LONG TERM OUTCOMES OF NEVIRAPINE CONTAINING ANTIRETROVIRAL THERAPY AT A CENTER IN THAILAND

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Abstract. This retrospective cohort study was conducted at Chon Buri Hospital, Thailand, to determine the long term outcomes of patients taking Nevirapine (NVP) containing antiretroviral therapy (ART). Patients taken NVP at least 5 years were included. Two hundred eighty-five patients met inclusion criteria and were included in the study. The median age of patients was 35 years; the median baseline CD4 was 66 cells/mm^3 and the median follow-up was 7 years. Ninety-two point four percent and 90.2% of patients achieved virological success at year 5 and year 7, respectively. The median rise in CD4 count from baseline to year 5 was 354 cells/mm^3 (IQR 235.5-487 cells/mm^3) and at year 7 was 387 cells/mm^3 (IQR 272-557 cells/mm^3). Thirty-eight point eight percent of patients had a CD4 count ≥ 500 cells/mm^3 at year 5 and 41.6% at year 7. Rash/hypersensitivity occurred in 2 patients after 5 years and was transient. Elevated liver enzymes occurred in 5 patients after 5 years. NVP-containing ART yielded high virological-success rates. Long-term immunological response, safety and durability were also high.

Keywords: antiretroviral therapy, long term outcomes NVP,ART

INTRODUCTION

HIV infection is a major health problem world-wide; the WHO has estimated 33.3 million people were living with HIV world-wide by the end of the year 2009 (WHO, 2009). Antiretroviral therapy (ART) is the mainstay of treatment for treating HIV infected patients. There were more than 5 million people world-wide receiving ART by the end of the year 2009 (WHO, 2010).

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Nevirapine (NVP) is a HIV-1 specific first generation non-nucleotide reverse transcriptase inhibitor (NNRTI) used in first-line ART regimens. Its mechanism of action is to bind directly to the non-catalytic site of reverse transcriptase causing conformational changes of enzymes that have catalytic action on it (de Bethune, 2010). There have been many studies comparing the efficacy of NVP with other NRRTI drug (Efavirenz, EFV) or protease inhibitor (PI) containing regimens showing NVP has comparable efficacy to those agents (van Leth *et al*, 2004; Soriano, 2009).

Since NVP has been used in ART regimens for more than 10 years, some studies have assessed the long term outcomes of NVP containing ART in HIV patients.

Most of the studies were conducted for 2-3 years; those results showed virological failure rates in NVP receiving patients were low (Bonjoch *et al*, 2006; Reliquet *et al*, 2006; Wit *et al*, 2007; Wester *et al*, 2010). As the duration of NVP use has became longer, treatment outcomes among patients receiving NVP for long durations need to be evaluated.

In Thailand, ART was introduced in 2002 in the Access to Care Program and in 2004 with the National Access to ART for people living with HIV/AIDS (Chaiwarith *et al*, 2007) with the aim of universal access to ART (Chasombat *et al*, 2009). First-line antiretroviral regimen commonly used in Thailand for ART naïve patients was a Stavudine (d4T), Lamivudine (3TC) and NVP containing regimen, especially in the early years. The current guidelines of the Thailand National AIDS Program (NAP) still include NVP containing ART, although other options are available (Sungkanuparpha *et al*, 2010). Cheaper price and safety in pregnancy favor the use of NVP, but the potential for severe adverse events, such as hypersensitivity reactions and hepatotoxicity are a cause of concern. As treatment duration became longer, assessment of long term efficacy of NVP is mandatory.

MATERIALS AND METHODS

Study design

This retrospective study was conducted at Chon Buri Hospital, Thailand. Chon Buri Hospital, a tertiary hospital with an HIV clinic, has been providing ART to HIV patients since the year 2001. Demographic data, viral load results, CD4 counts and adverse events were obtained from medical records.

Outcomes

The primary outcome in this study was virological success (viral load < 50 copies/ml) at 5 and 7 years after initiation of ART containing NVP. The secondary outcomes included the immunological response and adverse events in the same cohort of patients.

Inclusion and exclusion criteria

Inclusion criteria were having a positive test for HIV in patients aged ≥18 years, receiving ART containing NVP, initiating ART between January 2001 and December 2005, being ART naïve at the onset of treatment and having been treated with NVP containing ART for at least 5 years.

