DOI: 10.1111/hiv.12298

HIV Medicine (2015), **16**, 628–634

ORIGINAL RESEARCH

Outcome of neuropsychiatric symptoms related to an antiretroviral drug following its substitution by nevirapine: the RELAX study

E Pedrol,[1] JM Llibre,[2,3] M Tasias,[1] A Currán,[4] JM Guardiola,[5] E Deig,[6] A Guelar,[7] O Martínez-Madrid,[8] L Tikhomirova,[1] R Ramírez[1] and the RELAX Study Group*

[1]Sant Pau i Santa Tecla Hospital, Tarragona, Spain, [2]Germans Trias i Pujol Universitary Hospital, 'Lluita contra la SIDA' Foundation, Badalona, Spain, [3]Autónoma University of Barcelona, Barcelona, Spain, [4]Vall d´Hebró Universitary Hospital, Barcelona, Spain, [5]Sant Pau i Santa Creu Hospital, Barcelona, Spain, [6]Granollers Hospital, Barcelona, Spain, [7]Hospital del Mar, Barcelona, Spain and [8]Santa María del Rosell Hospital, Cartagena, Spain

Objectives

The primary objective was to evaluate the improvement in neuropsychiatric symptoms attributed to an antiretroviral drug after that drug was substituted with nevirapine. The secondary objective was to evaluate the impact on patient adherence and quality of life.

Methods

A prospective, observational study was carried out that included patients with HIV-1 plasma suppression for whom an antiretroviral drug was substituted with nevirapine because of central nervous system (CNS) side effects, a Pittsburgh Sleep Quality Index (PSQI) score > 5 or a Hospital Anxiety and Depression Scale (HADS) score ≥ 10, and who had not initiated psychoactive drug treatment during the prior 6 weeks. Evaluations were carried out at baseline and 1 and 3 months after the switch using the PSQI, HADS, Epworth Sleepiness Scale, Medical Outcomes Study-Short Form 30 items (MOS-SF-30) and Simplified Medication Adherence Questionnaire (SMAQ).

Results

A total of 129 patients were included in the study. The drug substituted was mainly efavirenz (89.9%), and reasons for the switch included sleep disturbances (75.2%), anxiety (65.1%), depression (38.7%), attention disturbances (31%), and other reasons (31%), with a mean of 2.4 neuropsychiatric disturbances per patient. A statistically significant improvement was observed in all the tests evaluating neuropsychiatric symptoms and adherence at 1 and 3 months. The CD4 lymphocyte count remained stable ($P = 0.096$). Three (2.3%) patients had a detectable plasma HIV-1 RNA at the end of the study. Nine patients (6.9%) withdrew because of nevirapine-related toxicity (rash in seven patients and hypertransaminasaemia in two patients, none of which were > grade 2).

Conclusions

The switch to nevirapine from a drug causing neuropsychiatric disturbances (primarily efavirenz) in subjects with virological suppression was effective in resolving those disturbances, with an improvement in all the parameters studied. This led to better adherence to treatment and quality of life, with no detrimental effect on their immunological and virological control.

Keywords: antiretroviral toxicity, antiretroviral treatment switch, efavirenz, HIV, neuropsychiatric symptoms, nevirapine.

Accepted 9 October 2014

Correspondence: Dr Rafael Ramírez, Montesinos, Internal Medicine Department, Sant Pau i Santa Tecla Hospital, Rambla Vella, 14, 43003 Tarragona, Spain. Tel: 0034 977259900; fax: 0034 977259914; e-mail: rafaelramirezmontesinos@hotmail.com

*See Appendix.

Introduction

Currently, toxicity is the most common cause of switching suppressive antiretroviral therapy (ART) [1], with short- and long-term neuropsychiatric toxicity being the main reason for switching. In clinical practice, the switch is brought about because toxicity eventually leads to poorer adherence and a higher risk of treatment failure. The drug most commonly associated with neuropsychiatric toxicity is efavirenz (EFV) (being associated with suicidal ideation, maniac symptoms, paranoid reactions, sleep disorders, irritability and instability), although, to a lesser extent, other drugs are also associated with neuropsychiatric adverse effects [2–10].

