# Nelfinavir and non-nucleoside reverse transcriptase inhibitor-based salvage regimens in heavily HIV pretreated patients

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**OBJECTIVE:** To assess the efficacy of nelfinavir mesylate (NFV) in combination with delavirdine mesylate (DLV) or efavirenz (EFV) and other antiretroviral agents following virological failure on other protease inhibitor (PI)-based regimens.
**DESIGN:** Multicentre, retrospective chart review.
**METHODS:** One hundred-one patients who were naive to both NFV and non-nucleoside reverse transcriptase inhibitors (NNRTIs) and who initiated NFV plus DLV or EFV-based salvage regimens were reviewed. Response to treatment was defined as a reduction in HIV ribonucleic acid (RNA) levels to unquantifiable levels (less than 50 copies/mL, less than 400 copies/mL, less than 500 copies/mL) on at least one occasion after the initiation of salvage therapy. Baseline correlates of response, including prior duration of HIV infection, prior number of regimens, viral load and CD4 cell counts were also evaluated.
**RESULTS:** Patients had a mean duration of HIV infection of 10 years, a mean duration of prior therapy of four years, a median of four prior nucleoside reverse transcriptase inhibitors and a median of two prior PIs. At the time of review the mean duration of salvage therapy was 63.4 weeks. Virological suppression was achieved in 59 (58.4%) patients within a mean of eight weeks and maintained for a mean of 44.9 weeks (the mean follow-up was 78 weeks). Of the non-responders, 16 (38%) achieved a less than 1 $\log_{10}$ decrease in HIV RNA levels. Although there was no association between baseline correlates, response rate (75.7%) was significantly higher in patients with HIV RNA levels of 50,000 copies/mL or lower and CD4 counts greater than 200 cells/mm$^3$.
**CONCLUSION:** NFV/NNRTI-based highly active antiretroviral therapy regimens are an effective therapy in many patients who have experienced virological breakthroughs on at least one prior PI-based regimen.

**Key words:** *Antiretroviral therapy; Nelfinavir; Non-nucleoside reverse transcriptase inhibitors; Salvage therapy*

## Traitement de rattrapage à base de nelfinavir et d'un inhibiteur non nucléosidique de la transcriptase inverse chez des patients porteurs du VIH déjà lourdement traités

**OBJECTIF :** Évaluer l'efficacité du mésylate de nelfinavir en association avec le mésylate de delavirdine, l'éfavirenz ou d'autres antirétroviraux à la suite de l'échec virologique de traitements antérieurs à un inhibiteur de protéase (IP).
**TYPE D'ÉTUDE :** Revue rétrospective, multicentre, de dossiers médicaux.
**MÉTHODE :** Nous avons passé en revue les dossiers de 101 patients jamais traités au nelfivanir et à un inhibiteur non nucléosidique de la transcriptase inverse (INNTI), qui ont reçu du nelfinavir en association avec de la delavirdine ou de l'éfavirenz à titre de traitement de rattrapage. La réaction au traitement a été définie comme une diminution du taux d'acide ribonucléique (ARN) du VIH à des valeurs indétectables (inférieures à 50 copies/ml, 400 copies/ml et 500 copies/ml) au moins une fois après l'amorce du traitement de rattrapage. Ont également été évalués les corrélats de base de la réaction, notamment la durée de l'infection à VIH, le nombre antérieur de traitements, la charge virale et la numération des lymphocytes T-CD4.
**RÉSULTATS :** Voici quelques caractéristiques : durée moyenne de l'infection à VIH : 10 ans; durée moyenne des traitements antérieurs : 4 ans; nombre médian de traitements antérieurs à un inhibiteur nucléosidique de la transcriptase inverse : 4; nombre médian de traitements à un IP : 2. Au moment de l'examen des dossiers, la durée moyenne du traitement de rattrapage était de 63,4 semaines. Il y a eu suppression virologique chez 59 patients (58,4 %) en l'espace de huit semaines en moyenne et pour une durée moyenne de 44,9 semaines (durée moyenne du suivi : 78 semaines). Parmi les patients non répondeurs, 16 (38 %) ont connu une diminution inférieure à 1 $\log_{10}$ du taux d'ARN du VIH. Même s'il n'y avait pas d'association entre les corrélats de départ, le pourcentage de réaction (75,7 %) était sensiblement plus élevé chez les patients ayant un taux d'ARN du VIH égal ou inférieur à 50 000 copies/ml et un nombre de lymphocytes T-CD4 supérieur à 200/mm$^3$.
**CONCLUSION :** Les traitements antirétroviraux fortement actifs à base de nelfinavir et d'un INNTI s'avèrent efficaces chez bon nombre de patients qui ont connu un rebond virologique pendant au moins un traitement antérieur à un IP.

