

Brief report

# Safety, efficacy, and tolerability of nelfinavir-containing antiretroviral therapy for patients coinfecting with HIV and hepatitis C undergoing methadone maintenance

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## Abstract

The safety, efficacy, and tolerability of nelfinavir (NFV)-containing antiretroviral therapy were evaluated in patients coinfecting with HIV and hepatitis C undergoing methadone maintenance at an urban outpatient opioid treatment program serving a minority adult population. Eligibility covered methadone-maintained patients coinfecting with HIV and hepatitis C who had received or were currently receiving NFV. The yield was 51 case patients. Parameters examined looked into safety, efficacy, and tolerability. Nelfinavir was discontinued in 2 patients for liver function abnormalities but resumed in 1 patient. One patient developed laboratory abnormalities during NFV therapy that were not present before NFV therapy; in 12 case patients, pre-NFV therapy liver function abnormalities resolved completely during NFV therapy. There was a statistically significant increase in CD4 count during NFV therapy. Viral load decreased or was unchanged in 10 case patients and increased in 8, of whom 5 had a CD4 count increase during NFV therapy. Three patients had diarrhea and 4 patients had constipation. Nelfinavir was not discontinued—neither was dose adjusted—in any of these patients. Patients who had received NFV  $\geq 36$  months had a smaller increase in mean methadone dose as compared with patients who had received NFV  $< 36$  months. The results show that NFV is safe, efficacious, and well tolerated. © 2006 Elsevier Inc. All rights reserved.

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## 1. Introduction

The treatment of HIV infection presents a number of challenges, even in patients without additional comorbidities. Among injection drug-using patients in substance abuse treatment programs who are HIV positive, 50%–80% are coinfecting with hepatitis C (Sulkowski, Thomas, Chaisson & Moore, 2000). Coinfection of HIV with hepatitis C is the comorbidity resulting in the greatest risk of accelerated liver damage, even when HIV antiretroviral therapy (ART) is instituted (Benhamou et al., 2001;

Sulkowski et al., 2000). For HIV-positive patients undergoing methadone maintenance for opiate dependence receiving ART, further management difficulties emerge, given that ART, particularly protease inhibitors (PIs), and methadone have inhibitory and/or inducing effects on cytochrome P450 3A4 (McCance-Katz, Rainey, Friedl, & Jatlow, 2003). There are also data suggesting that PIs directly accelerate methadone metabolism, probably through this same cytochrome system (McCance-Katz et al., 2003). In view of these challenges, the utility of nelfinavir (NFV) in this patient population was studied.

## 2. Materials and methods

The Addiction Research and Treatment Corporation (ARTC) is a private not-for-profit outpatient opioid treatment

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Table 1  
Patient characteristics

Characteristic	Value
Race/ethnicity [ <i>n</i> (%)]	
Black	27 (53)
Hispanic	23 (45)
White	1 (2)
Sex [ <i>n</i> (%)]	
Male	27 (53)
Female	24 (47)
Age (years)	
Mean	48
Range	35–62

program (OTP) with seven methadone maintenance clinics located in the boroughs of Brooklyn (3 sites) and Manhattan (4 sites) in New York City. The average daily census is approximately 3,000 adults, predominantly from minority population groups. In addition to methadone maintenance, the ARTC provides substance abuse counseling, vocational programs, primary medical and HIV/AIDS care, and HIV/AIDS case management.

This study was a retrospective chart review drawn from the entire OTP population. To be included in the review, patients had to be coinfecting with HIV and hepatitis C and receive both their methadone maintenance and HIV care at one of the ARTC clinics to provide ready access to sufficient clinical and laboratory data. In addition, the use of ART that included NFV could be either past or current at the time of the chart review.

The chart review provided for tabulation of both clinical and laboratory data. Clinical data consisted of antiretroviral regimen changes and adherence, methadone dose and stability of dose when NFV was initiated, presence or absence of diarrhea or constipation, other co-occurring medical conditions in addition to HIV and hepatitis C, alcohol consumption, and concurrent use of psychotropic agents. Laboratory data consisted of liver function tests (LFTs), including those for bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase; indirect measures of liver function (albumin, platelet count, cholesterol, triglyceride, and glucose); CD4 count; and HIV viral load.

