Studies on the efficacy and toxicity of highly active antiretroviral therapy
Wit, F.W.N.M.

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CHAPTER 3

EXPERIENCE WITH NEVIRAPINE IN PREVIOUSLY TREATED HIV-1 INFECTED INDIVIDUALS

Ferdinand WNM Wit
for the Dutch HIV treating physicians

Antiviral Therapy 2000; 5: 257-66
Chapter 3

Abstract

Objective To assess the virologic, immunologic, clinical effects and tolerability of nevirapine (NVP) in the setting of a compassionate use programme in pretreated HIV-infected individuals.

Design Retrospective observational cohort-study in 13 HIV-outpatient clinics in the Netherlands.

Methods Main outcome measures: plasma HIV-1 RNA levels; CD4 counts; incidence of new AIDS-defining diseases; multivariate analysis of predictors for virologic success; incidence of skin rashes.

Results 187 HIV-infected individuals treated with NVP in the Nevirapine Named Patient Program in the Netherlands were included. After 48 weeks 38% of patients had an HIV-1 RNA level below 1000 copies/mL. In multivariate regression analysis, prior treatment with 3 or less nucleoside analogue RT inhibitors, and a higher baseline CD4 cell count was predictive of virologic success. The median CD4 count remained stable during 48 weeks. Eleven patients experienced a new AIDS defining event. The total incidence of rash (including rash not leading to discontinuation of NVP) was 13.9%, 6.4% of the patients discontinued NVP because of rash. None of the 28 patients with undetectable HIV-1 RNA levels at baseline developed a rash.

Conclusions We conclude that NVP when used as part of salvage therapy is safe and most likely to give sustained suppression of HIV-1 in patients less extensively pretreated. CD4 counts remained stable despite the low rate of virologic success, also in patients not concurrently using PIs. The incidence of NVP-related rash in protease inhibitor-pretreated patients and especially in patients with undetectable HIV-1 RNA levels at the start of NVP, is considerably lower than previously reported for antiretroviral naive patients.
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Introduction

Nevirapine (NVP) is a potent non-nucleoside reverse transcriptase inhibitor (nNRTI) for the treatment of HIV-1 infection. Monotherapy with NVP universally and quickly leads to high level viral resistance [1-4]. The use of NVP in combination with one nucleoside analogue reverse transcriptase inhibitor (NRTI) like zidovudine (ZDV) only slightly delays the development of resistance [5,6]. First-line therapy with NVP in combination with two NRTIs however resulted in durable suppression of plasma HIV-1 RNA to below the level of detection [7-9]. In contrast, in pretreated patients using triple therapy including NVP, a high virologic failure rate was found [10,11]. Prior to licensing, NVP was available in the Netherlands through a Nevirapine Named Patient Program which ran from May 1997 to April 1998. Patients failing therapy and who in the opinion of their treating physicians could only be adequately treated if they could obtain NVP, were eligible for the program. Within the program it was recommended to combine NVP whenever possible with at least two other antiretrovirals expected still to be effective. Physicians were recommended to use the rash grading and management guidelines developed by Boehringer Ingelheim. We performed a retrospective evaluation of the efficacy and safety of NVP within this patient population.

Materials and methods

Patients
The patients from the major HIV-treatment centres in the Netherlands who were treated with NVP through the Named Patient Program were included.

Study sites
All patients were treated in academic centres or large hospitals by infectious diseases specialists experienced with the clinical management of HIV-infection.

Data collection
Information concerning the use of antiretroviral medication, body weight, and history of HIV related diseases was extracted retrospectively from patients' medical records and recorded onto standardised Case Record Forms. HIV-related events were diagnosed according to the Centers for Disease Control and Prevention (CDC) 1993 guidelines [12]. Data concerning toxicity were only recorded if the toxicity led to modification of the antiretroviral regimens. In contrast, the occurrence of skin rash was recorded in all
instances. Information on patients' adherence to their regimens was not collected. Source document verification was not performed, but data entry verification was.

**Plasma HIV-1 RNA**
HIV-1 RNA copy numbers were measured in plasma samples. HIV-1 RNA quantification techniques used in the different hospitals were: NASBA HIV-1 RNA QT technique (Organon Teknika, Boxtel, The Netherlands) with a lower limit of quantification (LLOQ) of 1000 copies/mL, the NASBA Nuclisens technique (Organon Teknika, Boxtel, The Netherlands) with a LLOQ of 400 copies/mL, and the Amplicor HIV Monitor Test (Roche Diagnostic Systems Inc., Branchburg, New Jersey, USA) with a variable LLOQ (median 262, range 40 – 840 copies/mL in the 118 samples which were below LLOQ in this study). However, for analysis purposes the LLOQ of the NASBA Nuclisens and Roche Amplicor assays was set at 1000 copies/mL.

