

# A randomized trial comparing the efficacy and tolerability of two HAART strategies at two years in antiretroviral naive patients

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**Background.** The use of HAART combining 2 nucleoside analogues reverse transcriptase inhibitors (NRTIs) plus one protease inhibitor (PI) or 2 NRTIs + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) has shown comparable efficacy. The study was designed to compare long term (2 years) effectiveness of two antiretroviral (ARV) treatment strategies in patients not previously treated: starting with a nelfinavir based HAART switching to nevirapine in case of failure or side effects or the reverse sequence.

**Methods.** This multicenter, randomized, open label clinical trial enrolled ARV-naïve HIV patients with CD4 counts below 500 cells/mm<sup>3</sup>. They were randomly assigned to start ddI + d4T + nelfinavir (switching to ZDV + 3TC + NEV in case of failure or toxicity) (PI-NEV arm) or ddI + d4T + nevirapine, switching to ZDV + 3TC + NFV in case of failure or toxicity (NEV-PI arm). The primary study endpoint was the Kaplan-Meier estimates of the time to failure after switching to second regimen if necessary (considering failure as two consecutive plasma HIV-1 RNA determinations above 200 copies/mL, death, a new category C event or toxicity leading to treatment discontinuation of the second regimen) after a minimum follow-up of two years.

**Results.** A total of 137 patients were evaluable (67 and 70 in the PI-NEV and NEV-PI arms respectively). Baseline characteristics did not differ among groups. Kaplan-Meier estimates of time to failure did not show differences between the two arms neither in the on-treatment (OT) analysis (log rank test,  $p = 0.81$ ) nor in the intent-to-treat (ITT) analysis ( $p = 0.58$ ). At 24 months, the estimated proportion of patients free of failure were 72% and 66% respectively in the PI-NEV and NEV-PI arms OT analysis ( $p = 0.54$ ) and 73% and 64% in the PI-NEV and NEV-PI arms in the ITT analysis ( $p = 0.49$ ). The difference in the median in CD4+ lymphocyte count at 24 months was not significantly different in the two groups: 393 and

Un ensayo randomizado que compara la eficacia y tolerancia de dos estrategias de HAART a dos años en pacientes sin tratamiento antirretroviral

**Introducción.** El uso del tratamiento antirretroviral de alta eficacia (TARGA) que combina 2 análogos de nucleósidos (NRTI) más un inhibidor de proteasas (IP) o 2 NRTI más 1 no-análogo de nucleósido (NNRTI) ha demostrado tener eficacia comparable. Este estudio fue diseñado para comparar la efectividad a largo plazo (2 años) de 2 estrategias de tratamiento antirretroviral (ARV) en pacientes no tratados previamente: empezando con un TARGA utilizando nelfinavir (NFV) y cambiando a nevirapina (NEV) en caso de fallo o de efectos adversos o viceversa.

**Métodos.** Este es un ensayo clínico, abierto, randomizado y multicéntrico que incluye pacientes infectados por el virus de la inmunodeficiencia humana (VIH) que nunca han recibido ARV y con menos de 500 CD4. Los pacientes fueron aleatorizados a recibir ddI más d4T más NFV (cambiando a ZDV más 3TC más NEV en caso de fallo o toxicidad; brazo PI-NEV) o ddI más d4T más NEV (cambiando a ZDV más 3TC más NFV en caso de fallo o toxicidad; brazo NEV-PI). El objetivo primario del estudio fue el tiempo estimado hasta el fracaso después de cambiar al segundo régimen terapéutico cuando fue necesario (considerando fracaso como 2 determinaciones de carga viral del VIH por encima de 200 copias/ml, muerte, un nuevo evento de la categoría C o toxicidad que lleve a la discontinuación del segundo régimen) después de un mínimo de seguimiento de 2 años.

