during Nvp therapy.

In this study, using data derived from the ATHENA project, we substantiated previous findings but in a larger cohort of patients with a more substantial follow-up period [9–12]. The data allowed us to compare a switch to Nvp with switches to second-line PIs in a multivariate analysis that included multiple predictors of treatment failure. This cohort also allowed us to explore different switches within the PI class, including switches at the level of individual antiretroviral agents. Results showed that a switch to Nvp was superior to all types of PI switches included in this study. For adequate analysis of the effects on virologic failure, use of a larger sample size may be necessary, because the rate of virologic failure in the present study was generally low.

Patients in the Nvp and PI groups appeared to be equally successful in resolving adverse events, although there were 2 deaths in the Nvp group. We were unable to exclude the possibility that Nvp was the cause of 1 of these deaths. No other serious adverse effects (e.g., severe hepatitis or skin rash leading to treatment discontinuation) were reported. The incidence of skin rash in the Nvp group was 2% (we had anticipated an incidence of \( \geq 5\% \) in this group) [7, 8]. The absence of severe skin reactions and severe clinically overt liver toxicity from Nvp [15–17] might indicate that the risk of these events is lower among patients with virus suppression than among patients with high virus loads, which is in line with previous speculation [18]. Potential under-reporting in the ATHENA project might also be responsible for the low incidences of skin rashes and hepatitis that were observed.

Our study was not aimed primarily at assessing the differences in adverse events after a switch. Nevertheless, despite the finding of comparable numbers of adverse events in the 2 groups, the number of discontinuations in the Nvp group was significantly lower, which suggests that tolerance of Nvp-based second-line regimens was better, relatively. Data from the ATHENA cohort were inadequate for analysis of the partial resolution of lipodystrophy, which is described elsewhere [19].

Possible limitations of observational studies are related to potential bias and confounding. Because we did not have data on the severity of adverse effects, we cannot exclude the effect of confounding due to the absence or presence of a simpler alternative (or a new class of antiretrovirals) to a regimen to which intolerance is experienced. The observed difference in the rate of treatment discontinuations might partially reflect different switching behavior in the treatment groups. If this bias indeed plays a role, the results suggest that the presence of an alternative, in addition to the presence of adverse effects, is a risk factor for treatment switches.

We aimed to create a study cohort that was homogeneous with respect to reasons for changing therapy by limiting the cohort to patients who were experiencing virus suppression at the time of the switch. As a result, the reasons for changing to a certain regimen were assumed to be unrelated to the risk of treatment failure. Nonetheless, there were important differences between patients who substituted Nvp for PIs and patients who switched to a second-line PI. For example, the proportion of patients treated with NRTIs before the start of treatment with the first PI was lower in the Nvp group. Nvp probably is prescribed less frequently for antiretroviral-experienced patients because of the potential for viral resistance to NRTIs, which makes these patients less likely to have a sustained virologic response to Nvp [20–22]. Furthermore, the duration of the first PI-containing regimen was longer and the type of antiretrovirals used in the first regimen was different for each group. Therefore, the risk profile for virologic failure among patients who substituted Nvp for PIs seemed more favorable. We were, however, able to adjust for factors that were associated with both the treatment group and treatment failure and for the reason for treatment switch by multivariate analysis.

Finally, we compared a switch to Nvp with a variety of switches between PIs. The types of switch used as a reference included change to another type of PI, a switch to a dual PI regimen or from a dual to a single PI regimen, a change in Sqv formulation, and a change in the PI dose frequency. The resulting treatment regimens were found to be effective in earlier documented studies [23–28]. However, to exclude the potential negative influence of lipodystrophy, which is described elsewhere [19].
ference of any of these switches, we also compared switching to Nvp with each single type of switch and individual type of PI. These subanalyses showed similar results across all types of switch.

In conclusion, this study showed that, in a group of patients with virus suppression, second-line PIs had a poorer performance under everyday circumstances than Nvp with respect to tolerability, as reflected by a higher rate of treatment discontinuations. For patients who achieve virus suppression with HAART 1, replacement of PIs by Nvp appears to be safe in terms of treatment endurance and, therefore, may improve the likelihood of long-term adherence and virus suppression. Further studies are needed to explore the benefits of a switch to an NNRTI, such as efavirenz.

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References