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Although the use of highly active antiretroviral therapy (HAART) (including protease inhibitors [PIs]) has had a significant impact in decreasing HIV-related morbidity and mortality (1), virological failure of PI-based regimens is fairly common in clinical practice (2). Several predictors of virological success have been identified, including low baseline plasma viral load (VL) and high baseline CD4 cell count (2-5). In addition, once therapy is initiated, adherence to the regimen (2,6,7) and the rate of the initial virological response (8) appear to be quite important to the long-term success of the regimen. Following confirmed virological breakthrough, current guidelines recommend using at least two new drugs in the new regimen, preferably agents to which the patient has not been previously exposed or developed resistance (9,10). Although response rates of up to 90% have been reported to initial HAART, these rates decrease significantly with each subsequent treatment regimen. Thus, the design of successful second and third line HAART regimens is more challenging.

Nelfinavir mesylate (NFV) is one of several currently available HIV PIs. Although it has been shown to be effective in naive patients (11-13), its role in subsequent therapy is not clearly defined. A limited number of studies have investigated the efficacy of NFV-based regimens in patients experiencing virological breakthroughs on other PI-based regimens (14-18).

Successful salvage therapy after PI failure may depend on the incorporation of a drug from a class to which the patient is naive, as shown with the use of the non-nucleoside reverse transcriptase inhibitors (NNRTI) delavirdine mesylate (DLV) (15) and efavirenz (EFV) (19). Medications in this class have been shown to be potent agents in reducing VL (20-22). Thus, in appropriate patients the combination of NFV with an NNRTI may form the basis of a salvage regimen following virological failure on one or more PI-based regimens.

Although pharmacokinetic interactions occur when NFV is combined with DLV (23,24) or EFV (25), no dose adjustments are recommended by the manufacturers or by current HIV guidelines (9) when these agents are used concomitantly.

The present study was undertaken to determine the efficacy of NFV used in combination with DLV or EFV and other antiretroviral agents in patients naive to the non-nucleoside class experiencing virological failure on other PI-based regimens .

## METHODS

A multicentre retrospective chart review of HIV-infected adult patients was conducted at five clinics across Canada (representing over 6000 HIV patients) to identify patients who had initiated therapy including NFV and DLV, or NFV and EFV between January, 1998 and November, 2000. Patients were included in the study if they had experienced virological breakthrough on one or more previous PI-containing regimen and had been naive to NNRTIs and NFV before starting their current salvage regimen. Past regimen failure was defined as failure reported in the chart by the treating physician or as documented outcome HIV ribonucleic acid (RNA) levels greater than the limit of detection while receiving a non-NFV PI-based regimen. One hundred-one (n=101) patients met the inclusion criteria and were included in the study.

A chart review was performed to collect patient demographic information, antiretroviral medication history and details of the current NFV/DLV- or NFV/EFV-based salvage regimen. During the time that the patient was on this therapy, information on clinical events, drug tolerability, HIV RNA levels (VL) and CD4 cell counts was recorded.