**Lymphocyte subsets**
CD4+ and CD8+ T-lymphocyte counts were determined by flow cytometry.

**Analysis**
Since the use of NVP was recommended whenever possible in combination with at least two other antiretrovirals expected still to be effective, we analysed the data separating the patients into a group who used at least three and a group who used less than three new antiretrovirals, one of which was NVP.

We considered the start of NVP treatment as the start of observation. Time points used for analysis were: baseline (with a window interval of eight weeks before the start of NVP), week 4 (with a window interval from week 2-6), week 8 (6-10), 12 (10-18), 24 (18-30), 36 (30-42), and 48 (42-54). Whenever more than one laboratory result was available the one closest to the particular time point was used for the analysis.

The primary objective was to determine the virologic efficacy of nevirapine used as part of salvage therapy within a heavily pretreated patient population. Virologic efficacy was studied by determining the proportion of patients who experienced an initial virologic treatment response, and the proportion of patients who maintained suppression of plasma HIV-1 RNA levels below 1000 copies/mL during the 48 weeks of follow-up once they achieved a treatment response. A virologic **treatment response** was defined as a decrease in plasma HIV-1 RNA from baseline to below 1000 copies/mL after the start of NVP. Virologic **treatment failure** was defined as not having reached a decrease in plasma HIV-1 RNA to below
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1000 copies/mL at any time after the start of NVP, or having an increase in plasma HIV-1 RNA to above 1000 copies/mL at two consecutive measurements during follow-up following an initial virologic treatment response. However, if no additional measurement was available the patient was still considered to be a virologic failure for the purpose of this analysis. Patients with a plasma HIV-1 RNA below 1000 copies/mL at baseline were included in the analysis of virologic efficacy. They were considered as virologic responders if their plasma HIV-1 RNA remained below 1000 copies/mL during all 48 weeks of follow-up, and as virologic treatment failures if their plasma HIV-1 RNA rose to above 1000 copies/mL at two consecutive measurements during follow-up. Again, if no additional measurement was available the patient was considered to be a virologic treatment failure.

A multivariate logistic regression model was constructed with virologic treatment success as the dependent variable to determine variables predictive of virologic treatment success. A stepwise selection method was employed using entry and removal criteria of 0.05. Baseline parameters considered as possible predictors of a virologic treatment success were: age, gender, HIV transmission category, plasma HIV-1 RNA, CD4 cell count, stage of HIV disease (AIDS vs. non-AIDS), number of concomitantly prescribed (new) antiretroviral agents, number of previously used antiretroviral agents, and duration of prior treatment.

The tolerability of NVP was investigated by performing a Kaplan-Meier analysis of the proportion of patients who discontinued NVP because of adverse events. NVP-related skin rashes were investigated by determining their overall frequency of occurrence as well as the proportion of rashes leading to discontinuation of NVP.

Data were analysed using SAS version 6.12 (SAS institute, Cary, North Carolina, USA). Group comparisons were performed using the Wilcoxon rank sum test for continuous data and the chi square statistic or Fisher's exact test for categorical data. Differences between groups were considered significant at a p < .05 level. All reported p values were two-sided. Clinical and laboratory data were censored at 48 weeks of follow-up.