Nelfinavir safety was evaluated via measures of liver function; efficacy, via serial CD4 counts and viral loads; and tolerability, via side effects, particularly constipation, diarrhea, and need for methadone or NFV dose adjustments.

Data analysis used paired-samples *t* tests to compare mean CD4 counts and mean methadone dose before NFV and during NFV therapy, with *p* values provided.

### 3. Results

Using the cited inclusion criteria, 51 patient charts were eligible for review. The review was done from June 23, 2003, to February 25, 2004, and the period of NFV therapy extended from July 1997 to February 2004. In 12 cases, the patient was undergoing NFV-containing ART before admis-

sion to the ARTC. As a result, pre-NFV clinical and laboratory data were unavailable in most of those cases. Pre-NFV viral load data were also unavailable for an additional 19 patients who started receiving NFV before 2000. This was because viral load was not generally used as a parameter for evaluating response to treatment before 2000, and reimbursement of periodic viral load testing through New York State Medicaid was not available. These factors accounted for virtually all of the clinical or laboratory data that could not be retrieved.

Patient characteristics and comorbid conditions, respectively, are listed in Tables 1 and 2. In addition, none of the 51 patients received treatment for hepatitis C before, during, or after NFV therapy and all antiretroviral regimens containing NFV consisted of at least three drugs.

In evaluating safety, NFV was discontinued in 2 of the 51 case patients for abnormal LFTs but resumed in 1 case patient. In the case patient in whom NFV was resumed, the pre-NFV LFT abnormalities were essentially unchanged from those present during NFV therapy. In the second case, markedly increased amylase occurred during NFV therapy. Other LFTs were only mildly elevated before NFV therapy and did not change during NFV therapy. It was noted that this patient had been receiving NFV for a total of 56 months before discontinuation, and the patient elected to receive no post-NFV ART.

In 42 of the 51 case patients, laboratory values were available before and during NFV therapy. Of 10 patients with no laboratory abnormality before NFV therapy, 1 developed laboratory abnormalities during NFV therapy, a glucose level of 160 mg/dL. In 32 case patients with laboratory abnormalities before NFV therapy, normalization occurred during NFV therapy in 12; in the remaining 20 patients, none developed new or worsening laboratory abnormalities during NFV therapy.

In evaluating efficacy, NFV was discontinued in 5 of the 51 case patients: 2 for loss of effect (after 26 and 52 months of receiving NFV), 2 related to adherence problems (after 14 and 59 months of receiving NFV), and 1 because of resistance on genotyping (after 67 months of receiving

Table 2  
Comorbid conditions

Condition	<i>n</i>
+PPD	23
Smoking	20
Hypertension	14
Alcohol use	13
History of other STD	12
Diabetes	9
Treated psychiatric conditions	8
Dyslipidemia	7
Chronic hepatitis B or other liver disease	6
Chronic obstructive pulmonary disease	3
Renal insufficiency	1
Carcinoma	1

PPD = purified protein derivative (used to test for tuberculosis).

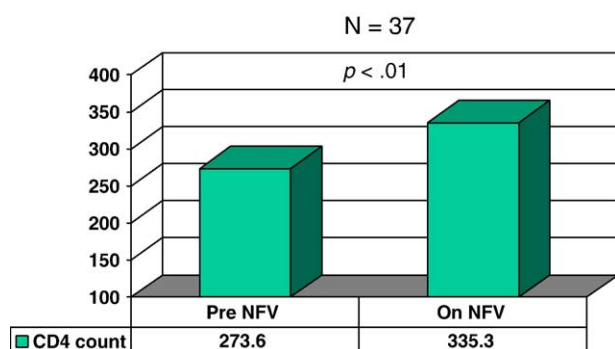


Fig. 1. CD4 count before and during NFV therapy.