**Resultados.** Se evaluaron un total de 137 pacientes (67 y 70 en el brazo PI-NEV y NEV-PI, respectivamente). Las características basales de los pacientes fueron similares en ambos grupos. El tiempo estimado hasta el fracaso del tratamiento mediante las curvas de Kaplan-Meier no mostraron diferencias entre los 2 brazos de tratamiento ni en el análisis por tratamiento (OT) ( $p = 0,81$ ) ni en el análisis por intención de tratar ( $p = 0,58$ ). A los 24 meses, la

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**307 CD4 cells/mm<sup>3</sup> in the PI-NEV and NEV-PI arms respectively ( $p = 0.167$ ).**

**The incidence of adverse events (AEs) in the two arms was very similar: 50 (75%) in the PI-NEV and 54 (70%) in the NEV-PI group, as it was for grade 3-4 AEs leading to drug switching.**

**Conclusion. At two years both treatments strategies (PI-NEV vs NEV-PI) had a high and comparable efficacy and were generally well tolerated.**

**KEY WORDS:** HAART strategies, nevirapine, nelfinavir, protease inhibitor.

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**proporción estimada de pacientes libres de fracaso fue del 72 y el 66%, respectivamente, en el brazo de PI-NEV y NEV-PI en el análisis OT ( $p = 0,54$ ) y del 73 y el 64% en el PI-NEV y NEV-PI en el análisis ITT ( $p = 0,49$ ). La diferencia en la mediana de linfocitos CD4 a los 24 meses no fue significativamente diferente entre ambos grupos: 393 y 307 CD4 células/mm<sup>3</sup> en el grupo PI-NEV y NEV-PI, respectivamente ( $p = 0,167$ ). La aparición de efectos adversos del tratamiento fue muy similar: 50 (75%) en el grupo PI-NEV y 54 (70%) en el grupo NEV-PI, así como los efectos adversos de grado 3-4 que llevaron a la discontinuación del tratamiento.**

**Conclusión. Las estrategias de tratamiento PI-NEV frente a NEV-PI tienen una eficacia alta y comparable a los 2 años de seguimiento y en general fueron bien toleradas.**

**PALABRAS CLAVE:** estrategias TARGA, nevirapina, nelfinavir, inhibidor de proteasa.

## Introduction

Currently, there are many drugs and combinations of drugs approved for the initial on therapy of human immunodeficiency virus type 1 infection (HIV-1). However, all these drugs belong to only three different classes: nucleoside or nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI)<sup>1,2</sup>. Because cross-resistance within classes is common, the failure of the initial regimen hinders the success of future regimens<sup>3-6</sup>. The current standard of care is to use two NRTI plus a third agent from another class (NNRTI or PI). Regimens should be well tolerated, provide durable viral suppression and preserve future treatment options. Many clinical trials have been conducted comparing a NNRTI or a PI as third drug with high success rate in both options but the optimal sequencing of antiretroviral regimen for HIV-1 infection is unknown. In fact, it is not clearly established if is better to start antiretroviral therapy with a NNRTI switching to a PI after failure or the reverse sequence<sup>7,8</sup>. We conducted a clinical trial to compare the efficacy and tolerance of treatment strategies using stavudine (D4T), didanosine (DDI) plus nevirapine (NVP) or nelfinavir (NFV), as initial antiretroviral therapy in naïve patients, switching to zidovudine (AZT) plus lamivudine (3TC) and NFV (if patient started with NEV) or NEV (if patient started with NFV) after development of virologic failure or intolerance to the first regimen.

## Methods

### Patients

The Transfer study was a multicenter, randomized, open-label, parallel-group clinical trial that was conducted at 8 clinical sites in Spain. The protocol was approved by the Institutional Ethics Committee at each center and by the Spanish Medicines Evaluation Agency.

Eligible patients were HIV-1-infected adults naïve for antiretroviral therapy, with plasma HIV-1 RNA levels above 3,000

copies/mL and CD4+ cell count below 500 cells/mm<sup>3</sup>. Exclusion criteria were current pregnancy, breastfeeding or wish to become pregnant during the study period, elevated aminotransferases (above 5 times the upper limit of normal) and serum creatinine (above 2.5 mg/dL). Written informed consent was obtained from all eligible patients before randomization.