Exclusion criteria were patients receiving ART not containing NVP, receiving chemotherapy or radiotherapy for cancer treatment during follow-up and pregnant women who had received ART for Prevention of Mother to Child Transmission (PMTCT).

Study definitions

Virological success is defined as a viral load that becomes undetectable (<50 copies/ml) while the patient is on NVP containing ART.

An adverse event from ART was defined as any adverse event experienced during the 5 year study determined to be due to ART.

Hypersensitivity reactions were reactions cause by ART presenting with or without a rash.

Hepatotoxicity was defined as an elevation in liver enzymes greater than twice the upper limit of normal. The liver enzyme used to determine hepatotoxicity was ALT (Alanine aminotransferase).

Statistical analysis

Analysis of data was done with statistical software SPSS 18.0 version (SPSS; Chicago, IL). Data was analyzed as fol-

lows: 1) Patient baseline characteristics were described by descriptive statistics. Continuous variables were described by means ± SD; 2) possible outcome characteristics were assessed by chi-square test, Fisher's exact test or Mann-Whitney *U* test where appropriate. Statistical significance was set at $p < 0.05$ and all tests were two-tailed.

Ethical approval

This study was approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University, Thailand and the ethics committee of Chon Buri Hospital, Thailand.

RESULTS

Baseline characteristics

Four hundred four patients were initiated on ART containing NVP at Chon Buri Hospital, Thailand during the study period, but 119 of these stopped NVP containing ART prior to 5 years due to a variety of reasons. The most common reasons were adverse events (12.4%), virological failure (7.9%), immunological failure (2.5%) or other causes, such as loss to follow-up or shortage of stock (6.7%). Two hundred eighty-five patients took the NVP containing ART for at least 5 years; only these patients were included in the study (Fig 1).

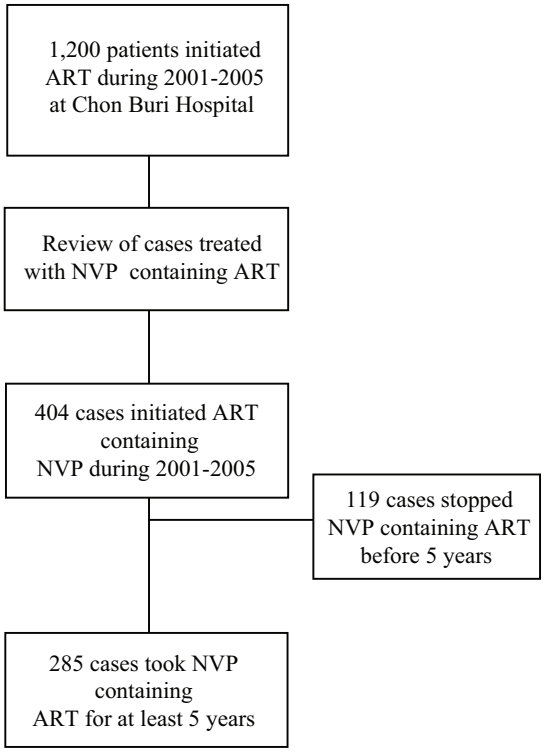

Fig 1–Flow diagram of study subjects.

The baseline characteristics of the patients are found in Table 1. More than half the patients were female and most were in the age group 30-49 years old. The median baseline CD4 count at initiation of ART was 66 cells/mm^3. Most patients (91.6%) were treated with more than 1 NRTI regimen; half had been treated with 3 NRTI regimens (48.1%) during the study.

Virological response

The virological response was assessed by viral load, but in the early years of the ART program in Thailand, viral load testing was not part of the program and viral loads were not available for all patients. After 5 years of NVP containing ART, 92.4% of 225 patients in whom a viral load test was available had virological success, and after 7 years 90.2% of 184 patients in whom a viral load test result was available had virological success. The proportions of patients with virological success by year is shown in Fig 2.

Characteristics for virological success

The possible factors for virological success at 5 and 7 years were analyzed using univariate analysis (Table 2). None of the factors were significant.