Nevirapine (NVP) is a nonnucleoside reverse transcriptase inhibitor (NNRTI) with similar efficacy to EFV and ritonavir-boosted atazanavir (ATV/r) [11,12] in treatment-naïve patients, is administered once a day as a single tablet [13,14] and has also shown efficacy in treatment simplification [15,16]. In addition, only in rare cases has it been linked to the occurrence of neuropsychiatric adverse effects, while in patients with suppressed viral load it can be initiated at any CD4 cell count [17]. Nevertheless, hypersensitivity reactions with subsequent withdrawal are present in 15% of NVP-treated patients [18].

This study sought to examine the course of neuropsychiatric symptoms attributed to an antiretroviral drug following its substitution with NVP.

Methods

A post-authorization, prospective, multicentre, observational study was carried out in 30 hospitals distributed across Spain. The recruitment period was from December 2010 to July 2011. The data were obtained in three visits, one at baseline and two at follow-up, which coincided with any of the visits the patient had to undergo regularly for his/her follow-up. No diagnostic or therapeutic procedure was carried out in this study. The decision to prescribe NVP had been made before and independently of the decision to offer the patient the opportunity to participate in the study, which was never considered a reason for taking part. The prescription was only determined according to routine clinical practice at the hospital. No restriction was set regarding the use of any type of concomitant treatment for patients included in the study.

Demographic and clinical data were collected systematically and included age, gender, race, risk behaviour for HIV infection, date of HIV diagnosis, stage of HIV infection attending to Centers for Disease Control and Prevention (CDC) classification, hepatitis B and C virus serology, viral load and immune status, ART history, including prior lines of treatment and reason for starting treatment with NVP, current ART and psychiatric history.

Patients of both genders who met the following criteria were included:

- age ≥ 18 years, HIV-1 infection diagnosis and HIV-1 viral load < 50 HIV-1 RNA copies/mL;
- an antiretroviral drug was substituted with NVP according to the physician's opinion, because of central nervous system (CNS) side effects attributed to the antiretroviral drug;
- existence of significant sleep disturbances in the physician's opinion, which were later documented using the Pittsburgh Sleep Quality Index (PSQI), and symptoms indicative of anxiety/depression that were rated using the Hospital Anxiety and Depression Scale (HADS);
- no physical and/or mental disability that would affect the patient's ability to complete the PSQI, HADS, Epworth Sleepiness Scale, Medical Outcomes Study-Short Form 30 items (MOS-SF-30), quality of life questionnaire and Simplified Medication Adherence Questionnaire (SMAQ).

The subjects gave their informed consent to take part in the study. The study was reviewed and approved by the appropriate institutional ethics committees and health authorities in accordance with current Spanish legislation and pursuant to the provisions of ministerial order SAS/3470/2009 on the conduct of observational studies. In addition, the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Patients who had begun antidepressant and/or anxiolytic and/or hypnotic treatment at the same time as NVP treatment, as well as those patients for whom data were missing for any of the parameters required to evaluate the primary objective, were excluded from the analysis.

Efficacy and safety assessments

The primary study endpoint was improvement of neuropsychiatric symptoms attributed to the antiretroviral drug following its substitution with NVP. The primary objective was defined using the progression of the score obtained at baseline, 1 month and 3 months on the PSQI and HADS questionnaires. Regarding the PSQI, patients were categorized into PSQI score < 5 (considered nonindicative of significant sleep disturbances) and PSQI score > 5 (considered indicative of significant sleep disturbances). In relation to HADS, patients were distributed in categories of HADS score 0–7 (absence of depression or anxiety), 8–10 (possible depression or anxiety) and ≥ 11 (clinical problem).