### Study design

Patients were randomized in a 1:1 fashion to start antiretroviral therapy with didanosine and stavudine plus either nelfinavir (PI-NEV arm) or nevirapine (NEV-PI arm). In case of virologic failure or toxicity, patients switched therapy to the following second regimens: zidovudine, lamivudine and nevirapine (PI-NEV arm) or zidovudine, lamivudine and nelfinavir (NEV-PI arm). Randomization was centralized. A random sequence was generated by a computer using blocks of variable size balanced within each site. The patient's identification number and the treatment arm were assigned at the coordinating center after fax reception of the randomization form. After randomization, patients were assessed at baseline, at 1 and 3 months and every 3 months thereafter until completing at least 24 months of follow-up. At each medical visit, clinical data were collected and fasting blood analyses including at least blood cells, CD4 cell count, plasma HIV-1 RNA, glucose, triglycerides, total cholesterol, and liver, kidney, and pancreatic function tests were performed. Laboratory parameters were measured by the routine assays used at each site throughout the whole follow-up period. Safety was assessed through reporting of adverse clinical events and abnormal laboratory measurements. Toxicity was described using the AIDS Clinical Trials Group toxicity grading scale<sup>9</sup>.

The patients who discontinued the second regimen because of adverse effects or virologic failure switched to a third regimen at the discretion of the treating physician.

Compliance was assessed by a simple questionnaire at each visit. The adherence was prospectively evaluated by the investigator and by the patient in three categories: 100 percent, 80-100 percent or less than 80 percent.

### Definitions

Virologic failure was defined as two consecutive determinations of plasma HIV-1 RNA above 200 copies/mL separated at least

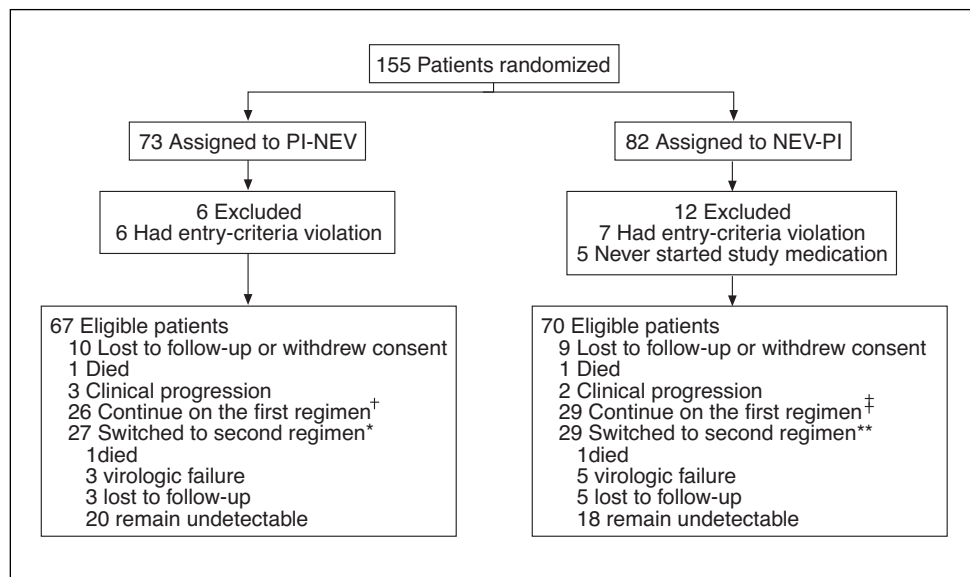


Fig. 1. Randomization, eligibility, and follow-up of the patients at 24 months. †7 patients continued on first regimen despite virological failure. ‡10 patients continued on first regimen despite virological failure. \*Reasons to switch to second regimen were adverse events (18), virological failure (8) and other (1). \*\*Reasons to switch to second regimen were adverse events (19), virological failure (9) and other (1). PI-NEV: protease inhibitor-nevirapine; NEV-PI: nevirapine-protease inhibitor.

two weeks. In case of developing virologic failure on the first regimen, therapy was switched to the second regimen specified by the protocol. If the virologic failure was observed on the second regimen, the therapy could be changed or maintained at the discretion of the physician and the patient continued in the study at least until the completion of the 24-month follow-up period. Progression to acquired immune deficiency syndrome (AIDS) was defined as the development of any new clinical event included in the category C of the CDC-1993 classification after 12 weeks of treatment<sup>10</sup>.

