High Treatment Success Rates When Switching to Once Daily Nevirapine Containing Antiretroviral Therapy

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Abstract: *Introduction*: Two recent studies have highlighted low rates of virological response to once daily nevirapine containing combination antiretroviral therapy (CART) in treatment naïve HIV-1 infected subjects.

Aim: We assessed factors associated with treatment responses in a cohort of HIV-1 infected, therapy naïve individuals, commencing nevirapine CART with two nucleoside reverse transcriptase inhibitors (NRTI) containing either lamivudine or emtricitabine.

Results: Between January 2002 and 2006, 173 subjects (80 female) met the study inclusion criteria. All subjects initially commenced on twice daily nevirapine with six different NRTI backbones. Mean follow up was 802 days. 49 (28%) subjects switched to once daily nevirapine, 23 (13%) within the first year. After 48 weeks of therapy, HIV RNA was < 50 copies/mL in 154/173 subjects (89%). A trend was observed towards improved virological outcome (HIV RNA < 50 copies/mL) and switching to once daily nevirapine during the first year of therapy (p=0.051).

Conclusion: Whilst awaiting the results of prospective studies assessing once daily nevirapine, our data describe high treatment success rates and good safety responses when switching to once daily nevirapine.

INTRODUCTION

Many different initial therapeutic options are available for HIV-1 infected subjects commencing combination antiretroviral therapies (CART). Recommendations from current treatment guidelines include the use of a non-nucleoside reverse transcriptase inhibitor (NNRTI) with a nucleoside reverse transcriptase inhibitors (NRTI) backbone [1].

Adherence to CART regimens remains paramount in the long term virological success of therapy and strategies to simplify CART, such as once daily dosing of therapy, may improve adherence [2]. Nevirapine, a frequently prescribed NNRTI as part of CART regimens, is currently licensed as a twice daily agent.

The pharmacokinetic characteristics of nevirapine include a long plasma elimination half life of 25-30 hours in steady state, suggesting once daily dosing may feasible in clinical practice. Indeed formal pharmacokinetic studies in HIV-1 infected subjects have demonstrated no significant difference in total nevirapine plasma exposure when dose once daily or twice daily [3] however median nevirapine plasma concentration at the end of dosing interval was 23% lower in the once daily dosing group.

Two recent studies have highlighted low rates of virological response to once daily nevirapine regimens [4, 5] in therapy naïve HIV-1 infected subjects. The DAUFIN study [4] compared the combination of nevirapine, zidovudine, lamivudine dosed at 200, 250, 150 mg twice daily versus nevirapine, lamivudine, tenofovir dosed at 400, 300, 245 mg once daily, respectively. This study was prematurely terminated after enrolling 71 subjects. The once daily arm resulted early virological failure with a high rate of HIV viral resistance.

However, in clinical practice, nevirapine is often dosed in once daily schedules after an initial lead-in period of twice daily therapy. We therefore aimed to determine factors associated with successful treatment outcomes in therapy naïve patients commencing on nevirapine containing CART in a large UK urban centre.

METHODS

All HIV-1 infected, antiretroviral naïve patients, commencing on nevirapine containing CART with lamivudine or emtricitabine plus one other nucleoside analogue at the department of HIV Medicine, St. Mary's Hospital London between January 2002 to January 2006 were eligible for this study. Subjects commencing any nevirapine dosing schedule were included and were required to have been on therapy for at least one year to be eligible. Exclusion criteria included baseline NRTI or NNRTI resistance and concomitant medications which may interact with nevirapine plasma concentration such as rifampicin.

Routine data on individuals who attend our department are collected at each clinic visit in our prospective clinic database. These data include demographic data, antiretroviral

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therapy history and laboratory parameters. Data downloaded for this analysis included a full dataset to 01 January 2007.

From this database antiretroviral history was collected. Baseline was considered the time CART was commenced. In addition, we collected the following data for each clinic visit from baseline until January 2007 (thereby providing the range of follow period for this cohort of a minimum of one year to a maximum of five years); CD4 lymphocyte count (cells/uL), plasma HIV RNA (copies/mL), serum alanine aminotransferase (ALT) and total cholesterol.