NFV). In addition, there were 12 patients for whom NFV therapy was stopped but not discontinued for varying lengths of time, 6 related to adherence problems. In 37 case patients for whom CD4 count was available before and during NFV therapy, the mean CD4 count was 273.6 before NFV therapy and 335.3 at the most recent measurements during NFV therapy, a statistically significant difference ( $p < .01$ ; Fig. 1). In 22 case patients for whom viral load was available before and during NFV therapy, the picture was mixed. Viral load decreased or remained unchanged in 12 case patients and increased in 10. In the former group, mean viral load decreased from 120,009 to 24,075 at the most recent testing, a change of 0.70 log. In the latter group, mean viral load increased from 40,641 to 153,329 at the most recent testing, a change of 0.58 log. Among 14 case patients for whom both CD4 count and viral load were available before and during NFV therapy, there were 5 in whom viral load increased but CD4 count also increased. A sixth case in whom this occurred was 1 of the 2 case patients cited previously for whom NFV was discontinued owing to loss of effect. In 3 of 4 case patients in whom CD4 count decreased, viral load also decreased. In the fourth case, NFV therapy was discontinued after 26 months and a new regimen was started, but CD4 and viral load information post-NFV were not available at the time of review.

In evaluating tolerability, diarrhea occurred in 3 case patients and constipation did in 6, but NFV was not discontinued and the dose of NFV or methadone did not require adjustment. In all instances, the symptoms quickly attenuated. In 42 case patients for whom data were available

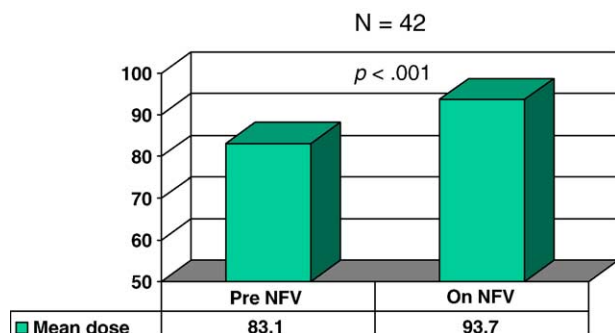


Fig. 2. Methadone dose before and during NFV therapy.

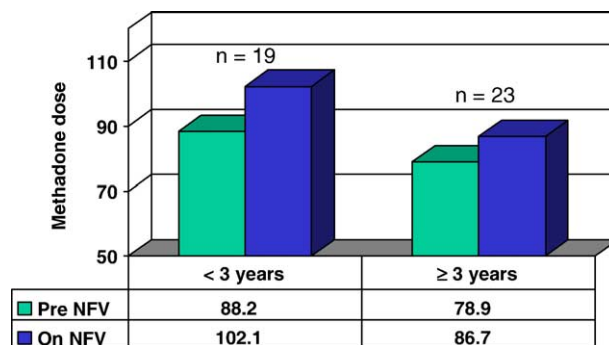


Fig. 3. Methadone dose before and during NFV therapy grouped by length of NFV treatment.

for methadone dose before and during NFV therapy, mean methadone doses were 83.1 mg before NFV therapy and 93.7 mg during NFV therapy, a statistically significant difference ( $p < .001$ ; Fig. 2). For these 42 case patients, mean length of time of having received NFV was 39.0 months. For 19 of these 42 patients receiving NFV therapy  $< 36$  months, mean methadone dose increased from 88.2 mg before to 102.1 mg during NFV therapy. For the remaining 23 patients receiving NFV therapy  $\geq 36$  months, mean methadone dose increased from 78.9 mg before to 86.7 mg during NFV therapy (Fig. 3). Although not statistically significant, there was a clear trend toward less change in methadone dose for patients receiving NFV therapy  $\geq 36$  months.

#### 4. Discussion

There are studies that have looked into potential acceleration of liver toxicity with treatment of HIV with PIs in the face of hepatitis C coinfection (Benhamou et al., 2001; Kottlil, Polis, & Kovacs, 2004; Mehta et al., 2005; Sulkowski et al., 2000; Sulkowski, Berk & Dieterich, 2003; Sulkowski, Mehta, Chaisson, Thomas & Moore, 2004). Although these studies suggest caution and more frequent monitoring of LFTs, PI therapy has generally been found to be relatively safe and effective, with the possible exception of full-dose ritonavir-containing regimens in which the findings have been mixed (Antoniu & Tseng, 2002; Sulkowski et al., 2000, 2003, 2004). The data from this study indicate that for the patient population evaluated, NFV therapy was extremely safe. It was permanently discontinued in only 1 patient for potential safety reasons (elevated amylase level), yet the finding that no other LFT worsened makes it unlikely that NFV was the cause. In addition, this patient was receiving NFV for a total of 56 months, an indication that it was an effective part of the patient's ART for a relatively prolonged period. The finding of 12 case patients in whom LFT abnormalities before NFV therapy resolved during NFV therapy was striking. A modestly elevated blood glucose level was the only laboratory abnormality that developed after NFV was started. In the 20 other case patients in whom laboratory abnormalities were

present before NFV therapy, no new or worsening laboratory abnormality occurred after NFV therapy was added.