**TABLE 1**
**Baseline demographics of study participants prior to the initiation of the salvage regimen**

| | |
|---|---|
| Total number of patients (n) | 101 |
| Male (%) | 91 (90.1) |
| Female (%) | 10 (9.9) |
| Race | |
| Caucasian (%) | 97 (96) |
| African American (%) | 3 (3) |
| Hispanic (%) | 1 (1) |
| Mean duration of HIV, years (range) | 9.8 (3.1 - 21.1) |
| Mean duration of AIDS (n=58), years (range) | 5.1 (0.6 - 10.6) |
| Median HIV RNA level at baseline (range) | |
| copies/mL | 31,050 (598-1,369,000) |
| $\log_{10}$ copies/mL | 4.49 (2.78-6.14) |
| Median CD4 count (cells/mm$^3$) at baseline (range) | 200 (3-760) |
| Previous anti-HIV therapies | |
| Median number of ARV agents (range) | 6 (3-9) |
| Median number of HAART regimens (range) | 2 (1-7) |
| Median number of PI regimens (range) | 3 (1-7) |
| Median number of PIs (range) | 2 (1-3) |
| Median number of NRTIs (range) | 4 (1-5) |
| Duration of previous anti-HIV therapies | |
| Mean duration of ARV therapy (months) | 47.8 |
| Mean duration of HAART therapy (months) | 21.9 |

*ARV Antiretroviral; HAART Highly active antiretroviral therapy; NRTIs Nucleoside reverse transcriptase inhibitors; PI Proteases inhibitors; RNA ribonucleic acid*

For HIV RNA levels, three clinics (n=90 patients) used the Quantiplex HIV RNA branched chain (bDNA) assay (Chiron Diagnostics, USA), with a limit of quantification of 500 copies/mL before May, 1999, and 50 copies/mL thereafter. Two clinics (n=11 patients) used the Amplicor HIV-1 Monitor assay (Roche Diagnostics, Laval) with a limit of quantification of 400 copies /mL before June, 2000, and 50 copies/mL thereafter.

Virological suppression or response was defined as a reduction in plasma HIV RNA levels to unquantifiable levels (less than 50 copies/mL, less than 400 copies/mL, less than 500 copies/mL, depending on the clinical assay in use at the time of evaluation) on at least one occasion after the initiation of NFV/DLV- or NFV/EFV-based therapy. The response rate was stratified according to baseline HIV RNA levels (above or below 50,000 copies/mL) and CD4 cell counts (above or below 200/mm$^3$). Additional endpoints that were examined included the duration of virological response and the ability to achieve a reduction in plasma VL of 90% (1.0 $\log_{10}$ copies/mL) or greater while on therapy. Baseline correlates of response, including prior duration of documented HIV infection and prior number of treatment regimens, as well as the reasons to discontinue NFV-based therapy were also evaluated. The time period for the analysis was from the initiation of NFV/DLV- or NFV/EFV-based therapy until there was any change in the antiretroviral regimen, including changes in the nucleoside reverse transcriptase inhibitor (NRTI) backbone. Virological response was analyzed at four, 12, 24, 36 and 48 weeks after initiation of the NFV/NNRTI-based salvage regimen. For this analysis, four patients who initiated the salvage regimen less than one year before review and were still continuing the

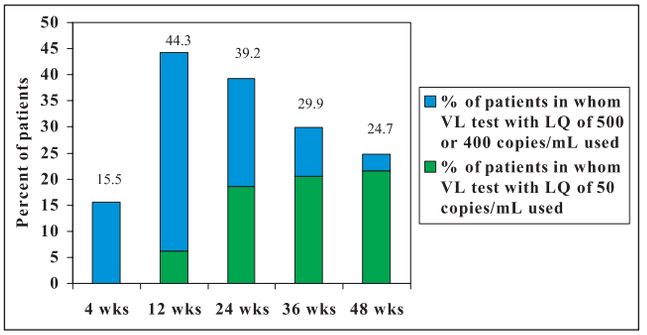


**Figure 1)** *Patients who achieve or maintain viral suppression at time-points after initiating NFV/DLV- or NFV/EFV-based therapy. Only patients who initiated NFV/NNRTI-based therapy at least one year before the review date were included (n=97). Patients who continued the NFV/NNRTI-based regimen but had changes in other agents due to side effects while virologically suppressed were also included. DLV delavirdine mesylate; EFV Efavirenz; LQ Limit of quatification; NFV Nelfinavir mesylate; NNRTI non-nucleoside reverse transcriptase inhibitor; VL Viral load; wks Weeks*