The following were evaluated as secondary endpoints:

- adherence to treatment using the SMAQ questionnaire;
- score on the Epworth Sleepiness Scale;
- quality of life assessed using the MOS-SF-30 questionnaire.

Statistical methods

Sample size was based on the number of patients that would allow the main objective of the study to be achieved. Secondary endpoints were obtained from size determined by the primary endpoint. Calculations were performed in order to observe statistically significant differences between baseline and final scores on the PSQI questionnaire (range 0–21) and HADS (range 0–42 points). As we did not find any data in the literature on changes in these scores in this group of patients, baseline and final scores on both questionnaires were mathematically transformed into a standardized scale between 0 and 1. Then, an average score for the change (the difference between baseline and final scores) and thus a standard deviation (SD), which also took values between 0 and 1, were obtained for both the PSQI and HADS.

To determine the sample size, the most conservative viewpoint was considered (to guarantee the representativeness of the sample), for which the principle of maximum variance (SD of 0.5 points) was accepted as there was no estimate of the expected value for each response. It was therefore proposed that the sample size be calculated by using a model of paired means repeated in a group. In addition, a minimum score difference between baseline and the final visit of 10 points, an alpha risk of 0.05 for a two-tailed test and a power of 80% were assumed. A maximum loss of data (of no more than 10%) was also assumed, because of loss to follow-up, or incomplete or inconsistent information.

The absolute and relative frequency distributions of the qualitative variables are presented, as well as measures of central tendency and dispersion (mean and SD, and median, minimum and maximum values) for the quantitative variables. The confidence intervals (CIs) at 95% for the main quantitative variables for results associated with the main objective and the key secondary endpoints are also presented. Regarding inferential analysis, parametric tests were used for continuous variables and nonparametric tests for ordinal, categorical or nonparametric variables. The hypothesis tests were used in all bilateral cases with a significance level of 0.05. The Mann–Whitney *U*-test (for unpaired data) or the Wilcoxon test (for paired data) was used for variables that did not conform to a normal (or parametric) distribution. The χ^2 test (or Fisher's exact test where appropriate) was used to analyse contingency tables and to compare proportions and/or frequency distributions. SPSS software version 17.0 was used to perform the analysis (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago, IL, USA).

Results

One hundred and forty-nine patients were recruited for the study, 20 of whom were excluded because they had a detectable viral load at baseline. Thus, 129 patients who met all the study criteria were included in the analysis. The mean (± SD) age was 43.2 ± 9.8 years. The mean (± SD) number of treatment regimens prior to baseline was 2.2 ± 2.3, while the mean (± SD) CD4 lymphocyte count was 582 ± 261 cells/μL. Table 1 shows the remaining demographic and HIV infection-related data at enrolment.

The substituted drugs were EFV in 89.9% of patients (116 patients), raltegravir in 3.1% (four patients), lopinavir/ritonavir in 3.1% (four patients), darunavir/ritonavir in 2.4% (three patients) and atazanavir/ritonavir in 1.5% (two patients). The neuropsychiatric symptoms that led to the switch were sleep disturbances (75.2%), anxiety (65.1%), depression (38.7%), attention disturbances (31%) and other (31%). The average number of neuropsychiatric disturbances per patient was 2.4.

Table 1 Demographic and HIV-infection-related data at baseline (n = 129)

Age (years) (mean ± SD)	43.2 ± 9.8
Gender, male [*n* (%)]	95 (73.6)
Race [*n* (%)]	
Black	7 (5.4)
Caucasian	117 (90.7)
Other	4 (3.1)
Risk behaviour [*n* (%)]	
Injecting drug user	37 (28.7)
Homosexual male	47 (36.5)
Heterosexual	39 (30.2)
Other	6 (4.6)
CDC stage [*n* (%)]	
A	79 (61.2)
B	16 (12.4)
C	34 (26.4)
CD4 count (cells/μL) (mean ± SD)	582 ± 261
Hepatitis serology [*n* (%) positive]	
HBV	10 (7.8)
HCV	36 (27.9)
HBV/HCV	3 (2.3)
Experience with antiretroviral drugs [*n* (%)]	
NNRTIs	122 (94.6)
NRTIs	129 (100)
PIs	50 (38.8)
Integrase inhibitors	4 (3.1)

CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

Table 2 Outcome of neuropsychiatric symptoms in terms of test scores following the substitution with nevirapine of the antiretroviral drug to which the neuropsychiatric symptoms were attributed

Area assessed	Test used	Baseline ($n = 129$)	1 month ($n = 122$)	3 month ($n = 100$)	p Baseline to 1 month	p Baseline to 3 month
Sleep quality	PSQI	96.90%	60.70%	44.00%	<0.001	<0.001
Anxiety and depression	HADS	86.80%	46.40%	32.00%	<0.001	<0.001
Sleeping	Epworth scale	8.3 ± 4.7 (65.90%)	6 ± 4 (89.30%)	5.5 ± 3.6 (91.00%)	<0.001	<0.001
Adherence	SMAQ	65.90%	75.90%	81.00%	<0.036	<0.013
Quality of life	MOS-SF-30	57.50%	69.80%	73.60%	<0.001	<0.001

Values shown in the table are as follows: for the Pittsburgh Sleep Quality Index (PSQI), the percentage of patients with an index > 5 (indicative of significant sleep disturbances); for the Hospital Anxiety and Depression Scale (HADS), the percentage of patients with clinical anxiety/depression; for the Epworth Sleepiness Scale, the mean score and the percentage of patients with normal sleepiness; for the Simplified Medication Adherence Questionnaire (SMAQ), the percentage of compliant patients; for the Medical Outcomes Study-Short Form 30 items (MOS-SF-30), the percentage of patients with a good quality of life.

At the time of inclusion, 42 patients (32.6%) were receiving psychiatric drug treatment (42 were receiving benzodiazepines, 19 antidepressants and four antipsychotics), whereas at the end of follow-up only 29 patients continued with such treatment (nine continued benzodiazepines, 16 antidepressants and four antipsychotics).

Table 2 shows the test results for sleep quality (PSQI), anxiety and depression (HADS), the Epworth Sleepiness Scale, quality of life (MOS-SF-30) and adherence (SMAQ) associated with substitution of the drug with NVP. There was a significant improvement in the percentages of subjects with abnormal values in all tests from baseline to 3 months.

The CD4 count increased from a mean (± SD) of 582 ± 261 cells/μL at baseline to 619 ± 299 cells/μL in the third month ($P = 0.096$). Three (2.3%) patients went on to have detectable HIV viral load at the end of the study.

Twenty-nine (22.5%) patients withdrew from the study prematurely. Nine (6.9%) withdrew because of toxicity attributed to NVP by the investigator in charge (seven cases of rash and two of hypertransaminasaemia), and nine patients (6.9%) for reasons unrelated to NVP: digestive disorders (nausea and vomiting) in four patients, reduced glomerular filtration in two patients (both patients were receiving NVP in combination with tenofovir disoproxil fumarate (TDF)), palpitations in one patient, arthralgia in one patient and anal pruritus in one patient. Seven patients (5.3%) were lost to follow-up, and there were four voluntary withdrawals. There were no grade 3/4 adverse reactions related to NVP.

Discussion

The substitution of a drug related to neuropsychiatric symptoms with NVP was associated with a significant improvement in sleep disturbances (PSQI and Epworth Sleepiness Scale), anxiety/depression (HADS), adherence to treatment and quality of life. This change was observed starting 1 month after substitution of the drug with NVP. In addition, the percentage of subjects who recovered normal sleep (Epworth Sleepiness Scale) significantly increased. A significant decrease was also observed in the number of patients receiving psychiatric treatment prior to the switch compared with those at the end of the study.

