



Response to efavirenz plus two nucleoside reverse-transcriptase inhibitors in patients with advanced stage human immunodeficiency virus-1 infection in Taiwan

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From July 1, 1999 to April 30, 2002, 111 consecutive human immunodeficiency virus-infected, antiretroviral-naïve Taiwan patients initiated highly active antiretroviral therapy with efavirenz plus 2 nucleoside reverse-transcriptase inhibitors. Their median baseline CD4⁺ count was 50×10^6 /L (0-559 $\times 10^6$ /L) and plasma viral load was 5.51 log₁₀ copies/mL (3.09 to >5.88 log₁₀) as assessed by reverse-transcriptase polymerase chain reaction. Of the patients, 52.3% had a CD4⁺ count of $\leq 50 \times 10^6$ /L, 74.8% had plasma viral load over 5 log₁₀ copies/mL, and 58.5% had active AIDS-defining opportunistic illnesses. The median observation duration of antiretroviral therapy was 350 days (range, 28-991 days). At week 48 to 52 following the initiation of highly active antiretroviral therapy, 81.8% (45/55) and 91.8% (45/49) of the patients achieved undetectable plasma viral load by intent-to-treat and on-treat analysis, respectively. At week 80 to 84, these percentages decreased to 69.7% (23/33) and 85.2% (23/27), respectively. Median CD4⁺ count increased from baseline to week 48 to 52 by 147×10^6 /L and to week 80 to 84 by 227×10^6 /L. The virologic and immunologic responses at each time period by intention-to-treat or on-treat analysis were similar between patients with baseline plasma viral load over or ≤ 5 log₁₀, CD4⁺ count over or $\leq 50 \times 10^6$ /L, and with or without active AIDS-defining opportunistic illnesses. After initiation of highly active antiretroviral therapy for a median duration of 57 days (range, 2-638 days), 11 episodes of AIDS-defining and 11 non-AIDS opportunistic illnesses occurred. The results of this study suggest that efavirenz plus 2 nucleoside reverse-transcriptase inhibitors is a potent antiretroviral combination regardless of whether the patient has a high baseline plasma viral load, low CD4⁺ count, or AIDS-defining opportunistic illnesses.

Key words: Efavirenz, highly active antiretroviral therapy, nonnucleoside reverse-transcriptase inhibitor

Introduction of highly active antiretroviral therapy (HAART) has brought with it significant reduction of mortality and opportunistic events, even in patients with very advanced stage of human immunodeficiency virus (HIV) infection [1,2]. In patients with high or low baseline CD4⁺ lymphocyte count and high plasma viral load (PVL), durable viral suppression can be achieved by HAART containing a protease inhibitor and 2 nucleoside reverse-transcriptase inhibitors (NRTIs) [3-5]. Such regimens, however, are often more complicated

to take, contain a higher pill burden, and may cause long-term metabolic complications [6]. Regimens consisting of non-NRTIs (nNRTIs), especially efavirenz, and 2 NRTIs have a smaller pill burden and have been shown to be as effective as protease inhibitor containing regimens in patients with high or low PVL [7,8]. Although efficacy and durability of viral suppression were demonstrated in clinical trials, data on response to nNRTI plus 2 NRTIs in patients with high PVL, low CD4⁺ counts, and active opportunistic illnesses has rarely been reported in Asian populations outside of the clinical trial study. In this study, we evaluated the response to an antiretroviral regimen consisting of efavirenz plus 2 NRTIs in Taiwan HIV-infected patients, most of whom were in an advanced stage of HIV infection with baseline CD4⁺ count $\leq 200 \times 10^6$ /L.

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Materials and Methods

From July 1, 1999 to April 30, 2002, consecutive anti-retroviral-naïve HIV-infected Taiwan patients who had initiated treatment with efavirenz plus 2 NRTIs were enrolled in a prospective observational study to assess the virologic, clinical, and immunologic responses to HAART. There was no restriction on CD4⁺ count, PVL, or concurrent opportunistic illnesses. The exclusion criteria included pregnancy and aminotransferase levels more than 5 times the upper limit of normal.

