NEVIRAPINE PLUS EFAVIRENZ PLUS DIDANOSINE: A SIMPLE, SAFE, AND EFFECTIVE ONCE-DAILY REGIMEN FOR PATIENTS WITH HIV INFECTION

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Conventional highly active antiretroviral therapy (HAART) regimens used to treat human immunodeficiency virus (HIV) infection typically use nucleoside reverse transcriptase inhibitors (NRTIs) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Because PI-based regimens are associated with significant long-term toxicity and adherence difficulty, there is a need for novel regimens that maximize combination treatment options. This 12-month, observational, cohort study evaluated the efficacy, safety, and tolerability of a novel three-drug HAART regimen. Drug treatment consisted of nevirapine (NVP), efavirenz (EFV), and didanosine (ddI). Twenty-six treatment-naive and -experienced HIV-1+ men and women were included in the study. Assessment consisted of CD4+ cell count, plasma HIV-1 RNA load, and adverse effects of study medications. After one year of therapy, 11/12 treatment-naive subjects (92%) and 8/9 treatment-experienced subjects (89%) had viral loads <400 copies/mL. Both groups also had an excellent immune response. At one year, there was a mean increase of 438 CD4+ cells/mm^3 among treatment-naive subjects and 367 cells/mm^3 among treatment-experienced subjects. Treatment-limiting adverse effects occurred in 3/15 treatment-naive (20%) and 2/11 treatment-experienced (18%) subjects. These preliminary data suggest that the combination of NVP, EFV, and ddI is simple, safe, and effective. (*J Natl Med Assoc.* 2003;95:1152–1157.)

Key words: HAART ♦ HIV ♦ nevirapine ♦ efavirenz ♦ didanosine

The rapid improvement over the last five years in the prognosis and outcome of patients with HIV disease is largely a result of the development of potent antiretroviral agents and the recognition that combination therapy is better than less-aggressive treatment regimens at inhibiting viral replication, preventing the development of drug-resistant isolates, and allowing immune reconstitution. The use of highly active antiretroviral therapy (HAART)—the combination of a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs)—has significantly reduced viral load and improved clinical outcome[1-4]. Despite these advances, HIV disease/acquired immunodeficiency syndrome (AIDS) remains an incurable disease, requiring >95% adherence to complex dosing regimens[5], often with high pill burdens. In addition, three-drug strategies that employ a PI and/or mul-

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Table 1. Baseline Characteristics

	Treatment-Naïve (n=15)	Treatment-Experienced (n=11)
Geometric mean viral load (HIV-1 RNA copies/mL)	38,603 (4.59 $\log_{10}$)	2,025 (3.31 $\log_{10}$)
Median viral load (range) (HIV-1 RNA copies/mL)	33,000 (576-180,000)	<400 (<400-18,000)
Mean CD4+ cell count (cells/mm^3)	351	368
Median CD4+ cell count (range) (cells/mm^3)	312 (110-800)	310 (1-800)

tiple NRTIs are associated with long-term toxicity[6-9], including hyperlipidemia[6,7], insulin resistance[6,7], lipodystrophy[6-8], and mitochondrial dysfunction [8,9].

NNRTIs have been investigated as alternatives to PIs in HAART. In HIV-1-infected adults, the combination of an NNRTI plus two NRTIs has been shown to have equivalent antiviral activity and to be better tolerated than the combination of a PI plus two NRTIs[4,10,11]. Since NRTIs have been associated with mitochondrial toxicity[8] and lipoatrophy[9], a need for NRTI-sparing, as well as PI-sparing regimens exists.

The challenge, then, was to determine a more tolerable, yet effective, three-drug combination. One alternative treatment strategy would be to combine two NNRTIs in a three-drug regimen. EFV and the nucleoside analogue didanosine (ddI) are both indicated for once-daily dosing. Pharmacokinetic studies of NVP have demonstrated that it has a plasma half-life of 25–30 hours, suggesting that once-daily dosing is feasible. The NNRTIs nevirapine (NVP) and efavirenz (EFV) have been shown to be safe and effective in the treatment of HIV-1 infection in once-daily regimens[12-14]. The combination of NVP, EFV, and an NRTI (such as ddI) would represent a simple treatment regimen, with a longer dosing interval and fewer pills than conventional three-drug HAART.

The pharmacokinetics of NVP and EFV in combination have recently been described, demonstrating that any drug-drug interactions are relatively minor and of only marginal clinical significance[15]. We report the results of the first study evaluating the efficacy and safety of a three-drug HAART regimen that employed two NNRTIs (NVP and EFV) for the treatment of patients with HIV-1 infection. This strategy represents a simple, seven-tablet/capsule-per-day, once-a-day dosing schedule and is both PI-sparing and NRTI-limiting, thereby potentially increasing future treatment options. Furthermore, because NNRTIs have yet to be associated with long-term metabolic toxicity, this approach may also reduce the incidence of metabolic side effects.

