Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2013 doi: 10.1111/jcpt.12120

Influence of adding etravirine on complexity index and patients' perceived complexity

E. Calvo-Cidoncha† PharmD, J. González-Bueno† PharmD, C.V. Almeida-González‡ MSc and R. Morillo-Verdugo* PharmD
**Pharmacy Department, Valme University Hospital, Seville, †Pharmacy Department, Virgen del Rocío Hospital, Seville and ‡Biostatistics and Investigation Department, Valme University Hospital, Seville, Spain*

Received 10 May 2013, Accepted 20 November 2013

Keywords: **etravirine, HIV, medication adherence, regimen complexity**

ABSTRACT

What is known and objective: **Adherence to highly active antiretroviral treatment (HAART) is an important predictive factor of treatment outcome. Medication regimen complexity can be one of the main causes of non-adherence. Thus, treatment simplification is a key strategy in the development of antiretroviral therapy. The aim of this study was to determine the influence of adding etravirine on complexity index and patients' perceived complexity of their treatment regimen.**

Methods: **We conducted a prospective two-centre observational study. Patients on etravirine-based therapy, for at least 6 months, who came personally to pharmacy departments for a drug refill from February to July 2012 were included. Data were collected for the current etravirine-based HAART and for the previous HAART without etravirine. The main variables were complexity index and patients' perceived complexity. We also evaluated the adherence during the 6 months before and after the introduction of etravirine into HAART. The complexity index was based on a score which takes into account the number of pills per day, the dosing schedule, the dosage form and any specific instructions linked to use of the drug. To evaluate the patients' perceived complexity of their current and previous HAART, patients were asked to assign a mark on a visual analogue scale ranging from 0 (minimum) to 10 (maximum). We assessed the differences in the variables collected between the current and previous antiretroviral therapy. Finally, we carried out a correlation analysis between the complexity index and the patients' perceived complexity.**

Results and discussion: **Eighty patients were included. The complexity index was significantly reduced after the addition of etravirine to HAART (P = 0·035). Perceived complexity was also reduced (P = 0·015). After the introduction of the drug, the proportion of adherent patients increased from 65% to 81·3% (P = 0·002). The correlation between the complexity index and the patients' perceived complexity was positive (r = 0·594). The correlation increased (r = 0·696) when the difference between the complexity index before and after the introduction of etravirine in HAART grew.**

What is new and conclusion: **The addition of etravirine to HAART results in a significant reduction in complexity index and patients' perceived complexity of their therapy. These changes were associated with better adherence to treatment.**

Correspondence: E. Calvo Cidoncha, Pharmacy Department, Valme University Hospital, Avenida de Bellavista S/N, 41014, Seville, Spain. Tel.: 0034955015465; fax: 0034955015461; e-mail: elena.calci@gmail.com

WHAT IS KNOWN AND OBJECTIVE

The natural history of the human immunodeficiency virus (HIV) has changed significantly since the appearance of highly active antiretroviral treatment (HAART) in 1996. Since then, the morbidity and mortality associated with the disease has drastically reduced and patients' quality of life has increased.[1]

Nowadays, HIV infection is considered a chronic illness. However, adherence to HAART is an important predictive factor in treatment outcome.[2,3] Adverse events related to therapy and drug–drug interactions are some of the main causes of non-adherence.[4,5]

Medication non-adherence has also been linked to medication regimen complexity.[6,7] However, medication count is not an adequate complexity measurement because it only addresses pill burden. Others factors such as dosing forms, dosing frequencies and special dosing instructions also contribute to complexity. Although complexity treatment is related to poor medication adherence, there is no objective and validated method to quantify antiretroviral regimen complexity, with the exception of the tool developed by Martin *et al.* in 2007.[8]

The relationship between adherence and treatment complexity, as well as their significant impact on virologic response and the selection of resistant strains, has revealed HAART simplification to be a key strategy in the development of antiretroviral therapy.[9–12] There are different strategies that reflect this new concept, such as the single-tablet regimen. In etravirine-based HAART, the recommended oral dose for adult patients is 200 mg of etravirine taken twice a day following a meal. Furthermore, it may be dispersed in water, thus simplifying treatment complexity.[13,14]

To date, no study has evaluated the effect of introducing etravirine in HIV therapy; therefore, the aim of this study was to determine the influence of adding etravirine on complexity index and patients' perceived complexity of their treatment regimen.

METHODS

We conducted a prospective two-centre observational study. Patients who had been on etravirine-based therapy for at least 6 months and came in person to pharmacy departments for a drug refill from February to July 2012 were included.