The daily oral dose of efavirenz was 600 mg given before bedtime. If combined with rifampin, the dose was increased to 800 mg. The choice of the 2 NRTIs administered and the decisions to switch NRTIs in the presence of adverse effects was made at the discretion of the physicians.

Outcome measures were the proportion of patients with PVL less than 400 copies/mL and changes of CD4⁺ count at week 48 to 52, and development of new acquired immunodeficiency syndrome (AIDS)-defining opportunistic illnesses [9] or non-AIDS-defining opportunistic illnesses during the observation period. Plasma viral load and CD4⁺ count were determined before HAART was initiated and at 1 month, and subsequently every 3 to 4 months after HAART. Plasma viral load was quantified using reverse-transcriptase polymerase chain reaction (RT-PCR) with ROCHE Amplicor (F. Hoffman-La Roche, Basel, Switzerland, with a lower detection limit of 400 copies/mL) and CD4⁺ count by flow cytometry (FACS Flow, Becton-Dickinson Diagnostic Instrument System, Sparks, MD, US). Hemogram and blood biochemistry were also determined with the same blood sampling schedule for quantification of PVL and CD4⁺ count.

Patients were followed in the outpatient department and seen every 1 to 3 months. The rate of compliance was not determined. Patients were admitted for investigation if symptomatology suggestive of AIDS-defining opportunistic illnesses developed. The protocol used to investigate the etiology of opportunistic illnesses was as previously described [10].

The proportion of patients achieving undetectable PVL (<400 copies/mL) was calculated, with missing values considered to be greater than 400 copies/mL. Fisher's exact test was used to compare patients with PVL over and $\leq 5 \log_{10}$ copies/mL; CD4⁺ count over and $\leq 50 \times 10^6$ /L; and patients with or without active opportunistic illnesses.

Results

From July 1, 1999 to April 30, 2002, 111 antiretroviral-naïve patients who had initiated treatment with

efavirenz plus 2 NRTIs were enrolled. The baseline characteristics of these patients are shown in Table 1. Their initial NRTI regimens included stavudine plus lamivudine in 64 patients, zidovudine plus lamivudine in 43, and didanosine plus lamivudine in 4. Most of the patients were in the advanced stage of HIV-1 infection and presented for treatment of opportunistic illnesses while HAART was begun. Their baseline CD4⁺ count was 50×10^6 /L (range, 0-559 $\times 10^6$ /L) and PVL 5.51 \log_{10} copies/mL (range, 3.09 to $>5.88 \log_{10}$) by RT-PCR. More than half (52.3%) of the patients had CD4⁺ count $\leq 50 \times 10^6$ /L and 76.6% CD4⁺ count $\leq 200 \times 10^6$ /L. About 75% of the patients had baseline PVL over 5 \log_{10} copies/mL and 58.5% had active AIDS-defining opportunistic illnesses. These opportunistic illnesses included *Pneumocystis carinii* pneumonia (PCP) (30 cases), tuberculosis (12), cryptococcosis (8), disseminated *Mycobacterium avium* complex (DMAC) infection or other non-tuberculous mycobacteriosis (8), cytomegalovirus (CMV) diseases (5), and others (6). Of the patients, 44.1% had both CD4⁺ count $\leq 50 \times 10^6$ /L and PVL over 5 \log_{10} copies/mL.

The median observation duration of the response to antiretroviral therapy was 350 days (range, 28-991 days). The proportions of PVL less than 400 copies/mL at each time period by intent-to-treat and on-treat analysis are shown in Fig. 1. At week 48 to 52 following initiation of HAART, 81.8% (45/55) and 91.8% (45/49) of the patients achieved undetectable PVL by intent-to-treat and on-treat analysis, respectively. At week 80 to 84, these percentage had decreased to 69.7% (23/33) and 85.2% (23/27), respectively. Median CD4⁺ count increased from baseline to week 48 to 52 by 147×10^6 /L and to week 80 to 84 by 227×10^6 /L. The virologic and immunologic responses at each time period by intent-to-treat or on-treat analysis were similar ($p > 0.05$) among patients with baseline PVL over or $\leq 5 \log_{10}$, CD4⁺ count over or $\leq 50 \times 10^6$ /L, with or without active opportunistic illnesses (Fig. 1).