METHODS

Patients

This was a 12-month retrospective observational study of patients with HIV-1 infection. Both treatment-naïve and treatment-experienced patients were evaluated. Treatment-naïve patients who requested a simple, once-daily initial regimen and who in fact agreed to initiate therapy only if there were a once-a-day regimen, and patients already on therapy who requested a switch to a simpler, more tolerable regimen, are included in this study.

There were no restrictions as to age, sex, race, HIV risk category, prior therapy, baseline viral load, or baseline CD4+ cell count. Enrolled subjects received NVP (400 mg qd) plus EFV (600 mg qd) plus ddI (400 mg qd). EFV was given at the usual recommended dose, and no adjustment was made for the potential interaction between NVP and EFV. NVP was initiated at 200 mg qd for the first 14 days and then increased to the full dose of 400 mg after day 14. Two hours later, ddI was given. All clients took their NNRTIs two hours before bedtime, followed with ddI at bedtime. This was the standard recommendation, and all clients followed this instruction.

Clinical and Laboratory Assessments

Subjects were assessed at baseline and on weeks four, 12, 24, 36, and 48. At each visit, subjects were interviewed and evaluated by a physician for potential adverse effects of study medications. Laboratory assessment of CD4+ cell count and plasma HIV-1 RNA load was also conducted. Liver function (ALT and AST) was monitored at baseline and every three months thereafter. HIV-1 RNA viral load was determined using the Roche

Amplicor HIV-Monitor assay (Roche Diagnostics Systems, Branchburg, NJ).

Statistical Analysis

The primary endpoints of the study were the effect of study treatments on HIV-1 RNA load and CD4+ cell count over time. Primary efficacy analyses were based on change from baseline in these parameters. The plasma HIV-1 load was log-transformed. Final reported measurements were derived from the results obtained at week 48. Safety analyses were completed on an intent-to-treat basis; all patients who had observations after initiation of study treatment were included in the analyses.

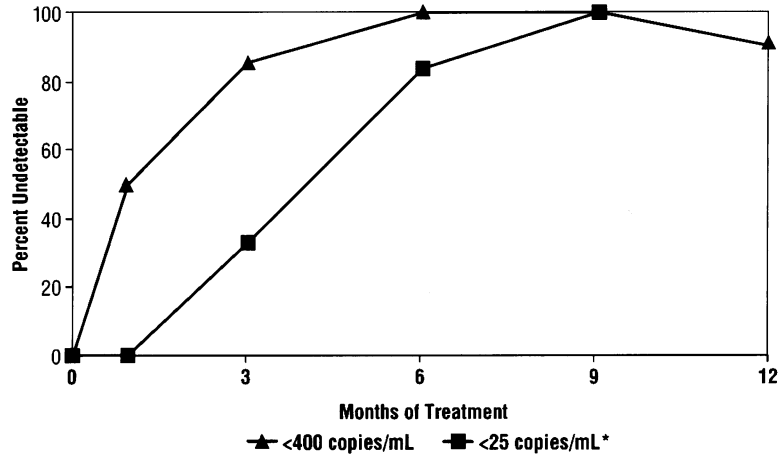

Figure 1. Virologic response in treatment-naïve subjects during one year of therapy with nevirapine (400 mg qd) plus efavirenz (600 mg qd) plus ddI (400 mg qd).

*Ultrasensitive data not routinely collected (not available at 12 months).

RESULTS

Patient Characteristics

A total of 26 subjects (24 male and two female) were enrolled in the study: 15 were treatment-naïve, and 11 were treatment-experienced. One female patient underwent elective hysterectomy to avoid pregnancy while receiving EFV. Treatment-experienced subjects had a mean prior use of 1.6 PIs, the majority switching because of a desire for a simpler, more tolerable regimen. The baseline characteristics of enrolled subjects are listed in Table 1. The mean baseline viral load among treatment-naïve subjects was 4.59 $\log_{10}$ (38,603) copies/mL, whereas the mean baseline viral load among treatment-experienced subjects was 3.31 $\log_{10}$ (2,025) copies/mL. The mean baseline CD4+ cell count among treatment-naïve subjects was 351 cells/mm^3, and that for treatment-experienced subjects was 368 cells/mm^3.

Response

Patients in this study were followed for 12 months. After one year of therapy, 11 of 12 treatment-naïve subjects (92%) and eight of nine treatment-experienced subjects (89%) had viral loads of <400 copies/mL (Figures 1 and 2, respectively). Both groups also had an excellent immune response. At one year, there was a mean increase of 438 CD4+ cells/mm^3 among treatment-naïve subjects, and 367 cells/mm^3 among treatment-experienced subjects (Figure 3). There were no treatment failures. Two subjects (one treatment-naïve and one treatment-experienced) who experienced a viral breakthrough did so because of a planned drug holiday while on vacation, rather than therapy failure.