The drug most commonly substituted was, as expected, EFV (in about 90% of cases; 116 patients), with other switches mainly involving the substitution of a protease inhibitor (in 7% of cases, the drugs substituted were lopinavir/ritonavir, darunavir/ritonavir or atazanavir/ritonavir), while the switch involved raltegravir in 3% of cases.

The reasons for the switch were fairly similar to those observed in clinical trials (2–10), while the coexistence of several reasons in one patient was common (an average of 2.4). In order of frequency, sleep disturbances (75.2%), anxiety (65.1%), depression (38.7%) and attention disturbances (31%) were observed.

Particularly striking is the significant improvement in depression when substituting EFV with NVP in our series. Depression is not an adverse effect associated with EFV in most clinical trials (4, 5), although a prospective study designed specifically to collect this neuropsychiatric adverse effect found a higher number of subjects with depression among those treated with EFV compared with those treated with etravirine (ETR) [7]. The discrepancies may be attributable to the absence of confirmation of the diagnosis by psychiatrists or specialized doctors in the clinical trials, leading to underreporting, with only isolated symptoms being reported.

The improvement in neuropsychiatric symptoms occurred without adverse effects on immunological and virological control.

Nine (6.9%) patients experienced toxicity (exanthema or hypertransaminasaemia) attributed to the introduction of NVP, which led to their withdrawal from the study. None of these adverse effects was grade 3/4, while the percentage of patients affected was similar to that observed in studies randomized for NVP in naïve subjects or in subjects whose treatment was switched [13–15].

The co-formulation of EFV/TDF/emtricitabine (FTC) in one tablet taken once daily is a preferred ART regimen in naïve subjects [19–21]. Despite its generally high efficacy and safety, its use is limited by the frequent occurrence of neuropsychiatric side effects, which are either acute (forcing 5% of patients to discontinue the drug in the first few weeks of administration) [3] or chronic [22]. In cohort analyses, 20–25% of subjects who began this treatment discontinued it at 48 weeks because of this toxicity, which may go unnoticed or be underestimated by both the doctor and the patient, through confusion of the origin of symptoms (insomnia, depression, anxiety, irritability, etc.) with the disease itself or changes in the patient's daily life (legal, work-related, family-related, associated comorbidities, toxic consumption, etc.). In fact, recent studies have confirmed that the long-term persistence of these adverse effects is not uncommon [6,22,23].

A previous analysis of the AIDS Clinical Trials Group (ACTG) A5095 study confirmed in 47 patients that most neuropsychiatric adverse effects related to EFV disappeared when it was substituted with NVP [24]. Compared with those subjects who remained on EFV, those who switched to NVP had similar rates of treatment discontinuation and virological failure. Our data are consistent with those of that study.

As this study was performed in routine clinical practice, few patients not taking EFV were included. Recruitment only of patients treated with EFV would probably have enhanced the value of our results, as in patients taking EFV neuropsychiatric symptoms can be attributed more safely to the drug. Also, the withdrawal rate in this real-life study might have been a limitation.

In conclusion, our results support the strategy of substituting EFV with NVP in subjects with virological suppression and treatment-limiting neuropsychiatric toxicity. The switch was associated with a significant improvement in all parameters studied (sleep quality, anxiety/depression scale, sleepiness, adherence and quality of life), which was already observed 1 month after the switch was made, without being detrimental to immunological and virological control.

Acknowledgements

This study was funded by an unrestricted grant from Boehringer Ingelheim Spain, which was not involved in its design, conduct or data analysis.

Conflicts of interest and sources of funding: EP has received funding for research or payment for attendance at conferences or service on advisory boards from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, Roche and ViiV Healthcare. JML has received funding for research or payment for attendance at conferences or service on advisory boards from Abbie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, Tibotec, and ViiV Healthcare. MT, AC, JMG, ED, AG, JGS, OMM, RR, LT and the remainder of the RELAX study group investigators declare no conflict of interest or source of funding.