Virological failure

Thirty-seven patients (13.0%) had a

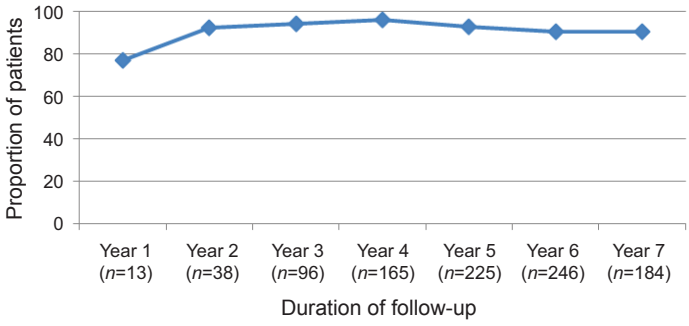

Fig 2–Proportion of patients having virological success at follow-up; *n*=number of patients whose viral load test were available.

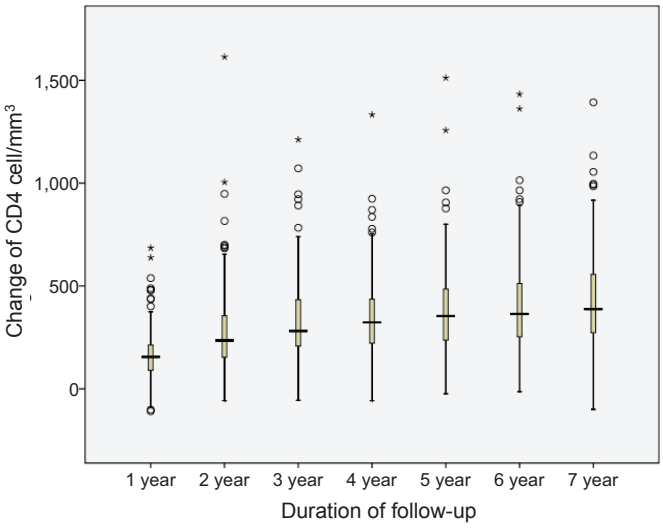

Fig 3–Median changes in CD4 counts yearly for 7 years follow-up.

viral load >50 copies/ml at 5 years follow-up. Of these, 21 (7.4%) had a viral load >2,000 copies/ml, which was the cut-off point for defining virological failure to conduct genotype testing in Thailand. Seventeen patients were examined by genotype testing for virological failure; resistance to non-nucleotide reverse transcriptase inhibitors (NNRIT) was found in 14 patients (4.9%); all those patients were changed to other regimens. To identify the characteristics of virological failure patients, we compared the demographic data, baseline clinical staging, baseline laboratory measures and duration of follow-up between virological failure patients and non-virological failure patients. There were no significant differences among the above variables between the 2 groups (data not shown).

Immunological response

The immunological response was assessed yearly by change in CD4 count from baseline for a total of 7 years. The median changes in CD4 counts are shown in Fig 2. At one year, the median change in CD4 counts was 155 cells/mm^3 (IQR 90-213.5 cells/mm^3); this gradually increased year by year. By the 5th year, the median rise in CD4 counts was 354 cells/mm^3 (IQR 235.5-487 cells/mm^3) and at the 7th year, it was 387 cells/mm^3 (IQR 272-557 cells/mm^3). Some patients had a decrease in CD4 count from baseline, which can be seen in Fig 2.

The immunological response was also assessed by determining the proportion of patients having a CD4 count ≥500 cells/mm^3, which is the target CD4 level for HIV patients on ART. At year 5, 105 patients (36.8%) had a CD4 count ≥500 cells/mm^3

Table 1
Characteristics of patients receiving NVP containing HIV therapy for at least 5 years, *N*=285.

	n (%)
Age at initiation of NVP containing ART, years (median, IQR)	35 (30-39)
18 - 30 years	72 (25.4)
30 - 49 years	198 (69.7)
> 50 years	14 (4.9)
Male (*n*, %)	133 (46.7)
Weight in kg (mean, ± SD) (*n*=269)	53.7 (± 10.1)
BMI in kg/m^2 (mean, ± SD) (*n*=108)	21.3 (± 3.5)
Age at first diagnosis of HIV in years (median, IQR) (*n*=268)	32 (28-38)
CDC classification (*n*=270) (%)	
A	69 (25.6)
B	96 (35.6)
C	105 (38.9)
Baseline CD4 count in cells/mm^3, median (IQR) (*n*=262)	66 (23.8-161.5)
Baseline viral load	NA
Opportunistic infections at the time of initiation of ART (*n*=273) (%)	126 (46.2)
Presence of underlying medical diseases before starting ART (*n*=252) (%)	64 (22.5)
Presence of drug treatment for opportunistic infections before starting ART (*n*=251) (%)	147 (58.6)
NRTI type ART	
d4T + 3TC	278 (97.5)
AZT + 3TC	213 (74.7)
ddI + 3TC	122 (42.8)
TDF + 3TC	145 (50.9)
Duration of receiving ART in years (median) (IQR)	6.9 (6.0-8.1)
Duration of follow-up in years (median) (IQR)	7.0 (6.0-8.2)
Hepatitis B co-infection (104 cases checked)	10 (9.6)
Hepatitis C co-infection (76 cases checked)	3 (4.0)