Results

Patients
Between May 1, 1997 and April 1, 1998 a total of 239 patients entered the Nevirapine Named Patient Program in the Netherlands. Data were collected from patients followed in the 13 largest clinical sites, and were available from 195 patients. Seven of these patients never started taking NVP, mostly
Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>1 or 2 new drugs including NVP</th>
<th>≥ 3 new drugs including NVP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number [n]</td>
<td>187</td>
<td>115</td>
<td>72</td>
<td>.</td>
</tr>
<tr>
<td>Age, median [years (IQR)]</td>
<td>40 (35-47)</td>
<td>40 (35-48)</td>
<td>40 (34-47)</td>
<td>.46</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>161 (87)</td>
<td>96 (84)</td>
<td>65 (90)</td>
<td>.29</td>
</tr>
<tr>
<td>Mode of infection [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>133 (72)</td>
<td>84 (73)</td>
<td>49 (66)</td>
<td>.10</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>31 (17)</td>
<td>22 (19)</td>
<td>9 (13)</td>
<td></td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>6 (3)</td>
<td>2 (2)</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>17 (8)</td>
<td>7 (6)</td>
<td>10 (15)</td>
<td></td>
</tr>
<tr>
<td>AIDS [n (%)]</td>
<td>106 (57)</td>
<td>68 (59)</td>
<td>38 (53)</td>
<td>.39</td>
</tr>
<tr>
<td>No of previously used antiretrovirals [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 3</td>
<td>23 (12)</td>
<td>9 (8)</td>
<td>14 (19)</td>
<td>.001</td>
</tr>
<tr>
<td>4</td>
<td>18 (10)</td>
<td>5 (4)</td>
<td>13 (18)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>37 (20)</td>
<td>13 (11)</td>
<td>24 (33)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>39 (21)</td>
<td>25 (22)</td>
<td>14 (19)</td>
<td></td>
</tr>
<tr>
<td>7 or more</td>
<td>70 (37)</td>
<td>63 (55)</td>
<td>7 (10)</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment with NRTI [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>any NRTI</td>
<td>181 (97)</td>
<td>115 (100)</td>
<td>66 (92)</td>
<td>.002</td>
</tr>
<tr>
<td>ZDV</td>
<td>174 (93)</td>
<td>110 (96)</td>
<td>64 (89)</td>
<td>.14</td>
</tr>
<tr>
<td>ddI</td>
<td>108 (58)</td>
<td>88 (77)</td>
<td>20 (28)</td>
<td>.001</td>
</tr>
<tr>
<td>ddC</td>
<td>97 (52)</td>
<td>63 (55)</td>
<td>34 (47)</td>
<td>.37</td>
</tr>
<tr>
<td>d4T</td>
<td>153 (82)</td>
<td>108 (94)</td>
<td>45 (63)</td>
<td>.001</td>
</tr>
<tr>
<td>3TC</td>
<td>173 (93)</td>
<td>113 (98)</td>
<td>60 (83)</td>
<td>.001</td>
</tr>
<tr>
<td>Pre-treatment with protease inhibitors [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>any PI</td>
<td>184 (98)</td>
<td>115 (100)</td>
<td>69 (96)</td>
<td>.056</td>
</tr>
<tr>
<td>IDV</td>
<td>85 (46)</td>
<td>64 (56)</td>
<td>21 (29)</td>
<td>.001</td>
</tr>
<tr>
<td>SQV-HGC</td>
<td>146 (78)</td>
<td>94 (82)</td>
<td>52 (72)</td>
<td>.15</td>
</tr>
<tr>
<td>RTV</td>
<td>86 (46)</td>
<td>57 (50)</td>
<td>29 (40)</td>
<td>.23</td>
</tr>
<tr>
<td>NFV</td>
<td>8 (4)</td>
<td>6 (5)</td>
<td>2 (3)</td>
<td>.71</td>
</tr>
</tbody>
</table>

Continued...
**Salvage therapy with nevirapine**

**Table 1. continued...**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>1 or 2 new drugs including NVP</th>
<th>≥ 3 new drugs including NVP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment with nNRTI [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Loviride</td>
<td>11 (6)</td>
<td>7 (6)</td>
<td>4 (6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>.</td>
</tr>
<tr>
<td>Total duration of pre-treatment median [years (IQR)]</td>
<td>3.1 (1.7-4.4)</td>
<td>3.4 (2.1-4.5)</td>
<td>2.3 (1.4-4.1)</td>
<td>.033</td>
</tr>
<tr>
<td>Duration of pre-treatment with NRTI, median [years (IQR)]</td>
<td>3.0 (1.8-4.4)</td>
<td>3.1 (1.8-4.4)</td>
<td>2.3 (1.4-4.1)</td>
<td>.09</td>
</tr>
<tr>
<td>Duration of pre-treatment with PI median [years (IQR)]</td>
<td>1.1 (0.9-1.4)</td>
<td>1.1 (0.9-1.4)</td>
<td>1.1 (0.9-1.3)</td>
<td>.50</td>
</tr>
<tr>
<td>HIV RNA load median [log_{10} copies/mL (IQR)]</td>
<td>4.6 (3.9-5.1)</td>
<td>4.5 (3.4-5.0)</td>
<td>4.8 (4.3-5.2)</td>
<td>.0043</td>
</tr>
<tr>
<td>CD4 cell count median [cells×10^6/L (IQR)]</td>
<td>170 (74-300)</td>
<td>150 (74-300)</td>
<td>180 (80-300)</td>
<td>.95</td>
</tr>
<tr>
<td>CD8 cell count median [cells×10^6/L (IQR)]</td>
<td>897 (540-1407)</td>
<td>900 (540-1407)</td>
<td>894 (535-1370)</td>
<td>.79</td>
</tr>
<tr>
<td>Duration of follow up median [weeks (IQR)]</td>
<td>55 (36-69)</td>
<td>57 (39-71)</td>
<td>52 (32-66)</td>
<td>.40</td>
</tr>
</tbody>
</table>