Author contributions

EP provided scientific input in the study design and study protocol. EP, MT and JML prepared the first draft of the manuscript. All authors assessed clinical data for the study and reviewed and edited the manuscript.

Appendix: the RELAX study group investigators

Hospital de Sant Pau i Santa Tecla (Tarragona): E. Pedrol, M. Tasias, R. Ramírez, L. Tikhomirova, S. Ruiz, A. Delegido. Hospital Germans Trías i Pujol (Badalona, Barcelona): B. Clotet, J. M. Llibre. Hospital Universitari Vall d'Hebrón (Barcelona): A. Curran. Hospital de Sant Pau i de la Santa Creu (Barcelona): J. M. Guardiola. Hospital Granollers (Barcelona): E. Deig. Hospital del Mar: A. Guelar, M^{a}M. Montero. Hospital Creu Roja (L'Hospitalet, Barcelona): I. García, C. Cortes. Hospital de Viladecans (Barcelona): M. Javaloyas. Hospital de Mataró (Barcelona): L. Force, P. Barrufet. Hospital de Calella (Barcelona): S. Valero. Hospital de Palamós (Girona): A. Massabeu. Hospital Verge de la Cinta (Tortosa, Tarragona): E. Chamarro, C Escrich, A. Ortí. Hospital Universitario de Canarias (Tenerife): J. Gomez-Sirvent. Complexo Hospitalario Universitario de Vigo: A. Ocampo. Hospital de Donostia: F. Rodriguez Arrondo. Hospital Santa María del Rosell (Cartagena, Murcia): O. Martínez Madrid. Hospital Arquitecto Macide (El Ferrol, A Coruña): A. Mariño. Hospital de Navarra (Pamplona, Navarra): J. Reparaz. Hospital Clínico de Zaragoza: J. A. Amiguet, M^{a} J. Crusells. Hospital Carlos Haya (Málaga): F. Orihuela. Hospital Virgen de las Nieves (Granada): M. A. Lopez Ruz, J. Pasquau. Centro Penitenciario La Model (Barcelona): A. Marco. Complexo Hospitalario Universitario de A Coruña: S. Lopez, A. Castro. Hospital Virgen de la Victoria (Málaga): J. Santos. Hospital Universitario de San Juan (Alicante): J. M^{a}. Cuadrado. Hospital de Cruces (Bilbao): K. Aguirrebengoa. Complexo Hospitalario Universitario de Santiago de Compostela (A

Coruña): A. Antela. Hospital San Pedro. CIBIR (Logroño): J. A. Oteo, J. R. Blanco. Hospital Miguel Servet (Zaragoza): D. Gil, P. Arazo. Hospital Arnau de Vilanova (Valencia): J. Flores.

References

1 Jarrin I, Hernández-Novoa B, Alejos B *et al*. Persistence of novel first-line antiretroviral regimens in a cohort of HIV-positive subjects, CORIS 2008-1010. *Antivir Ther* 2013; **18**: 161–170.

2 Boyle A. *Chelsea & Westminster Cohort: Probability of Switch Due to Toxicity for Individual ARVs*. Glasgow, HIV11, 2012. O312.

3 Sustiva©. Available at http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000249/WC500058311.pdf (accessed 20 July 2015).

4 Sierra-Madero J, Di Perri G, Wood R *et al*. Efficacy and safety of maraviroc versus efavirenz, both with zidovudine/lamivudine: 96-week results from the MERIT study. *HIV Clin Trials* 2010; **11**: 125–132.

5 Rockstroh JK, DeJesus E, Lennox JL *et al*. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr* 2013; **63**: 77–85.

6 Nelson MR, Elion RA, Cohen CJ *et al*. Rilpivirine versus efavirenz in HIV-1-infected subjects receiving emtricitabine/tenofovir DF: pooled 96-week data from ECHO and THRIVE Studies. *HIV Clin Trials* 2013; **14**: 81–91.