Forty-one (36.9%) patients experienced dizziness with or without sleep disturbance, 27 (24.6%) skin rashes, and 7 (6.3%) grade 3 to 4 hepatotoxicity which was defined as elevation of aminotransferase levels more than 5 times the upper limit of normal. Nineteen (17.1%) patients discontinued or switched efavirenz because of virologic failure after a median treatment duration of 260 days (range, 134-501 days) in 4 patients, death after 123 (18-201) days in 6, intolerance or adverse effects after 27 (6-84) days in 6, loss to follow-up after 168 days in 2, and structured therapeutic interruption after 147 days in 1 patient. Of the 4 patients with virologic failure, 3 had baseline PVL over 5.88

Table 1. Clinical characteristics of HIV-infected patients who received efavirenz plus 2 NRTIs (n = 111)

| Category | No. of patients (%) |
|-------------------------------------------------------------------------------------------|----------------------|
| Median age (yr) | 34 (20-73) |
| Sex (M/F) | 102/9 |
| Patients with AIDS-defining OI | 62 (58.5) |
| Median baseline CD4 ⁺ cell count (x 10 ⁶ /L) | 50 (0-559) |
| Baseline CD4 ⁺ ≤50 x 10 ⁶ /L | 58 (52.3) |
| Baseline CD4 ⁺ ≤200 x 10 ⁶ /L | 85 (76.6) |
| Median baseline PVL (log ₁₀ copies/mL) | 5.51 (3.09 to >5.88) |
| Baseline PVL >5 log ₁₀ copies/mL | 83 (74.8) |
| Baseline CD4 ⁺ ≤50 x 10 ⁶ /L and PVL >5 log ₁₀ copies/mL | 49 (44.1) |
| Initial 2 NRTIs | |
| Stavudine plus lamivudine | 64 (57.7) |
| Zidovudine plus lamivudine | 43 (38.7) |
| Didanosine plus lamivudine | 4 (3.6) |
| Median observation duration (d) | 350 (28-991) |
| Adverse effects of efavirenz | |
| Dizziness | 41 (36.9) |
| Skin rashes | 27 (24.6) |
| Grade 3-4 hepatotoxicity | 7 (6.3) |
| 2 NRTI changed or stopped | 41 (36.9) |
| Cause of efavirenz plus 2 NRTIs discontinued or stopped | |
| Death | 6 (5.4) |
| Virologic failure | 4 (3.6) |
| Intolerance or adverse effects | 8 (7.2) |
| Loss to follow-up | 2 (1.8) |
| Structured therapeutic interruption | 1 (0.9) |
| Clinical outcome | |
| New episodes of OI | 22 (19.8) |
| New episodes of AIDS-defining OI | 11 (9.9) |

Abbreviations: OI = opportunistic illness; AIDS = acquired immunodeficiency syndrome; PVL = plasma viral load; NRTIs = nucleoside reverse-transcriptase inhibitors

log₁₀ copies/mL. Two of them had achieved PVL below 400 copies/mL after 1 month of HAART. Lipoatrophy and peripheral neuropathy developed in 2 and 4 patients, respectively, who received efavirenz plus stavudine and lamivudine. Bone marrow suppression developed in 5 patients receiving efavirenz plus zidovudine and lamivudine. Five patients died of opportunistic illnesses and one of complications of preexisting diabetes mellitus. The causes of the 5 AIDS-related deaths were non-Hodgkin's lymphoma (1), Hodgkin's disease (1), PCP and cryptococcosis with respiratory failure (1), *Penicillium marneffe*i infection (1), and tuberculosis (1).

After initiation of HAART for a median duration of 57 (range, 2-638) days, 11 episodes of AIDS-defining opportunistic illnesses and 11 non-AIDS opportunistic illnesses occurred, which included herpes zoster (10 episodes), CMV retinitis (3), relapse of cryptococcosis (3), tuberculosis (2), DMAC infection (2), Kaposi's sarcoma (1), and Hodgkin's disease (1). The median CD4⁺ count at the onset of these 22 episodes of opportunistic illnesses was 74 x 10⁶/L while the median

PVL was 400 copies/mL (range, 400-37 130 copies/mL).