NVP = nevirapine; n = number of patients; IQR = inter quartile range; MSM = men having sex with men; NRTI = nucleoside reverse transcriptase inhibitor; ZDV = zidovudine; ddI = didanosine; ddC = zalcitabine; d4T = stavudine; 3TC = lamivudine; PI = protease inhibitor; IDV = indinavir; SQV-HGC = saquinavir hard gel capsule; RTV = ritonavir; NFV = nelfinavir; nNRTI = non-nucleoside reverse transcriptase inhibitor.

because the patients withdrew consent. One patient had no follow up visits. Thus data from 187 patients were available for analysis. The baseline characteristics of these 187 patients are listed in Table 1. There were no statistically significant differences between the group who used 3 or more new antiretrovirals and the group who used one or two new antiretrovirals with regard to age, gender, mode of infection, stage of HIV-disease, and baseline CD4 and CD8 cell count. The plasma HIV-1 RNA copy number was slightly higher in the group using at least 3 new antiretrovirals. This difference disappeared when the 28 patients with undetectable baseline...
Table 2. Concomitant medication with nevirapine.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>All</th>
<th>1 or 2 new drugs including NVP</th>
<th>( \geq 3 ) new drugs including NVP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>187</td>
<td>115</td>
<td>72</td>
<td>-</td>
</tr>
</tbody>
</table>

Total number of antivirals, including nevirapine [n (%)]

- 2: 3 (2), 3 (3)
- 3: 106 (57), 68 (59), 38 (53)
- 4: 61 (32), 37 (32), 24 (33)
- 5: 16 (8), 7 (6), 9 (13)
- 6: 1 (1)

Number of new antivirals, including nevirapine [n (%)] *

- 1: 39 (21), 39 (29)
- 2: 76 (40), 76 (71)
- 3: 59 (32), 59 (82)
- 4: 12 (6), 12 (17)
- 5: 1 (1)

Concomitantly used antivirals [n (%)] †

- ZDV: 27 (14, 15), 19 (17, 5), 8 (11, 38)
- ddI: 79 (42, 56), 34 (30, 3), 45 (63, 96)
- ddC: 11 (6, 73), 3 (3, 33), 8 (11, 88)
- d4T: 109 (58, 22), 72 (63, 3), 37 (51, 60)
- 3TC: 50 (27, 20), 37 (32, 3), 13 (18, 69)
- hydrea: 36 (19, 100), 16 (14, 100), 20 (28, 100)
- IDV: 39 (21, 56), 24 (21, 29), 15 (21, 100)
- SQV-HGC: 24 (13, 38), 16 (14, 13), 8 (11, 88)
- RTV: 25 (13, 68), 15 (13, 47), 10 (14, 100)
- NFV: 61 (33, 93), 39 (34, 92), 22 (31, 96)

Most often used combinations [n (%)]

- NVP d4T NFV: 22 (12), 21 (18), 1 (1)
- NVP d4T 3TC: 17 (9), 13 (11), 4 (6)
- NVP ddI hydrea: 12 (7), 4 (4), 8 (11)
- NVP d4T ddI IDV: 11 (6), 6 (5), 5 (7)
- NVP d4T IDV: 10 (5), 8 (7), 2 (3)
- NVP d4T SQV-hgc RTV: 8 (4), 4 (4), 4 (6)
- NVP ZDV ddI hydrea: 8 (4), 6 (5), 2 (3)
- NVP ddI NFV: 7 (4), 3 (3), 4 (6)
- NVP d4T ddI hydrea: 6 (3), 4 (4), 2 (3)
- NVP d4T ddI NFV: 5 (3), 0 (0), 5 (7)

NVP = nevirapine; n = number of patients; NRTI = nucleoside reverse transcriptase inhibitor; ZDV = zidovudine; ddI = didanosine; ddC = zalcitabine; d4T = stavudine; 3TC = lamivudine; PI = protease inhibitor; IDV = indinavir; SQV-hgc = saquinavir hard gel capsule; RTV = ritonavir; NFV = nelfinavir; nNRTI = non-nucleoside reverse transcriptase inhibitor; * new = no prior exposure; † new = percentage without prior exposure to this particular drug.
plasma HIV-1 RNA levels were excluded: 4.7 vs 4.8 \( \log_{10} \) copies/mL, \( p = 0.13 \) (see Virology paragraph below). Duration of follow up since the initiation of NVP was similar in both groups. Patients in the group using at least 3 new antiretrovirals were pretreated with fewer drugs for a shorter period of time.