7 Nelson M, Stellbrink HJ, Podzamczer D *et al*. A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. *AIDS* 2011; **25**: 335–340.

8 Bánhegyi D, Katlama C, da Cunha CA *et al*. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. *Curr HIV Res* 2012; **10**: 171–181.

9 Shubber Z, Calmy A, Andrieux-Meyer I *et al*. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS* 2013; **27**: 1403–1412.

10 Honda M, Ishisaka M, Ishizuka N, Kimura S, Oka S, Japanese Anti-HIV-1 QD Therapy Study Group. Open-label randomized multicenter selection study of once daily antiretroviral treatment regimen comparing ritonavir-boosted atazanavir to efavirenz with fixed-dose abacavir and lamivudine. *Intern Med* 2011; **50**: 699–705.

11 van Leth F, Phanuphak P, Ruxrungtham K *et al*. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004; **363**: 1253–1263.

12 Soriano V, Arastéh K, Migrone H *et al*. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. *Antivir Ther* 2011; **16**: 339–348.

13 Gathe L, Andrade-Villanueva J, Santiago S *et al*. Efficacy and safety of nevirapine extended-release once daily versus nevirapine immediate-release twice-daily in treatment-naive HIV-1-infected patients. *Antivir Ther* 2011; **16**: 759–769.

14 Arasteh K, Ward D, Plettenberg A *et al*. Twenty-four-week efficacy and safety of switching virologically suppressed HIV-1-infected patients from nevirapine immediate release 200 mg twice daily to nevirapine extended release 400 mg once daily (TRANxITION). *HIV Med* 2012; **13**: 236–244.

15 Martínez E, Arnaiz JA, Podzamczer D *et al*. Substitution of nevirapine, efavirenz or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med* 2003; **349**: 1036–1046.

16 Negredo E, Cruz L, Paredes R *et al*. Virological, immunological, and clinical impact of switching from protease inhibitors to nevirapine or to efavirenz in patients with human immunodeficiency virus infection and long-lasting viral suppression. *Clin Infect Dis* 2002; **34**: 504–510.

17 European Medicines Agency. Viramune. Procedural steps taken and scientific information after the authorisation. Resolution N° II/0094; 26-08-2010.

18 Miller V, Staczewski S, Boucher C *et al*. Clinical experience with non-nucleoside reverse transcriptase inhibitors. *AIDS* 1997; **11**: 157–164.

19 AIDS Study Group (GESIDA) and the Spanish Secretariat for the National Plan of AIDS (SNPS). Consensus document of GESIDA and Spanish Secretariat for the National Plan on AIDS (SPNS) regarding combined antirretroviral treatment in adults infected by the human immunodeficiency virus. (January 2013 Update). Available at http://www.gesida.seimc.org/pcientifica/dconsensos.asp (accessed 19 August 2013).

20 Thompson MA, Aberg JA, Hoy JF *et al*. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society–USA Panel. *JAMA* 2012; **308**: 387–402.

21 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. February 2013. Available at http://aidsinfo.nih.gov/Contentfiles/adultandadolescentGL.pdf. (accessed 19 August 2013).

22 Martínez E, Arnaiz JA, Podzamczer D *et al.* Three-year follow-up of a simplification trial with nevirapine, efavirenz or abacavir as substitutes of protease inhibitors in patients with human immunodeficiency virus infection. *AIDS* 2007; **21**: 367–369.

23 Babiker AG, Emery S, Fätkenheuer G *et al.* Considerations in the rationale, design and methods of the Strategic Timing of Antiretroviral Treatment (START) study. *Clin Trials* 2013; **10**: S5–S36.

24 Schouten JT, Krambrink A, Ribaudo HJ *et al.* Substitution of nevirapine because of Efavirenz toxicity in AIDS Clinical Trials Group A5095. *Clin Infect Dis* 2010; **50**: 787–791.