Ultrasensitive (25 copies/mL limit of detection) viral load determinations were made at three, six, and nine months. At nine months, 100% of treatment-naïve and 100% of treatment-experienced subjects had viral loads of <25 copies/mL.

Toxicity

Adverse effects deemed by the study investigators to be NNRTI-related were intractable insomnia (two cases), rash (two cases), and CNS toxicity (one case). These side effects were the reasons for treatment discontinuation in three of 15 treatment-naïve (20%) and two of 11 treatment-experienced (18%) subjects. No increase above the expected incidence of NNRTI-related adverse effects was observed. Among subjects who remained on study medications throughout the course of the trial, treatment was generally well tolerated.

DISCUSSION

Patients with HIV/AIDS continue to represent a difficult and complex group to manage optimally. Aggressive, multidrug HAART is often difficult to adhere to and tolerate. PI-based HAART is associated with various metabolic abnormalities, includ-

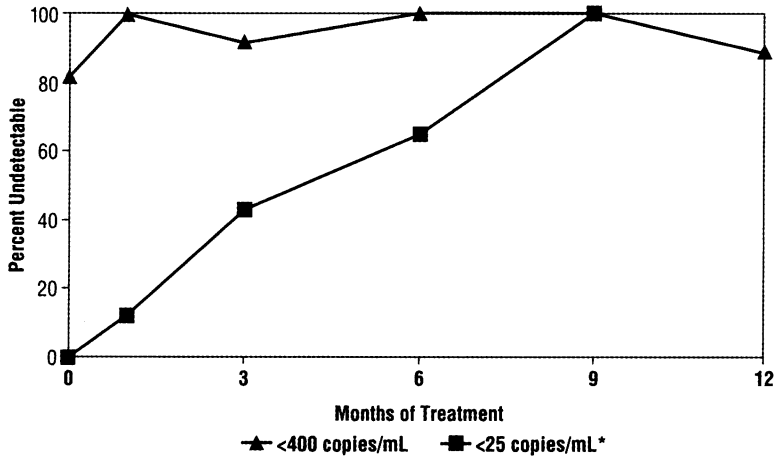

Figure 2. Virologic response in treatment-experienced subjects during one year of therapy with nevirapine (400 mg qd) plus efavirenz (600 mg qd) plus ddI (400 mg qd).

*Ultrasensitive data not routinely collected (not available at 12 months).

ing hyperlipidemia[6,7], insulin resistance[6,7], and other forms of lipodystrophy[6-8]. In addition, use of multiple NRTIs may induce mitochondrial dysfunction[8]. In some reports, switching to PI-sparing HAART may have actually reversed these metabolic abnormalities[16,17]. Martínez et al.[16] demonstrated statistically significant improvements in serum triglycerides and fasting serum insulin-resistance index following substitution of PI by NVP. Similar results were reported in a composite retrospective analysis of all relevant studies published or presented between 1998 and February 2000[17]. NNRTIs have not been implicated in the development of lipodystrophy[18]. Use of NNRTI-based HAART has proven to be a simple, safe, and effective alternative to PIs[4,10,11].

The results presented here indicate that a once-daily dual NNRTI-based regimen of NVP+EFV+ddI provided HIV suppression in 92% of treatment-naïve patients and 89% of treatment-experienced patients. A potential advantage of relatively simple, once-daily HAART regimens would be increased adherence, especially among HIV-infected intravenous drug users (IVDUs), a population that is generally considered to be poorly adherent. The efficacy and safety of various multidrug regimens and the effect of once-daily dosing on adherence have been evaluated in this population[19,20]. Proença et al.[19] performed a retrospective analysis of the results of a study that evaluated the safety and efficacy of once-daily NVP plus ddI plus lamivudine. Sixty-six percent of treatment-naïve patients in this IVDU population had viral loads <50 copies/mL at their latest follow-up. A separate prospective analysis of the IVDU cohort of the Frankfurt HIV study, which employed the same HAART regimen, yielded similar results[20]. A good virologic response was also seen with an all once-a-day regimen of emtricitabine plus ddI plus EFV[14]. The results of these trials support the presumption that simple, once-daily regimens would be well suited for directly observed therapy (DOT), which may be necessary in the IVDU population and other difficult-to-reach groups in order to ensure adherence. In the general HIV-infected population, DOT has been demonstrated clearly to improve clinical outcomes[21].