### End points

The primary study endpoint was time to virologic failure (HIV-VL > 200 copies/ml) after switching to the second antiretroviral regimen, clinical progression or death. Secondary endpoints were time to virologic failure while on the first regimen, changes in CD4 cell count, side effects and mortality.

### Statistical analysis

Patients were followed for the entire duration of the trial regardless of premature discontinuation of assigned therapy. All randomized patients, except those who violated entry criteria or never started the study medication, were included in the analysis.

TABLE 1  
Baseline characteristics of the patients

Characteristic	PI-NEV (n = 67)	NEV-PI (n = 70)
Age in years, median (range)	42 (29-63)	41 (24-70)
Male gender, n (%)	53 (79)	50 (71)
Route of HIV infection, n (%)		
Male homosexuality	14 (21)	14 (20)
Heterosexual transmission	23 (34)	25 (36)
IV drug use	18 (27)	24 (34)
Other or unknown	12 (18)	7 (10)
Acquired immunodeficiency syndrome, n (%)	24 (36)	17 (24)
CD4 cells per mm <sup>3</sup> , median (range)	93 (0-435)	142 (2-442)
Log <sub>10</sub> plasma HIV-1 RNA, median (range)	5.2 (3.5-6.9)	5.0 (3.7-6.0)

In the intent-to-treat (ITT) analysis, treatment failure was defined as virologic failure, progression to AIDS or death; in this analysis, patients who discontinued study medication were not considered as failures as long as HIV-1 RNA remained below 200 copies/mL. The patients who withdrew consent or who were lost to follow-up were censored. In the analysis of patients according to the treatment received (on treatment), treatment failure was defined as virologic failure, progression to AIDS or death; data on patients who withdrew consent, were lost to follow-up or switched or stopped the medication were censored. Patients who did not switch to second regimen despite developing virologic failure were considered in both analysis as treatment failure and were not censored. Switches in backbone nucleosides were not considered failures as long as HIV-1 RNA remained below 200 copies/mL.

The sample size was calculated to detect differences between the treatment arms in the proportion of patients experiencing failure. For this purpose, we assumed that the proportion of patients with virologic suppression would be close to 80% at

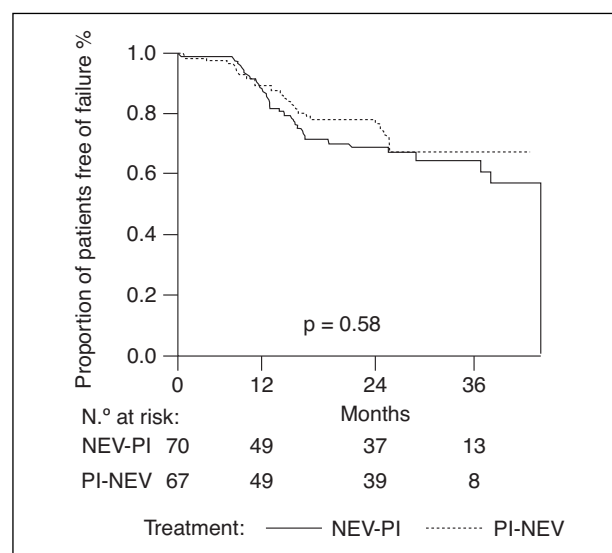


Fig. 2. Kaplan-Meier plots of time to primary study endpoint by intent-to-treat analysis.

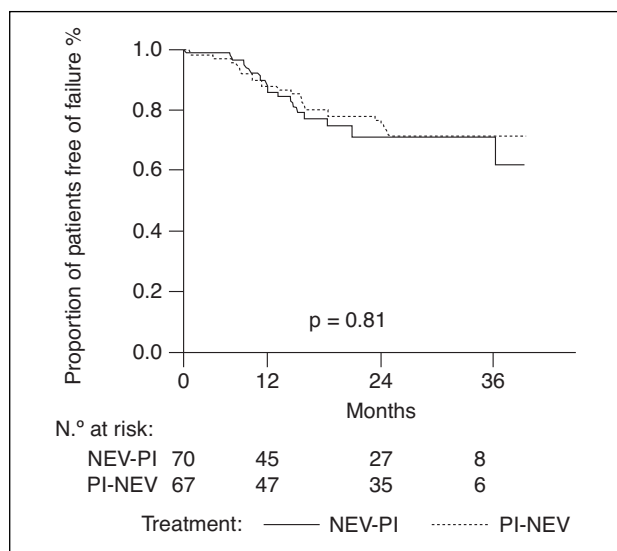


Fig. 3. Kaplan-Meier plots of time to primary study end point by on-treatment analysis.