Statistical Analyses

All statistical calculations were performed using SPSS for Windows version 14.0. Factors associated with virological response, changes in CD4+ lymphocyte count and changes in total cholesterol over 48 weeks were assessed in a univariate model by linear regression. The potential predictors assessed were baseline and nadir CD4+ cells/μL, gender, baseline HIV RNA log10 copies/mL, NRTI backbone and switching NRTI backbone or to once daily nevirapine in the first year of therapy. Multivariate analyses were performed on parameters in univariate models with p-values less than 0.10, using a stepwise-forward method.

RESULTS

Baseline

During this four year period, 173 previously therapy naive HIV-1 infected subjects commenced a nevirapine containing CART regimen and were eligible for the analysis. All patients commenced on twice daily nevirapine initially. Baseline characteristics are shown in Table **1**. Within this cohort, six different initial NRTI backbones were prescribed based on clinician choice with zidovudine-lamivudine the most frequently used (68%) reflecting prescribing practices at this time.

Patient Follow Up, Virological and Immunological Responses

Total patient follow up on nevirapine in this cohort represents 380 person years. Mean (range) follow up from the start of nevirapine to the last date when data analysis performed was 802 (60 -1824) days. At week 48, 85% of subjects had a viral load < 50 copies/mL and a mean CD4 cell count increase of 204 cells/μL. Follow up parameters over the five year period are shown in Table **2**.

Changes to Antiretroviral Therapy

Over the five year study period, forty-nine (28%) of subjects switched from twice daily to once daily nevirapine dosing, with a median time to switch of 576 days. Of interest, all subjects had an undetectable plasma HIV RNA prior to this switch and 23 (13%) of subjects switched to once daily nevirapine during the first year of therapy at a mean (SD) time of 140 (107) days.

Forty-two subjects (24%) ceased nevirapine CART which was due to virological failure in 11 and physician de-

Table 1. Patient Characteristics, Baseline Antiretroviral Therapy

		Number	(%) Unless Otherwise Stated
Baseline Characteristics			
Number of Patients		173	(100.00)
Gender	male	93	54.0
	female	80	46.0
NRTI Backbone (baseline)	AZT +3TC	117	(68.0)
	TDF + 3TC	17	(10.0)
	ABC + 3TC	11	(6.0)
	d4T + 3TC	2	(1.0)
	ddI + 3TC	1	(1.0)
	TDF + FTC	25	(14.0)
CD4 nadir (cells/uL), *mean (range)*		170	(10 - 490)
CD4 at start of nevirapine (cells/uL),	overall	207	(10 - 540)
mean (range)	male	214	(20 - 540)
	female	201	(10 - 520)
Male with baseline CD4+ > 400 cells/uL		4	4
Female with baseline CD4+ > 250 cells/uL		16	20
Ethnicity	Caucasian	131	76
	African origin	39	22
	Other	3	2
Viral load at start of CART (log10 copies/mL), *mean (range)*		4.98	(1.90 - 6.69)

Table 2. Laboratory Parameters and Dosing Schedules Over Study Period

Time on Nevirapine	Total Number	Detectable HIV RNA, >50 Copies/mL (%)	Mean CD4 Count, Cells/uL (SD)	Switch to Once Daily Nevirapine, n (%)	ALT, IU(SD)	Total Cholesterol, mmol/L (SD)	HDL, mmol/L (SD)
Baseline	173		232 (121)	-	27 (25)	3.98 (0.75)	1.08 (0.30)
Week 8	173			-	60 (11)	-	
One year	169	15 (8.7)	362 (159)	23 (13.3)	28 (19)	4.89 (1.0)	1.40 (036)
Two years	129	8 (6.2)	388 (183)	9 (5.2)	31 (24)	4.96 (0.8)	1.46 (0.44)
Three years	84	7 (8.3)	466 (200)	6 (3.5)	39 (33)	4.96 (1.1)	1.47 (0.50)
Four years	52	2 (3.8)	402 (207)	8 (4.6)	36 (26)	5.09 (0.96)	1.43 (0.46)
Five years	22	1 (4.5)	418 (186)	2 (1.2)	24 (13)	-	

cision in the remaining group. Mean time to ceasing nevirapine was 252 days (range 110 - 1184). Interestingly, no patients ceased nevirapine after switching to a once daily regimen. Neither gender, baseline CD4 lymphocyte count or ALT at week 8 were significantly associated with ceasing nevirapine CART.