The most common toxicities seen in this trial were CNS and rash. CNS symptoms, including dizziness, insomnia, vivid dreams, impaired concentration, and depression, are side effects commonly associated with EFV. Rash is associated with all of the NNRTIs, although it is more frequent in patients receiving NVP. The incidence of CNS side effects and rash seen in this study was similar to that expected for EFV and NVP when given alone. Therefore, despite the small study size, it is encouraging that the incidence of these side effects was not increased when these two drugs from the NNRTI class were given simultaneously. It is also noteworthy that no hepatotoxicity was observed in this study, although both EFV and NVP are potentially hepatotoxic agents.

The use of NVP in combination with EFV and ddI could also be considered to be NRTI-sparing, because only one NRTI was used instead of two. This combination, therefore, might reduce the potential for both PI- and NRTI-associated metabolic effects.

The use of NNRTIs has led to the emergence of drug-resistant HIV-1 variants, the most common being the mutations at positions K103N and Y181C[22,23]. This potential for cross-resistance may limit the possibility of sequencing the various

NNRTIs in successive treatment regimens. The K103N mutation can occur after exposure to both NVP and EFV, resulting in high-level resistance to all currently available NNRTIs[22-24]. Although MacArthur et al.[24] suggested that it might be possible to select for the Y181C mutation by using NVP in combination with zidovudine—thereby potentially allowing subsequent use of EFV—it is unlikely that effective sequencing of NNRTIs will be possible clinically.

It was not possible to determine from this study whether the antiviral action of NVP and EFV in combination was additive or synergistic, or even if multiple resistant mutations, rather than a single-point mutation, are required for resistance. Nevertheless, these results indicate that the advantages of a simple, tolerable, once-daily, dual NNRTI-containing HAART regimen outweigh the potential for the development of a single-point mutation. Because no virologic failures were observed in this study, we have been unable to evaluate resistance patterns to dual NNRTI-based regimens. Further follow-up of these patients, with genotypic analysis of any virologic failures, is planned.

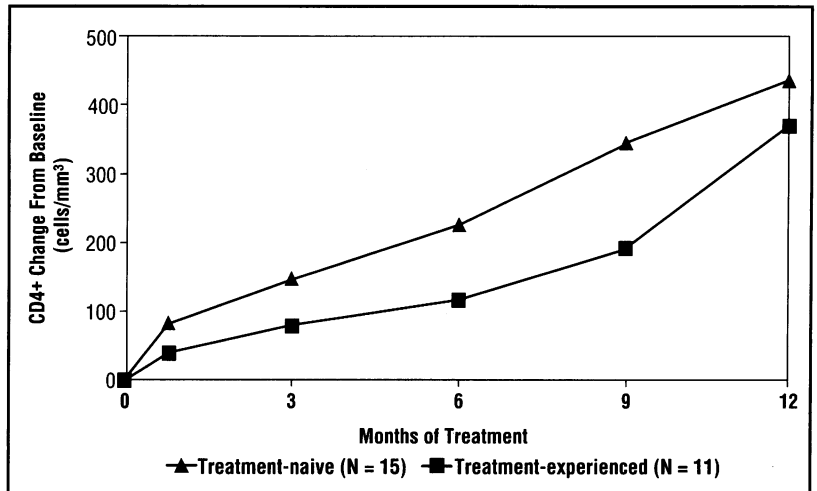

Figure 3. Mean CD4+ cell count response in treatment-naïve and -experienced subjects during one year of therapy with nevirapine (400 mg qd) plus efavirenz (600 mg qd) plus ddI (400 mg qd).

It is generally accepted that little benefit can be derived from using an NNRTI following virologic failure with an initial NNRTI. The new combination of two NNRTIs plus an NRTI allows maximum strategic benefit to be obtained from the combination of NVP and EFV, either as first- or possibly second-line therapy. A recent study by Olivieri demonstrated the efficacy and safety of a dual NNRTI-based regimen that included NVP plus EFV in heavily pretreated patients and also suggested that this approach could have a role in PI-experienced patients[25]. These results are consistent with those of earlier studies that have examined the efficacy and safety of NNRTIs as a substitute for PIs in HAART[4,10,11]. This pilot study demonstrated that a simple, once-a-day combination of two NNRTIs (NVP plus EFV) plus ddI provided effective virologic suppression and substantial increase in CD4+ cell count in a majority of patients, with no increase in NNRTI-associated side effects.

As initial HAART, this regimen might provide the best chance for adherence and long-term tolerability, while sparing PIs and at least one NRTI for second- or third-line options. For patients who have experienced PI failure or toxicity, the strategy of NVP plus EFV plus ddI affords a simple and effective alternative. Further data from large-scale clinical trials are required to fully evaluate the efficacy and safety of dual NNRTI-based regimens in various treatment scenarios. It is important to remember that this was observational and the participants were patients who elected themselves to take a once-a-day regimen. Therefore their motivation was very high. This was not a funded study; there was no support from any of the manufacturers of the three drug or any other pharmaceutical company.

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