d4T, stavudine; 3TC, lamivudine; AZT, zidovudine; ddI, didanosine; TDF, tenofovir

and at year 7, 77 patients (41.6%) achieved the target CD4 count.

At year 5, gender, CDC stage having a baseline CD4 count >50 cells/mm^3 and a rise in the CD4 count to ≥350 cells/mm^3 by 1 year were significantly associated with having a CD4 count ≥500 cells/mm^3 at year 5. At year 7, gender, having a baseline CD4 count >100 cells/mm^3 and a rise in the CD4 count to ≥350 cells/mm^3 by 1 year were still significantly associated with having a CD4 count ≥500 cells/mm^3 Table (3).

Adverse events

Among the studied patients, adverse events probably due to NVP were rash and elevated liver enzymes: 7 cases with rash were seen, 4 were mild and the rest were moderate; 2 cases of rash occurred

Table 2
Tested characteristics for having virological success at years 5 and 7.

Characteristics	Year 5		Year 7	
	Odd ratios	*p*-value	Odd ratios	*p*-value
Age (<50 *vs* ≥50 years)	NE	0.309[a]	0.42 (0.04-3.97)	0.406[a]
Gender (female *vs* male)	1.27 (0.47-3.47)	0.637	2.30 (0.79-6.76)	0.120
Body weight (<40 kg *vs* ≥40 kg)	1.75 (0.36-8.44)	0.367[a]	1.23 (0.26-5.89)	0.680[a]
BMI (<18.5 kg/m^2 *vs* ≥18.5 kg/m^2)	4.87 (0.89-26.48)	0.082[a]	5.36 (0.81-35.28)	0.092[a]
CDC stage	0.316	0.669		
C	1	1		
B	0.38 (0.10-1.49)	0.165	0.81 (0.27-2.46)	0.714
A	0.36 (0.09-1.51)	0.163	1.50 (0.37-6.11)	0.576
Baseline CD4 (<50 *vs* ≥50 cells/mm^3)	0.77 (0.27-2.19)	0.617	0.75 (0.27-2.07)	0.576
Baseline CD4 (<100 *vs* <100 cells/mm^3)	0.87 (0.31-2.44)	0.793	0.70 (0.25-1.95)	0.493
Baseline CD4 (<200 *vs* ≥200 cells/mm^3)	1.59 (0.20-12.73)	1.000[a]	0.78 (0.16-3.76)	0.670[a]
CD4 rising to 350 cells/mm^3 at 1 year (no *vs* yes)	0.54 (0.17-1.70)	0.331[a]	0.94 (0.25-3.52)	1.000[a]

[a] Fisher's exact test

Table 3
Possible characteristics associated with having a CD4 count ≥500 cells/mm^3 at years 5 and 7.

Characteristics	Year 5		Year 7	
	Odd ratios	*p*-value	Odd ratios	*p*-value
Age (<50 *vs* ≥50 years)	0.45 (0.12-1.66)	0.220	NE	0.077[a]
Gender (female *vs* male)	0.28 (0.17-0.48)	<0.001	0.48 (0.26-0.86)	0.014
Body weight (<40 kg *vs* ≥40 kg)	0.46 (0.19-1.11)	0.079	0.67 (0.22-2.00)	0.472
BMI (<18.5 kg/m^2 *vs* ≥18.5 kg/m^2)	1.60 (0.60-4.30)	0.349	0.52 (0.18-1.58)	0.248
CDC stage	0.002		0.182	
C	1		1	
B	0.54 (0.30-1.00)	0.048	0.89 (0.44-1.82)	0.754
A	1.77 (0.96-3.28)	0.068	1.80 (0.85-3.82)	0.128
Baseline CD4 (<50 *vs* ≥50 cells/mm^3)	1.67 (1.00-2.78)	0.050	1.21 (0.65-2.25)	0.541
Baseline CD4 (<100 *vs* <100 cells/mm^3)	2.32 (1.38-3.88)	0.793	1.99 (1.04-3.83)	0.038
Baseline CD4 (<200 *vs* ≥200 cells/mm^3)	1.30 (0.57-2.96)	0.527	2.34 (0.86-6.39)	0.089
CD4 rising to ≥350 cells/mm^3 by 1 year (no *vs* yes)	5.52 (2.81-9.82)	<0.001	4.26 (1.87-9.72)	<0.001