**Concomitant antiretroviral medication**
Concomitantly used NRTIs and PIs are listed in Table 2. Patients did not differ in the total number of antiretroviral drugs in their regimen. By definition, the patients in the 3 or more new antiretrovirals-group, used more new drugs. Regimens from patients in this category more often contained ddI, ddC, 3TC, and/or hydroxyurea. However, PIs were not more frequently used.

**Virology**
One or more plasma HIV-1 RNA results were available from 184 out of 187 patients. The course of the median plasma HIV-1 RNA copy number over time is shown in Figure 1A. In both groups the median drop in HIV-1 RNA was about 1.5 \( \log_{10} \) copies/mL after 4 weeks of therapy, rebounding to and remaining about 0.5 \( \log_{10} \) copies/mL below baseline from week 8 onward. There were no significant differences between groups.

At baseline 16% of all patients had a plasma HIV-1 RNA level below 1000 copies/mL and after 48 weeks this was 38% (Figure 1B). Because of the relatively high proportion of patients with an unquantifiable HIV-1 RNA copy number at baseline, we repeated the analysis stratified for baseline plasma HIV-1 RNA copy number below or above the lower limit of quantification. Of the patients who had a plasma HIV-1 RNA copy number above the lower limit of quantification at baseline, 36.8% had become undetectable at week 4 (Figure 1C). From week 8 until week 48 this proportion remained stable between 23 and 33%. Of the patients who had a plasma HIV-1 RNA below the lower limit of quantification at baseline, the proportion which remained undetectable slowly declined to 74% at week 48 (Figure 1C). Twenty-one of these patients substituted NVP for an antiretroviral agent for which they were intolerant: 9 nucleoside analogue RT inhibitors (mostly stavudine-related peripheral neuropathy), and 10 protease inhibitors (mostly gastro-intestinal complaints). Nine patients added NVP to their regimen because of frequent “blips” of their plasma HIV-1 RNA levels. Virologic failure occurred in 4 out of 19 intolerant patients (21%), and in 3 out of the 9 patients with “blips” (33%).

A total of 111 out of 186 patients (60%, 95% CI 53-67%) experienced a virologic treatment response. There was no significant difference between the group using 3 or more new antiretrovirals (43 of 71 patients (61%, 95% CI 48
**Figure 1. Virology.**

Group using 1 or 2 new antiretrovirals including nevirapine (straight line), group using 3 or more new antiretrovirals including nevirapine (dashed line), numbers represent number of available laboratory results for particular timepoint.

**Panel 1A:** median plasma HIV-1 RNA copy number per group during the first 48 weeks of follow up, bars represent interquartile ranges. Horizontal dashed line represents the lower limit of quantification of 1000 copies/mL plasma.

**Panel 1B:** proportion of patients with less than 1000 HIV-1 RNA copies/mL per group during the first 48 weeks of follow up, bars represent 95% confidence intervals.

**Panel 1C:** proportion of patients with less than 1000 HIV-1 RNA copies/mL stratified by above (straight line) or below (dashed line) this level at the start of nevirapine, bars represent 95% confidence intervals.
Salvage therapy with nevirapine

-72%), and the group using 2 or less new antiretrovirals (68 of 115 patients (59%, 95% CI 50-68%)) (Fisher's exact test, p = .88).

The number of patients maintaining plasma HIV-1 RNA levels below 1000 copies/mL during the 48 weeks of follow-up once they achieved an initial treatment response was 61 out of 186 patients overall (33%, 95% CI 26-40%): 21 of 71 patients (30%, 95% CI 19-42%) in the group using 3 or more new antiretrovirals, and 40 of 115 patients (35%, 95% CI 26-44%) in the group using 2 or less new antiretrovirals (Fisher's exact test, p = .52). Thirty-nine patients had no plasma HIV-1 RNA measurement available at 48 weeks of follow-up: 13 patients were evaluable up to 36 weeks, 10 up to 24 weeks, and the remaining 16 up to 12 weeks or less. Twelve of these patients had died (see below), 1 patient moved to another hospital, 2 patients stopped antiretroviral therapy altogether because of multi-drug resistance, and 15 patients had started using NVP less than 48 weeks before data collection. Seventy-nine percent of these 39 patients were virologic treatment failures.