Changes to NRTI backbones were frequently observed in this cohort with 76 (44%) of the cohort undergoing at least one switch. This was predominantly in subjects commencing on a zidovudine containing regimen with 58 of 117 subjects (50%) switching in this group.

Factors Associated with Virological Response and Changes in Laboratory Parameters Over 48 Weeks

Factors associated with an undetectable plasma HIV RNA to less than 50 copies/mL at week 48 are shown on Table **3**. Although no parameter was statistically significantly associated with virological response, both baseline viral load and switching to once daily nevirapine in the first year of therapy had p-values below 0.10 in univariate and multivariate analyses.

No associations were observed between the NRTI backbones most frequently prescribed at baseline in this cohort and changes in CD4 lymphocyte count, total plasma cholesterol over 48 weeks or having an undetectable plasma HIV RNA at week 48. During the first year of therapy, seven subjects switched NRTI backbone, all from a zidovudine containing regimen. When excluding these subjects from this analysis, no significant associations were observed with the above parameters.

Furthermore, no significant association between changes in alanine aminotransferase (ALT) and switching to once daily nevirapine were observed at weeks 8, 24 or 48 (p-values above 0.20 all analyses).

DISCUSSION

In this study, high treatment success rates were observed in subjects receiving nevirapine containing CART regimens including once daily nevirapine regimens; overall total patient follow up represented 380-patient-years, and low rates of virological failure were observed (6.3%). Female subjects are often under-represented in studies assessing antiretroviral treatment responses and gender differences are often not addressed. Our data is of importance as 46% of our cohort were female, with no gender differences in treatment responses observed.

Although numbers were small, there was a trend towards improved outcomes (p=0.051, multivariate analysis) using once daily nevirapine containing regimens. This may be associated with the improved adherence and tolerability of once daily antiretroviral therapy compared to more frequent dosing schedules [2].

Several factors may explain the high treatment success rates observed with once daily nevirapine dosing in this cohort, compared to other studies [4]. Firstly all subjects were commenced on twice daily nevirapine as initial CART therapy, and then switched to once daily dosing. Prospective studies are needed to assess once daily nevirapine as initial antiretroviral therapy and two international randomised controlled trials are currently underway. Secondly, all subjects in our study had no documented NNRTI resistance at baseline, whereas baseline resistance data have not been presented for all subjects in other studies [5].

Low rates of success of once daily nevirapine in therapy naïve subjects has been associated with a high baseline viral load (above 100 000 copies/mL) [5]. This result was not repeated in our study where baseline characteristics, in terms of mean baseline viral load 4.98 log10 copies/mL (95 000 copies/mL), and nadir CD4+ lymphocyte count 170 cells/μL, were comparable. Furthermore, many different NRTI backbones have been assessed in our cohort, including 17 subjects (10%) who commenced therapy with the NRTI backbone tenofovir and lamivudine, with no sub-optimal virological response.

Studies have also reported increased rates of adverse events with the use of once daily nevirapine, both in treatment naïve subjects [6-8] and as a switch strategy [9]. In general, the increased rates of toxicity observed in these studies leads to questions regarding the pharmacokinetic-pharmacodynamic relationship between nevirapine plasma exposure and adverse events [10]. However, in the therapy naïve studies, these adverse events were predominantly observed in subjects of Thai ethnicity [6] and in many of these studies, nucleoside backbones associated with greater toxicity profiles such as didanosine + stavudine [7, 8] or tenofovir + didanosine [9] have been utilised. Our study differs by describing data on subjects switching to once daily nevi-

Table 3. Factors Associated with Changes in Laboratory Parameters Over 48 Weeks

Factors Associated with an Undetectable Plasma HIV Viral Load (< 50copies/mL) at 48 Weeks			
		p-Value	
	95% CI	Univariate	Multivariate
baseline CD4	-0.058 to 0.074	0.808	
nadir CD4	-0.058 to 0.107	0.560	
baseline VL	-0.006 to 0.131	0.074	0.085
gender	-0.11 to 0.12	0.864	
ethnicity	-0.13 to 0.12	0.956	
NRTI backbone	-	0.516	
switch in NRTI backbone during first year	-0.12 to 0.41	0.267	
switching to once daily nevirapine during first year	-0.329 to 0.001	0.051	0.051
Association Between Changes in Laboratory Parameters Over 48 Weeks and Baseline NRTI Backbone			
		All Cases	Excluding Cases Switching NRTI Backbone in First Year
change in CD4 count (cells/uL)		0.553 *	0.638 *
AZT + 3TC	-	ref	
TDF + 3TC or FTC	-45 to 72	0.643	
ABC + 3TC	-70 to 220	0.304	
HIV RNA < 50 copies/mL (%)		0.450 *	0.509 *
AZT + 3TC	-	ref	
TDF + 3TC or FTC	-0.21 to 0.51	0.232	
ABC + 3TC	-0.287 to 0.35	0.794	
change total cholesterol (mg/L)		0.602 *	0.580 *
AZT + 3TC	-	ref	
TDF + 3TC or FTC	-0.62 to 0.38	0.639	
ABC + 3TC	-0.56 to 1.4	0.407	