[a] Fisher's exact test

after 5 years of follow-up. All the cases of rash were reversible and none of the patients needed to stop NVP. Fifteen cases of elevated liver enzymes occurred, 8 were mild, 5 were moderate and 2 were severe; 10 cases occurred before 5 years and 5 cases occurred after 5 years. One patient had to discontinue the NVP

containing ART, which the others did not.

Due to the small number of patients with adverse events after year 5, we could not analyze the possible factors associated with the outcomes. All the adverse events were probably due to the NVP. Being male and having a hepatitis C infection were associated with elevated liver enzymes in study population (data are not shown here).

Concerning the lipid profiles of patients receiving NVP containing ART, nearly all median lipid values were within the normal range except the high density lipoprotein was higher than normal. The median total cholesterol level at year 5 was 202 mg/dl (IQR 176-232.5 mg/dl), the triglyceride level was 125 mg/dl (IQR 84-199 mg/dl), the high density lipoprotein level was 60 mg/dl (IQR 49-72 mg/dl) and the low density lipoprotein level was 113.5 mg/dl (IQR 94-135.9 mg/dl). One hundred one patients (35.4%) needed to take lipid lowering agents for lipid abnormalities.

DISCUSSION

The proportions of patients who had virological success (a viral load <50 copies /ml) during the 7 years studied were high (>90% for most years). One study from Thailand assessing NVP containing ART at 96 weeks was 87% in the treatment population (Manosuthi *et al*, 2008). Another study from Africa had a success rate at 3 years of 90.6% (Wester *et al*, 2010). These findings are comparable to our virological success rates. A study from Spain with follow-up for 43 months found a virological success rate of 76% (Bonjoch *et al*, 2006) and another with follow-up for 6 years found a success rate of 94% (Rodriguez-Arrondo *et al*, 2009).

Although our definition for virological success was strict (viral load <50 copies/ml), the success rate was high. This finding illustrates the high efficacy of ART containing NVP for more than 5 years regardless of the NRTI backbone. These patients had regular follow-up for 5 years. Their adherence to therapy should be considered as one of the factors for the high virological success rate of this study.

There were no definite variables for virological success in our study. All patients aged >50 years had virological success but the difference from other age groups was not statistically significant. These findings are similar to those of Greenbaum *et al* (2008) who found older age was associated with a shorter time to achieve virological success than younger age. Hinkin *et al* (2004) found this success was due to better adherence in the older age group.

A heavier baseline body weight was not associated with outcome or CDC staging at year 5 but was at year 7. The longer the treatment duration, the greater the chance of virological success. Baseline CD4 count in our study was not associated with virological success. Other studies also found no association between baseline CD4 count and virological success (Manosuthi *et al*, 2007, 2008; Liu *et al*, 2009) except for one study showing an association between a high baseline CD4 (>400 copies/ml) and virological success (Bonjoch *et al*, 2006). Our study could not determine that association due to the low baseline CD4 count among all study subjects. These findings pointed out ART can achieve virological success in HIV patients regardless of their baseline clinical stage or immunological status, but their baseline clinical status may have some effect on their long-term virological response.

Only 21 patients (7.4%) had a viral

load >2,000 copies/ml after 5 years. this is because we excluded cases that did not take NVP containing ART for 5 years. Only a small number of virological failure cases were assessed among patients having NVP containing ART although further studies are needed. We could not determine the characteristics indicating virological failure in this study because of the low number of virological failure patients.