Predictors of sustained HIV-1 suppression
To investigate possible predictors of sustained HIV-1 suppression a multivariate logistic regression analysis was done excluding the patients with an undetectable HIV-1 RNA load at baseline. In the final model a higher baseline CD4 cell count (odds ratio 1.35 per 100 cells/mm$^3$ increase, 95% confidence interval 1.05-1.75) and less prior therapy with nucleoside analogue RT inhibitors (odds ratio 4.51 for prior therapy with 3 or less agents, 95% confidence interval 1.86-10.94) was predictive for a virologic treatment success.

Immunology
The CD4 and CD8 cell response to treatment is shown in Figures 2A and 2B. Median CD4 and CD8 cell counts did not change significantly from baseline over 48 weeks of follow up, regardless of whether the treatment regimen included 3 or more new antiretrovirals. To investigate the CD4 cell response in case of incomplete viral suppression we divided the 127 patients who failed virologically in a group concomitantly using a PI (n=89) or not (n=38). After 48 weeks the median change in CD4 cell count was equal in both groups (-10 and -20 CD4 cells/mm$^3$ respectively, p = .38).

Discontinuation of NVP
Figure 3A shows the likelihood of discontinuing NVP use over time. After 48 weeks 52% of patients had discontinued NVP (95% CI 43-60%), with this rate being similar in both groups (p = .70). Eighteen percent of patients
Figure 2. Immunology.
Group using 1 or 2 new antiretrovirals including nevirapine (straight line), group using 3 or more new antiretrovirals including nevirapine (dashed line), bars represent interquartile ranges, numbers represent number of available laboratory results for particular timepoint.
Panel 2A: median change in CD4 cell count from baseline per group during the first 48 weeks of follow up.
Panel 2B: median change in CD8 cell count from baseline per group during the first 48 weeks of follow up.
discontinued NVP because of treatment-related (but not necessarily NVP-related) toxicities, 16.6% because of virologic treatment failure, and 8.6% for other reasons (Table 3). These figures were similar for both groups. Of the adverse events leading to discontinuation of NPV, rash was the most common (6.4%). Figure 3B shows a Kaplan-Meier estimate for discontinuation of NVP due to severe rash. There were no significant differences between both groups. All but two cases of severe rash were observed in the first 8 weeks of therapy. The total incidence of rash (including rash not leading to the
discontinuation of NVP) was 13.9% (26 cases). Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN) was not reported. None of 28 patients with undetectable HIV-1 RNA levels at baseline developed a rash (0%, 95% CI 0-12.3%).

**Table 3. Reasons for stopping nevirapine.**

<table>
<thead>
<tr>
<th>Reason</th>
<th>All</th>
<th>1 or 2 new drugs including NVP</th>
<th>≥ 3 new drugs including NVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>187 (100)</td>
<td>115 (100)</td>
<td>72 (100)</td>
</tr>
<tr>
<td>Number of patients on drugs [n (%)]</td>
<td>106 (56.7)</td>
<td>67 (58.3)</td>
<td>39 (54.2)</td>
</tr>
<tr>
<td>Number of patients stopped [n (%)]</td>
<td>81 (43.3)</td>
<td>48 (41.7)</td>
<td>33 (45.8)</td>
</tr>
<tr>
<td>All toxicities [n (%)]</td>
<td>34 (18.2)</td>
<td>21 (18.3)</td>
<td>13 (18.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (6.4)</td>
<td>7 (6.1)</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>6 (3.2)</td>
<td>3 (2.6)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Raised liver enzymes</td>
<td>2 (1.1)</td>
<td>1 (0.9)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>2 (1.1)</td>
<td>2 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>1 (0.5)</td>
<td>0</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Malaise</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Other gastrointestinal event</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>5 (2.7)</td>
<td>2 (1.7)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Elevated HIV-1 RNA [n (%)]</td>
<td>31 (16.6)</td>
<td>18 (15.7)</td>
<td>13 (18.1)</td>
</tr>
<tr>
<td>Other reason [n (%)]</td>
<td>16 (8.6)</td>
<td>9 (7.8)</td>
<td>7 (9.7)</td>
</tr>
</tbody>
</table>

NVP = nevirapine, n = number of patients, % = percentage of patients.

**New AIDS defining events and deaths**

Within 48 weeks after the start of NVP a total of 12 new (non-recurrent) AIDS-defining events occurred in 11 patients (AIDS dementia complex (n=1), Candida esophagitis (3), CMV retinitis (1), chronic HSV ulcer (1), Kaposi's sarcoma (1), non-Hodgkin's lymphoma (1), disseminated *Mycobacterium*
Salvage therapy with nevirapine

*Avium* / *kansasi* infection (2), extrapulmonary tuberculosis (1), cerebral toxoplasmosis (1). Ten of these 11 patients experienced virologic treatment failure (91%). All of these 11 patients had experienced at least one HIV-related event prior to the start of NVP; 10 of them had a prior AIDS diagnosis. Ten of the 11 patients had a baseline CD4 cell count of 200 cells/mm$^3$ or less, and 3 of these 11 patients died. Nine of the 12 AIDS-defining events occurred within 4 months after the initiation of NVP.