Discussion

This study showed that in HIV-1-infected patients with severe immunosuppression, high PVL, and active opportunistic illnesses, a simple regimen containing efavirenz plus 2 NRTIs was effective and a high percentage of patients could achieve undetectable PVL outside of a clinical trial study. Only 4 patients developed virologic failure after a median observation of 50 weeks. The overall virologic response in this study was similar to that observed in previous clinical trials involving efavirenz in antiretroviral-naïve patients, although the study designs were different [7,8].

Patients with active opportunistic illnesses and CD4⁺ count <50 x 10⁶/L are often not enrolled in clinical trials. Although this study was limited by inclusion of patients from only a single clinic, smaller case number, and shorter observation duration, the findings were consistent with those observed by Phillips *et al* [11] that virologic outcome was not associated

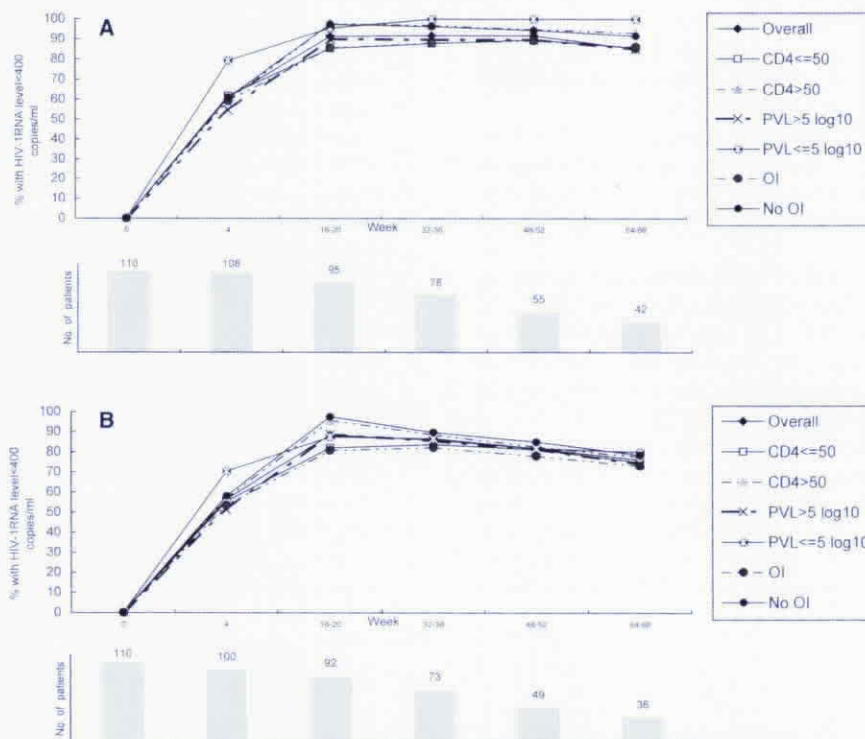


Fig. 1. Proportion of patients with plasma viral load less than 400 copies/mL according to **(A)** intent-to-treat analysis and **(B)** on-treat analysis. OI = opportunistic illness; PVL = plasma viral load.

with baseline CD4⁺ count or PVL. Nearly 20% of the patients in this study experienced opportunistic illnesses at about 2 months after initiation of HAART. This result might not be unexpected because higher rates of disease progression to AIDS or death are clustered among patients with depleted baseline CD4⁺ count [12]. The baseline CD4⁺ count of patients in this study was low (50×10^6 /L) and the rise of CD4⁺ count remained modest (74×10^6 /L) during the short treatment period. In addition, several opportunistic illnesses may become manifest after immune restoration, such as CMV retinitis or lymphadenitis due to *M. avium* complex [13].

The regimens appeared to be well tolerated in view of the severe immunosuppression and concurrent use of multiple therapeutic or prophylactic antimicrobial agents for opportunistic infections in most of the patients, such as PCP, tuberculosis, and cryptococcosis. Although a higher percentage of patients experienced skin rashes and dizziness with or without sleep disturbance, efavirenz was switched because of intolerance or adverse effects in only 6 patients. We conclude that efavirenz plus 2 NRTIs could be an appropriate first-line alternative to protease inhibitor-containing HAART in patients with an advanced stage of HIV-1 infection.

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