Immunological responses were assessed by following CD4 counts from baseline yearly for 7 years. Wit *et al* (2007) and Wester *et al* (2010) found similar changes in CD4 counts as in our study. The median CD4 count gradually increased with a 5 years median increase in CD4 count from baseline of 354 cells/mm^3 (IQR 235.5-487 cells/mm^3) and a 7 years median increase in CD4 count of 387 cells/mm^3 (IQR 272- 557 cells/mm^3). Our findings are consistent with those of Mocroft *et al* (2007) and Hunt *et al* (2003) who found the CD4 count continued to increase for 5 years and even longer although the rate of increase slowed over time. Other studies found a median increase in CD4 count was 224 cells/mm^3 at 4 years and 189 cells/mm^3 at 6 years (Bonjoch *et al*, 2006; Rodriguez-Arrondo *et al*, 2009). NVP containing ART can prove good immunological responses regardless of baseline CD4 count for up to 5 years.

Thirty-six point eight percent of patients in our study had a CD4 count ≥500 cells/mm^3 at year 5 and 41.6% at year 7. The association between CD4 target and clinical outcomes needs to be studied further.

Female gender was significantly associated with achieving a CD4 count ≥500 cells/mm^3 at both year 5 and year 7. This is in contradiction to other studies which showed age and gender had no effect on CD4 change (Greenbaum *et al*, 2008, López de Castilla *et al*, 2008). But the target CD4 counts and study lengths in those studies were different from our study. One long term study did show female gender was associated with immunological response (Hunt *et al*, 2003). Further studies of the role of gender on long term CD4 responses are needed.

In one study, older age was negatively associated with target CD4 count (Kaufmann *et al*, 2005). But our study findings contradict this. In our study patients with a BMI ≥18.5kg/m^2 and CDC class A were more likely to obtain a CD4 ≥500 cells/mm^3 at both 5 and 7 years but the differences were not significant.

In our study, the higher the baseline CD4 count, the more likely the subject was to reach target CD4 count by 7 years and to achieve a target increase in CD4 count of >350 cells/mm^3, unlike the findings of Garcia *et al* (2004). This could be because the duration of follow-up and definition of a low CD4 count were not the same. For achieving a target CD4 count ≥500 cells/mm^3, the baseline CD4 count is important and patients who had an early immunological response maintained their response longer.

There were few adverse events in our study by 5 years due to our study design which excluded the cases that stopped taking NVP containing ART before 5 years. Most of the adverse events due to NVP occurred shortly after initiation of therapy. Grade 3/4 laboratory toxicity due to NVP was not different from efavirenz by 1 year (Wit *et al*, 2007). The VIRGO study showed satisfactory long term acceptability and safety with no unexpected toxicity, although the sample size in the extension study was small (Reliquet *et al*,

2006). Colafigli *et al* (2009) carried out a single center cohort study of 600 patients to determine long term safety; they found half the patients discontinued NVP containing ART by 18.4 months because of toxicity. Bonjoch *et al* (2006) found adverse events in 17% but only 5.7% of the adverse events could be attributed to NVP, and grade 3/4 adverse laboratory events were not common during the 2 years study period.

The lipid profile statuses of the patients in our study were in the normal range at year 5. Since a lipid profile was not routinely taken as a baseline laboratory test at initiation of ART, we cannot compare with baseline values. The high HDL cholesterol values were comparable to other studies, although 1/3 of patients in our study were taking lipid lowering agents (Bonjoch *et al*, 2006). A study by van Leth *et al* (2004) found the rise in HDL cholesterol among patients taking NVP containing ART was greater than patients taking ART containing efavirenz and the rise in non-HDL cholesterol was less in patients taking NVP containing ART at 48 weeks. The longer the duration of treatment in longer studies, the more likely it was necessary to prescribe lipid lowering agents to prevent long term cardiovascular complications.

There were some limitations in our study. Because the study was retrospective, we could not obtain all required information for all patients and could not control the timing of clinical and laboratory studies. To reduce this effect, we used strict case definitions and a flexible time frame to obtain uniformity. Another limitation of the study was it was a long term study requiring the patient to have taken the NVP containing ART for 5 years; therefore it did not assess all patients taking NVP containing ART.

NVP containing ART had a high efficacy in virological responses and immunological responses long-term. Adverse events were not common. These findings provide useful information for ART programs using NVP as part of their regimen for a number of years.

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