A further 9 patients died, all of whom had an AIDS-diagnosis prior to the start of NVP, and 7 had a baseline CD4 cell count below 200 cells/mm$^3$. Seven of these deaths were HIV-related, one was a suicide, and one was a ruptured aneurysm of the abdominal aorta.

**Post-hoc analysis**

Because no differences were observed between the two groups concerning their virologic and immunologic response to treatment, we repeated part of the above analysis using more stringent criteria for considering an antiretroviral agent to be "new". Use of any PI available in the Netherlands during the Nevirapine Named Patient Program may lead to cross-resistance with other PIs [13-19]. Furthermore, several clinical studies have shown that PI-containing salvage therapy is less likely to give a prolonged virologic response than first-line PI-containing HAART [20-23]. As genotypic and phenotypic resistance testing was not routinely available in the Netherlands at the time of this study, physicians could only guess for which antiretrovirals cross-resistance might exist. Therefore, for this post-hoc analysis, a PI was only considered a new drug if the patient was PI-naïve at the time NVP was initiated. An NRTI was still considered new if the patient had not been previously exposed to the drug, in spite of possible prior exposure to other NRTIs. Furthermore, patients who had a plasma HIV-1 RNA below 1000 copies/mL at baseline were excluded.

There were 19 patients who were classified as using at least 3 new drugs, and 139 patients who only used 1 or 2 new drugs. The main findings of the post-hoc analysis were that after 24 weeks 67% of patients in the group using 3 or more new drugs had a plasma HIV-1 RNA below 1000 copies/mL, and this was 28% in the group using less than 2 new drugs (Fisher Exact test, $p = .002$). After 48 weeks these percentages were 58% and 28% respectively ($p = .0495$). In the group using 3 or more new drugs 84% experienced a virologic treatment response, in the group using less than 2 new drugs this was 48% (Chi-square, $p = .003$). In the group using 2 or more new drugs 42% experienced a virologic treatment success, in the group using less than 2 new drugs this was 23% (Fisher's Exact test, $p = .09$).
Chapter 3

Discussion

This observational study has several limitations. Data were collected retrospectively from patients' charts. Several HIV-1 RNA quantification techniques used in the different hospitals, each having a different lower limit of quantification. The cut-off value of 1000 copies/mL we used in our analysis is rather high when compared with the ultra-sensitive techniques used today.

The vast majority of our patients (78%) were pretreated with 5 or more antiretroviral drugs, indicating that NVP was used as salvage rather than second line therapy. Our results illustrate the low rate of success when using NVP as part of insufficiently suppressive antiretroviral combination regimens. Approximately 38% of these extensively NRTI- and PI-pretreated patients achieved sustained suppression of plasma HIV-1 RNA over 48 weeks, more or less regardless of the number of other "new" antiretrovirals that NVP was combined with. Some improvement in response was observed when in the post-hoc analysis the use of PIs as new agents was limited to patients being truly naive for PIs. These results are in agreement with findings from several studies which reported low success rates of antiretroviral therapy after failure of PI-based regimens in heavily pretreated patients [15,16,20-23]. The use of one of the alternative nNRTIs, delavirdine, in patients failing prior PI-containing therapy, likewise was shown to result in similarly low success rates [24]. Potential explanations for the low rates of success observed include the presence of viral cross-resistance within the drug class of both NRTIs [25,26] and PIs [13-19]. In addition, impairment of the intracellular phosphorylation of "new" NRTIs after the prior use of other NRTIs, may have resulted in a form of "pharmacologic" resistance [27,28].

Despite the low rate of virologic success observed, the median CD4 count did not significantly decrease over time. Continued immunologic benefit in the setting of incomplete HIV-1 suppression when using a PI-containing regimen has been previously described [20,29,30]. It has been suggested that this may be related to direct beneficial effects of PIs on the immune system separate from their antiretroviral properties [31-33]. However, there were no differences in CD4 cell counts between virologically failing patients who did or did not use one or more PIs in their regimens, suggesting that this phenomenon might not be exclusively linked to the use of PIs.