**TABLE 2**
**Predictors of virological response**

| | Responders* (n=59) | Non-responders (n=42) | P value (Mann-Whitney U test) |
|---|---|---|---|
| Median number of ARV agents tried | 6 | 6 | 0.1663 |
| Median number of PIs tried | 2 | 2 | 0.2348 |
| Median duration of documented HIV Infection (months) | 9.1 | 9.8 | 0.8877 |
| Median baseline plasma HIV RNA levels (copies/mL) | 18,720 | 49,453 | 0.0710 |
| Median baseline plasma HIV RNA levels ($log_{10}$ copies/mL) | 4.27 | 4.69 | 0.0699 |
| Median baseline CD4 count (cells/$mm^3$) | 219 | 148 | 0.0668 |

**Virological response is defined as achieving undetectable HIV ribonucleic acid (RNA) levels on at least one occasion following the initiation of NFV/EFV- or NFV/DLV-based salvage therapy. ARV Antiretroviral; DLV Delavirdine mesylate; EFV Efavirenz; NFV Nelfinavir mesylate; PI Protease inhibitor*

NFV/NNRTI-based regimen were excluded because they would not yet have reached some of the time points of the analysis.

### Statistical analysis

Fisher's exact test was used to determine statistical significance between groups stratified according to baseline HIV RNA levels and CD4 cell counts. Trends for differences between groups were analyzed using the $\chi^2$ test. The significance of differences between the median values for responders and nonresponders for demographic variables (number of ARV agents, numbers of PIs, duration of documented HIV infection, baseline HIV RNA levels, log of baseline HIV RNA levels and CD4 count) was tested using the Mann-Whitney U test with SPSS for Windows (SPSS Inc, USA). A 5% limit was used as the cutoff for significance.

## RESULTS

### Baseline demographics

A total of 101 patients met the eligibility criteria and were included in the analysis. Of these, 81 (80%) received EFV as their NNRTI and 20 (20%) received DLV. Baseline demographic characteristics of study participants before the initiation of the current salvage regimen are summarized in Table 1. Most patients were white men infected with HIV for a mean of 10 years who had been receiving antiretroviral treatment for a mean of four years and HAART for a mean of 22 months. Approximately half of the patients (58 of 101, 57%) had a prior diagnosis of AIDS for a mean duration of five years. On average, most patients had moderately advanced immune disease (median CD4 count of 200 cells/$mm^3$), half with HIV RNA levels above 30,000 copies/mL. Most patients were heavily pretreated, having received between three and nine different agents, including two separate HAART regimens. Patients had tried a median of two PIs with 82% having tried indinavir sulfate, 82% having tried saquinavir and 62% having tried ritonavir.

### Effects on HIV RNA levels and CD4 cell counts

At the time of data collection, all patients had received NFV/DLV- or NFV/EFV-based therapy for a mean of 63.4 weeks.