In light of the comorbidities of the patients evaluated, which in this review likely exceeded those of most other patient populations, NFV-containing ART regimens were quite efficacious. CD4 counts increased significantly, and patients were maintained on NFV for prolonged periods. Viral load decreased to or remained undetectable (<400) in 20 of 29 patients for whom data were available, and the mean length of time of having received NFV for these 20 patients was 43.4 months.

The patients in this study had the additional burden of undergoing methadone maintenance treatment. As with PI therapy and liver toxicity, studies have indicated the potential for PIs, including NFV, and methadone to interact via the cytochrome *P*450 system to cause opiate withdrawal (Antoniou & Tseng, 2002; Gourevitch & Friedland, 2000; McCance-Katz et al., 2003, 2004). In view of these findings, the tolerability of NFV was impressive. There was no instance of opiate withdrawal seen in this patient population. Diarrhea, a common side effect of NFV therapy, was infrequent, was short-lived, and did not require dose change or discontinuation of NFV. Constipation, a common side effect of methadone, was also infrequent, was short-lived, and did not require dose change or discontinuation of methadone. These represent a rare clinical situation in which a common side effect of one medication was counterbalanced by a side effect of another medication. In clinical practice, when this type of situation is sought in treating more than one condition with more than one medication, the result is generally a multiplication of side effects.

Although methadone dose changes were statistically significant when pre-NFV therapy methadone dose was compared with methadone dose during NFV therapy, the magnitude of the change was considerably lower the longer the patient was receiving NFV. This could indicate that methadone dose changes, if caused by NFV, occurred early in the course therapy. The interaction of PIs and methadone on the cytochrome *P*450 system, particularly 3A4, has been difficult to characterize (McCance-Katz et al., 2003, 2004). In addition, given the racemic formulation of methadone used in the United States, the inactive enantiomer may be responsible for the cytochrome *P*450 3A4 effects. This would mitigate potential adverse interactions between PIs and methadone. Furthermore, with all of the clinical factors that go into determining appropriate methadone dose apart from comorbidities and concurrent medication, it is likely that measures of methadone dose change for any patient population would yield similar results.

Given the physiological burden of hepatitis C, other medical comorbidities, methadone treatment, and use of at least two other antiretroviral drugs, more laboratory abnormalities would have been expected. Furthermore, the normalization of LFT abnormalities suggests that the antiretroviral regimen was more effectively treating the patients' HIV disease than any potential negative impact of the noted factors.

#### 4.1. Limitations

There were several limitations to this study. First, this was a retrospective chart review and not a prospective study, which generally provides the most statistical power. Second, the sample size was relatively small with 51 patients, creating potential underascertainment bias. However, for CD4 count changes, methadone dose changes, and length of time of having received NFV, the mean values reported were close or nearly identical to the median values, indicating little or no skewing of the results by extreme outliers. Third, 50 of the 51 patients were from a racial or ethnic minority group; therefore, the findings could be different with a different population mix. Finally, it would have been useful to have had comparison groups of patients on methadone and ART with and without NFV, and patients on methadone not on ART to determine whether the methadone dose changes seen in this study were any more pronounced than in other patient populations.

#### 4.2. Conclusions

The relative absence of laboratory abnormalities during NFV therapy and the correction of pre-NFV laboratory abnormalities support the safety of NFV. The combination of CD4 and viral load assessments was generally consistent with clinical improvement. Diarrhea and constipation, frequent side effects of NFV and methadone, respectively, occurred infrequently, and there was no instance of opiate withdrawal while the patients were undergoing NFV-containing ART. Increases in methadone dose were more likely to occur early in the course of NFV therapy, suggesting either that NFV was not the cause of increasing methadone dose over time or that its impact on methadone dose attenuates over time. Collectively, the findings from this study support the safety, efficacy, and tolerability of NFV in methadone-maintained patients coinfecting with HIV and hepatitis C.

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