* Overall p-value for group.

rapine in combination with nucleoside backbones containing either lamivudine or emtricitabine, the NRTI backbones recommended in current treatment guidelines [1]. Interestingly, no toxicity related treatment discontinuation was observed in our cohort in subjects switching to once daily nevirapine.

Frequently observed adverse events associated with nevirapine use include rash and hepatotoxicity. Safety analyses of nevirapine in different populations of HIV infected patients [11] with the recognition of a relationship between hepatotoxicity and CD4+ lymphocyte count lead to modification of nevirapine prescribing recommendations [12]. In our cohort, 4 (4%) male and 16 (20%) female subjects commenced nevirapine prior to the introduction of these recommendations (CD4+ lymphocyte count < 400 and <250, for male and female subjects, respectively), however no increased rates of toxicity were observed, probably due to small numbers.

Limitations of this study include the retrospective cohort nature of the data and no therapeutic drug monitoring performed to assess plasma exposure of once daily nevirapine in our cohort. Furthermore many subjects switched NRTI backbone during the study period, and although switching NRTI therapy from thymidine analogues is in keeping with current clinical practice, this is a un-controlled variable in our analysis. Whilst awaiting the results of prospective studies assessing once daily nevirapine, data from this study suggests that switching to once daily nevirapine containing regimens results in durable virological responses, is safe and well tolerated.

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REFERENCES

[1] Gazzard B, Bernard AJ, Boffito M, *et al*. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy. HIV Med 2006; 7(8): 487-503.

[2] Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med 2008; 31(3): 213-24.

[3] van Heeswijk RP, Veldkamp AI, Mulder JW, *et al*. The steady-state pharmacokinetics of nevirapine during once daily and twice daily dosing in HIV-1-infected individuals. AIDS 2000; 14(8): F77-82.

[4] Rey D, Schmitt M, Hoisey G, *et al*. editors. Early virologic non-response to once daily combination of lamivudine, tenofovir and nevirapine in antiretroviral naïve HIV-infected patients: preliminary results of the DAUFIN study. Fourteenth Conference on Retroviruses and Opportunistic Infections; Los Angeles February 2007.

[5] Towner W, Kerrigan HL, LaRiviere M, Eds. Efficacy of a once daily (QD) regimen of nevirapine (NVP), lamivudine (3TC) and tenofovir (TDF) in treatment-naive HIV infected patients: a pilot study. Seventh International Congress on Drug Therapy in HIV Infection; Glasgow, UK November, 2004.

[6] 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(9417): 1253-63.

[7] Garcia F, Knobel H, Sambeat MA, *et al*. Comparison of twice-daily stavudine plus once- or twice-daily didanosine and nevirapine in early stages of HIV infection: the scan study. AIDS 2000; 14(16): 2485-94.

[8] Raffi F, Reliquet V, Ferre V, *et al*. The VIRGO study: nevirapine, didanosine and stavudine combination therapy in antiretroviral-naive HIV-1-infected adults. Antivir Ther 2000; 5(4): 267-72.

[9] Negredo E, Molto J, Munoz-Moreno JA, *et al*. Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. Antivir Ther 2004; 9(3): 335-42.

[10] Kappelhoff BS, van Leth F, Robinson PA, *et al*. Are adverse events of nevirapine and efavirenz related to plasma concentrations? Antivir Ther 2005; 10(4): 489-98.

[11] Stern JO, Robinson PA, Love J, *et al*. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. J Acquir Immune Defic Syndr 2003; 34(1): S21-33.

[12] Boehringer-Ingelheim-Pharmaceuticals. http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Viramune/Viramune.pdf [Accessed on April 1, 2008].

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