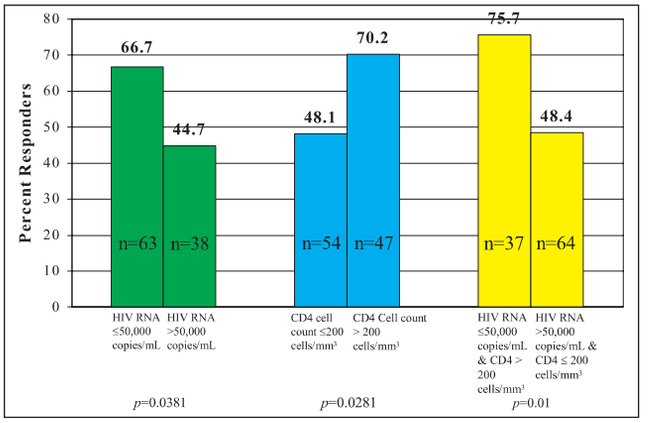


**Figure 2)** *Response according to baseline HIV ribonucleic acid (RNA) level and CD4 cell count*

Virological suppression was achieved on at least one occasion in 59 (58.4%) patients (the mean follow-up was 78 weeks). At the time of first VL suppression, the standard sensitive test with a limit of quantification of 500 copies/mL or 400 copies/mL was being used in 44 (43.6%) patients and the ultrasensitive test with a limit of quantification of 50 copies/mL was being used in 15 (14.9%) patients to measure HIV RNA levels. At the time of data collection, the median HIV RNA levels in responders compared to baseline had decreased from 4.27 $log_{10}$ copies/mL to 2.78 $log_{10}$ copies/mL and the median CD4 cell count had increased from 219 cells/$mm^3$ to 263 cells/$mm^3$. The mean follow-up in 42 (41.6%) patients who did not achieve undetectable HIV RNA levels (ie, nonresponders) was 43 weeks. In the 42 (41.6%) patients who did not experience virological suppression at any time (ie, who did not achieve undetectable HIV RNA levels), 16 (38%) still showed a 90% (1.0 $log_{10}$) decrease in HIV RNA levels, with an overall increase in median CD4 cell count in these 42 individuals from 148 cells/$mm^3$ to 181 cells/$mm^3$.

**TABLE 3**
**Patient disposition at time of analysis**

| | No. of Patients (n=101) | % |
|---|---|---|
| Continuing the same NFV+NNRTI-based regimen | 25 | 24.80% |
| Changes in ARV agents other than NFV+NNRTI | 25 | 24.80% |
| Due to virological rebound* | 7 | 6.90% |
| Due to clinical deterioration | 2 | 1.98% |
| Due to side effect† | 11 | 10.90% |
| Due to patient preference | 4 | 3.96% |
| Due to physician preference | 1 | 0.99% |
| Discontinued NFV or EFV or DLV | 46 | 45.50% |
| Due to virological rebound* | 23 | 22.80% |
| Due to clinical deterioration | 6 | 5.90% |
| Due to side effect‡ | 10 | 9.90% |
| Due to patient preference | 5 | 4.90% |
| Due to other or unknown reason | 2 | 1.98% |
| Lost to follow-up | 5 | 4.90% |

**As determined by physician; †Due to neuropathy (n=3), diarrhea (n=1), lipodystrophy (n=1) or not documented/unknown causes (n=6); ‡Due to diarrhea (n=4), neuropsychiatric effects (n=2), anemia (n=1), glucose intolerance (n=1), pancreatitis (n=1) or not documented/unknown causes (n=1). ARV Antiretroviral; DLV Delavirdine mesylate; EFV Efavirenz, NFV Nelfavir mesylate; NNRTI Non-nucleoside reverse transcriptase inhibitor*

### Duration of response

On average, suppression was achieved in eight (range: 1 to 30) weeks, and maintained for 44.9 (range 1.3 to 145.3) weeks. At 48 weeks, when the ultrasensitive test with a limit of quantification of 50 copies/mL was being used in the majority of individuals, 24 (24.7%) patients remained virologically suppressed (Figure 1).

### Predictors of virological response/suppression

As shown in Table 2, there was no association between median duration of documented HIV infection, prior antiretroviral therapy, baseline HIV RNA levels or CD4 cell counts. A multiple regression analysis indicated that the combination of HIV RNA levels and CD4 cell counts was also not predictive of response (P=0.0847). However, stratification by baseline HIV RNA levels and CD4 cell counts showed a statistically significant difference in response for those patients with values above or below 50,000 copies/mL (66.7% response versus 44.7% response, P=0.0381) and above or below 200 cells/mm$^3$ (70.2% response versus 48.1% response, P=0.0280) (Figure 2). In combining these two parameters, the best response rate (75.7%) was seen in patients with baseline HIV RNA measures of 50,000 copies/mL or lower and CD4 cell counts above 200 cells/mm$^3$. In contrast, only 48.4% of patients who started therapy with higher HIV RNA levels and lower CD4 cell counts achieved virological suppression (P=0.01, Figure 2).