24 months<sup>11,12</sup>. A sample of 81 patients per arm was necessary to detect a difference of 20% percentual points between arms with a two-sided 5% alpha significance level and an 80% statistical power. Statistical analysis was performed using SPSS Software 10.0 (SPSS Inc. Chicago, IL, USA). Chi-square or Fisher's exact tests were used to compare proportions between treatment groups. Differences in continuous variables between groups were analyzed using Mann Whitney's U test. Time to development of failure was estimated using the Kaplan-Meier product-limit method and the equality of the time to event distributions using the log-rank test. Comparisons were made using a two-sided significance level of 0.05.

## Results

### Population

155 patients were randomized between May 1999 and February 2001, 73 were assigned to PI-NEV arm and 82 to NEV-PI arm. 18 subjects were excluded of the study because of entry-criteria violation

or because the patients never started the study medication (6 in the PI-NEV; 12 in the NEV-PI) (fig. 1). The baseline characteristics of the 137 patients eligible for the study are shown in table 1. There were no significant differences between the two arms in age, gender, exposure to HIV, AIDS diagnosis, CD4 cell count or plasma viral load.

13 patients in the PI-NEV arm and 14 in the NEV-PI arm were lost to follow-up or withdrew consent during the study follow-up.

### Outcomes

#### Primary endpoint

At the end of the study, the Kaplan-Meier estimates of time to failure on the second line treatment did not show differences between the two arms neither in the intention-to-treat analysis ( $p = 0.58$ , log-rank test) (fig. 2) nor on-treatment analysis ( $p = 0.81$ , log-rank test) (fig. 3).

At 24 months, the percentages of patients free of failure were 73 percent and 64 percent respectively in the PI-NEV and in the NEV-PI ( $p = 0.49$ , Fisher's exact test). Considering an on-treatment analysis, the percentage of patients free of failure were 72 percent and 66 percent respectively in the PI-NEV and in the NEV-PI ( $p = 0.54$ , Fischer's exact test).

#### Secondary endpoint

The Kaplan-Meier estimates of time to failure on the first line treatment did not show differences between the two arms neither in the intention-to-treat analysis ( $p = 0.83$ , log-rank test) nor on-treatment analysis;  $p = 0.97$ , log-rank test).

#### CD4 cell count

The difference in the median in CD4+ lymphocyte count at 24 months was similar in the two groups: 393

TABLE 2  
Clinical adverse events

Adverse event (AE)	PI-NEV (n = 67)		NEV-PI (n = 70)	
	Number of patients with adverse events	Grade 3-4 AEs leading to discontinuation	Number of patients with adverse events	Grade 3-4 AEs leading to discontinuation
Metabolic and nutritional (hyperlipidemia and lipodystrophy)	17	11*	9	4*
Peripheral neuropathy	15	3	18	9
Digestive (diarrhea)	27	10**	18	2**
Systemic (asthenia...)	22	0	22	1
Skin rash	16	0	21	3
Hepatic	3	2	4	2
Other	33	1	43	0
Total		27 (40)		21 (30)

\* $p = 0.05$ , Fisher's exact test.

\*\* $p = 0.01$ , Fisher's exact test.

and 307 CD4 cells/mm<sup>3</sup> in the PI-NEV and NEV-PI arms respectively ( $p = 0.167$ , Mann Whitney's U test).

### Tolerability

The incidence of adverse events in the two arms was very similar: 50 (75%) in the PI-NEV and 54 (70%) in the NEV-PI group.