Our finding that most patients who substituted nevirapine for an antiretroviral agent for which they were intolerant, maintained viral suppression below 1000 copies/mL, supports recent reports by others [34-36].
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However, in our study we could not compare the failure rate of these patients with a control group.

In general NVP was well tolerated, with an overall rate of skin rash and rate of NVP-discontinuation because of rash of 13.9% (95% CI 8.9-18.9%) and 6.4% (95% CI 2.9-9.9%) respectively. Previous studies reported a much higher overall incidence of rash of 22% to 48% and a discontinuation rate of 10% to 28% [1,2,5,7]. Given the retrospective observational nature of this study, there may have been underreporting of mild rashes not leading to discontinuation of NVP, resulting in a lower than expected overall rate of rash. We are confident however concerning the reliability of the NVP-related discontinuation rate because of rash, since the reasons for a change in therapy are routinely recorded in the patient’s chart. A possible explanation for the lower incidence of rash might be that hepatic enzymes involved in the metabolism of NVP are already induced by prior PI-treatment, leading to lower peak levels during the lead-in phase of NVP dosing. The even more pronounced diminished incidence of rash in patients with undetectable HIV-1 RNA levels at baseline was unexpected. One might speculate that more profound HIV-1 suppression might result in a reduced degree of generalised immune activation, possibly leading to a lesser likelihood of drug hypersensitivity. Another frequent side effect of NVP, hepatitis, was reported in only 2 (1.1%) patients.

In conclusion, our findings illustrate that NVP should not be expected to result in lasting virologic benefit when used as part of incompletely suppressive antiviral combination regimens. This is in contrast with high rates of sustained HIV-1 suppression when NVP is used as part of adequate first line regimens [7-9]. When using NVP as part of salvage regimens the effect of treatment may be improved by determining the choice of concomitantly administered antiretrovirals not only by prior treatment history but also by performing genotypic and/or phenotypic testing for drug resistance [37,38]. CD4 cell counts remained stable despite the low rate of sustained HIV-1 suppression, also in patients not concurrently using PIs. The incidence of NVP-related rash in our study is lower than previously reported in randomized trials.
Chapter 3

The members of the writing committee of this paper are:
Ferdinand WNM Wit, MD, Gerrit Jan Weverling, MD PhD, Sven A Danner, MD PhD, Peter Reiss, MD PhD, Joep MA Lange, MD PhD (Academic Medical Center, Amsterdam), Ineke E van de Ende, MD (Academisch Ziekenhuis Rotterdam Dijkzigt, Rotterdam), Chris HH ten Napel, MD PhD (Medisch Spectrum Twente, Enschede), Pieter L Meenhorst, MD PhD (Slotervaart Ziekenhuis, Amsterdam), Margriet ME Schneider, MD (Academisch Ziekenhuis Utrecht, Utrecht), Robert H Kauffmann, MD PhD (Ziekenhuis Leyenburg, Den Haag), Job R Juttmann, MD PhD (St. Elisabeth Ziekenhuis, Tilburg), Jacob H ten Veen, MD PhD (Prinsengracht Ziekenhuis, Amsterdam), Robert Vriesendorp, MD PhD (Westeinde Ziekenhuis, Den Haag), Frank P Kroon, MD PhD (Leiden University Medical Center, Leiden), Frans AP Claessen, MD (Academisch Ziekenhuis Vrije Universiteit, Amsterdam), Herman G Sprenger, MD (Academisch Ziekenhuis Groningen, Groningen), Clemens Richter, MD PhD (Ziekenhuis Rijnstate, Arnhem).

The other Dutch HIV treating physicians who participated in this study are:
J.T.M. van der Meer, J.K.M. Eeftinck Schattenkerk, J. Prins, T. van de Poll, M. Godfried, D.W. Notermans, E.H. Gisolf, T. Halaby (Academic Medical Center, Amsterdam); M. Hillebrand (Prinsengracht Ziekenhuis, Amsterdam); P.H.P. Groeneveld (Leiden University Medical Center, Leiden); R. Van Leusden (Ziekenhuis Rijnstate, Arnhem); G. Law (Academisch Ziekenhuis Groningen, Groningen); J.C.C. Borleffs (Academisch Ziekenhuis Utrecht, Utrecht); I.C. Gyssens, S. De Marie (Academisch Ziekenhuis Rotterdam Dijkzigt, Rotterdam); J.W. Mulder, W.A. Scheele (Slotervaart Ziekenhuis, Amsterdam); J.M. Henrichs (Ziekenhuis Leyenburg, Den Haag); C. van der Heul (St. Elisabeth Ziekenhuis, Tilburg); K. Pogany (Medisch Spectrum Twente, Enschede)

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