### Patient disposition

At the time of evaluation, 24.8% of patients remained on their initial regimen (Table 3). In an additional 24.8% of patients, only the NRTI backbone had been modified. Thus, 50% of patients remained on the same NFV/NNRTI combination. Overall, 30% required a change in therapy (either NFV, NNRTI, or NRTI) due to virological breakthrough, while 20% experienced significant toxicity, most often diarrhea, neuropathy, or neuropsychiatric symptoms (Table 3). Only 5% of patients were lost to follow-up.

### Response to DLV versus EFV

Of the 101 patients included in the present study, 81 (80%) received EFV and 20 (20%) received DLV as their NNRTI. Given the limited number of patients on DLV (n=20) versus EFV (n=81), it is difficult to interpret the role of a specific NNRTI on response during the salvage therapy.

## DISCUSSION

Virological failure with PI-based regimens is common in clinical practice and the response to second-line or salvage therapy is often unsatisfactory due to the presence of resistance mutations that frequently confer cross-resistance to other members of the same drug class. Most current guidelines would favour the use of triple-class regimens in this setting, selecting an NNRTI and new PIs/NRTIs chosen to minimize the potential for cross-resistance with agents to which the individual patient may already have been exposed. The selection of specific agents may be better informed by the use of drug resistance testing.

In this context, our retrospective analysis shows that in many patients who have experienced a virological breakthrough while on one or more prior PI-based regimens, NFV plus NNRTI-based HAART regimens can be effective salvage treatment options. Although this was a retrospective study our results are similar to those reported in other randomized and non-randomized salvage studies with NFV and EFV or DLV conducted in NNRTI- and NFV-naive patients who have been heavily pretreated with PI/NRTI regimens (14-18). Hammer et al (17) report that treatment with a background of NFV/EFV/adefovir dipivoxil and either abacavir sulfate or NRTIs resulted in virological suppression (VL of less than 500 copies/mL) in 45% of patients at 16 weeks (17). In the AIDS Clinical Trials Group Study 359 (15), virological suppression (VL of less than 500 copies/mL) was achieved in 47% and 36% of patients randomized to NFV/DLV/saquinavir or NFV/DLV/saquinavir/adefovir, respectively after 16 weeks. The regimens consisting of NFV/EFV with either stavudine or didanosine/hydroxyurea led to virologic suppression in 41% to 46% of patients over 24 weeks, results similar to those presented in this report (14,18). The durability of virologic suppression that we have observed (25% over 48 weeks) is also similar to that obtained by Cassado et al (26) at 52 weeks with NFV and the NNRTI nevirapine.

Major causes of antiretroviral therapy treatment failure that have been identified include advanced stage of HIV disease, development of viral resistance during prior therapy, and insufficient drug exposure due to poor adherence, inadequate drug absorption, and unfavourable pharmacokinetics (9). In our retrospective analysis, the only factor that seemed to be associated with the inability to achieve virological suppression was more advanced immune suppression and a higher plasma VL. This confirms the observation that success of the regimen can be enhanced by making a change in therapy as soon as a true virological breakthrough is confirmed, minimizing the evolution of drug resistance to NRTIs and PIs that may be occurring and maximizing the potential benefit of introducing NNRTIs as a new drug class in salvage therapy. It may be that the use

of resistance-testing (to allow for a more insightful selection of NRTIs and PIs) could have improved the results. Unfortunately, in the setting of this retrospective analysis, this tool was not yet available for use in our centres when the salvage regimen was being selected.

In summary, our data indicate that NFV/NNRTI-based HAART regimens offer effective therapy in many patients who have experienced a virological breakthrough on at least one prior PI-based regimen. The efficacy of this approach could be enhanced by its use in patients with early virological breakthrough, with the regimen optimized by the use of drug resistance testing and drug level monitoring. Comparison of different NNRTI-based regimens in prospective studies is definitely warranted to help establish if one regimen is systematically better than others in specific patient populations. Nonetheless, our data suggest that NFV is useful in patients who have already experienced virological breakthrough on one or more prior PI-based regimens.

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