There were no significant differences between the two arms in the number of adverse events per group. The adverse event profile was the expected for each drug. During the whole duration of follow-up (median 21 months, inter-quartile range 8-31 months), twenty-seven patients in the PI-NEV arm and twenty-one in the NEV-PI arm discontinued the study medication because of adverse events. The number of patients switching treatment because of metabolic and nutritional adverse events (hyperlipidemia or lipodystrophy) was significantly lower in the NEV-PI than in the PI-NEV arm (4 patients *vs* 11 patients;  $p = 0.05$ ). However, the number of patients discontinuing because digestive adverse events (mainly diarrhoea) was significantly higher in the PI-NEV arm than in the NEV-PI (10 patients *vs* 2 patients;  $p = 0.01$ ) (table 2).

Two patients in the PI-NEV arm and two in the NEV-PI died during the 24 months of follow-up. The causes of death were progressive multifocal leucoencephalopathy and metastatic giant cell carcinoma of unknown origin in the PI-NEV arm, and lymphoma and acute respiratory failure secondary to *P. carinii* pneumonia in the NEV-PI arm. None of them were considered related with the study medication.

### Adherence

Proportions of patients with full adherence to medication (100 percent of compliance) were 86.7 % in the PI-NEV arm and 79.2% in the NEV-PI arm. There were no significant differences between the two arms in any moment of the study.

### Discussion

Although highly active antiretroviral therapy was primarily defined as triple therapy including two nucleoside retrotranscriptase inhibitors plus one protease inhibitor, concerns about tolerance and toxicity promptly became very important. Consequently, other treatment approaches such as 2 nucleosides plus 1 non-nucleoside were to those treatments considered standard. Comparative studies among both simple regimen showed at least similar benefits in terms of virologic and immunologic outcomes<sup>13</sup>. However, few data are available on what is the best option to start antiretroviral therapy: a protease inhibitor containing regimen switching to a non-nucleoside containing regimen when failure or intolerance occurs or the reverse sequence<sup>7,8</sup>. This clinical trial was designed to evaluate the strategy to compare antiretroviral therapy including a pro-

tease inhibitor regimen switching to a non-nucleoside containing regimen versus the reverse sequence due to treatment failure (virologic failure or toxic effects) using as a primary end point the treatment failure of the second scheduled treatment.

There was no significant difference in the duration of successful treatment, as measured in terms of the time to the primary end point, between the two comparing arms and at 24 months of commencing the antiretroviral therapy the percentages of patients free of failure were 72 percent and 66 percent respectively in the PI-NEV and in the NEV-PI groups in the intention-to-treat analysis. There were also no significant differences between the protease inhibitor starting treatment and the nevirapine starting therapy in the changes in the CD4 cell count. The definition of the primary end point was designed to capture all possible reasons for the premature discontinuation of treatment in addition to virologic rebound and protocol-specified toxic effects. In terms of the time to the secondary end points, the time to treatment failure of the first line therapy was very similar in both groups, the mean increase in CD4 cell count was not significant different among two arms as well as the incidence in adverse events. However, side effects leading to treatment discontinuation like gastrointestinal intolerance or metabolic disorders (hyperlipidemia or lipodystrophy) were significantly higher among patients included in the protease inhibitor starting arm. Conversely, neurological side-effects leading to treatment discontinuation (mainly peripheral neuropathy) were more frequent in the non-nucleoside starting arm<sup>14-16</sup>.

It is important to note that 10 out of the 67 patients included in the PI-NEV arm were lost to follow-up or withdrew consent while on first line treatment of the study, and the same was reported for 3 additional patients during the second line treatment in this arm<sup>17</sup>. In the NEV-PI arm a total of 9 out of the 70 patients included were lost to follow-up or withdrew consent while on first line therapy and the same occurred in 5 patients during the second therapy. Although it may be a relatively high percentage of patients lost during the follow-up median of 2 years of this study, it must be considered as results of the «real-life» taking into account that about one third of the patients included in the study were intravenous drug users and the duration of the study may be considered long. In any case, the overall incidence of patients lost to follow-up or withdrawn from the study were very similar between the 2 arms.

In conclusion, at two years both treatment strategies (PI-NEV *vs* NEV-PI) had a high and comparable efficacy.

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