The data collected included age, gender, weeks on etravirine-based therapy and number of previous HAART schemes. Additionally, the following data related to the current etravirine-based HAART and previous etravirine-free HAART schemes were collected: HAART drugs and doses, complexity index, patients' perceived complexity of their treatment regimen, viral load (RNA copies/mL) and CD4+ T-cell count. A second objective was to

determine adherence before and after etravirine treatment, and the correlation between complexity index and patients' perceived complexity.

The complexity index was calculated using a web application[15] based on an adaptation of the score created by Martin *et al.*[8] This score takes into account the number of pills per day, the dosing schedule, the dosage form and any specific instructions related to drug use. This score has previously been validated[8,16] and is applicable to children and adults with HIV.

To evaluate the perceived complexity, patients on etravirine therapy who came to pharmacy departments for a drug refill were asked to assign a mark on a visual analogue scale (VAS) ranging from 0 (minimum) to 10 (maximum) according to their perceived complexity of their current HAART scheme and the previous one. The perceived complexity value was categorized as low (0–3), medium (4–6) or high (7–10) following the VAS used in studies of other diseases[17]. Although there are no methods described for assessing perceived complexity in HIV patients, we decided to use a VAS as it provides a simple technique for measuring subjective experience and it is more reliable in low-literacy populations.[18]

Medication adherence was assessed using electronic pharmacy refill records and was calculated based on the formula: [(pills dispensed/pills prescribed per day)/days between refills] × 100. The threshold for optimal adherence was set at 95% and above. Adherence was assessed during the 6 months before and after etravirine introduction to HAART.

Viral load and CD4+ T-cell counts were collected 1 month before and after the addition of etravirine to HAART. HIV viral load was considered undetectable when it was lower than 50 copies/mL.

The remaining data were collected through electronic outpatient medical records and by reviewing the medical history of each patient.

Quantitative variables are expressed as mean and standard deviation or as median and percentile P25 and P75 in the case of a skewed distribution. Qualitative variables are expressed as percentages (%).

To assess the differences in the variables collected between the current and previous antiretroviral therapy, we ran the following statistical analysis: when data were consistent with a normal distribution, a *t*-test for related samples was used to compare two means of quantitative variables. Otherwise, a nonparametric Wilcoxon test was performed. The confidence interval established to determine the differences between mean or median was 95%. The McNemar's test was applied to analyse the changes in dichotomous variables before and after adding etravirine to HAART.

Finally, we performed a correlation analysis between the complexity index and the patients' perceived complexity. To do this, we calculated the Pearson's correlation coefficient and applied the test of independence.

The same correlation analysis was also performed after establishing two subgroups displaying low (0–1) or high (1·25–5·25) differences between the complexity index before and after the introduction of etravirine to HAART. Data analysis was carried out using the statistical package SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Eighty patients were included in the study, 54 from a tertiary hospital and 26 from a secondary one. Demographics and baseline patient characteristics are outlined in Table 1. The median duration of the treatment was 94·9 ± 45 weeks. None of the patients had to change the etravirine-based therapy during the study period.

Table 1. Demographic and clinical characteristics of the study population

Characteristics	Frequency
Age (years)	47 ± 11·4
Sex: male/female (% male)	69/11 (86·3)
Race (Caucasian%)	100
Treatment duration of etravirine (weeks)	94·9 ± 45
Number of different previous HAART schemes	3·5 ± 2·3

Table 2 shows the pharmacotherapy characteristics of the two groups before and after adding etravirine to HAART. The number of doses per day was reduced after the introduction of etravirine to HAART (50% of the non-etravirine group versus 71·3% of the etravirine group). The antiretroviral regimen based on two active drugs was the most frequent (63·7%) in contrast to those with three or four drugs. Considering the antiretroviral drug classes, the most common regimens were those including a combination of a non-nucleoside and a nucleoside reverse transcriptase inhibitor. The most prescribed regimen consisted of abacavir + lamivudine/etravirine (35%) and emtricitabine + tenofovir/etravirine (25%).

Based on the complexity index, the median value before and after the addition of etravirine to HAART was 4·8 and 4·5, respectively. The median difference between the current and the previous index was 0·5 (95% CI: 0·0005–0·75, $P = 0·035$).

Furthermore, there were also statistically significant differences between the previous and current values for perceived complexity, with median values of 2·5 and 2·0 respectively, and a median difference of −1·0 (95% CI: −1·625–0·0005, $P = 0·015$). From a qualitative point of view, the number of patients who perceived a low complexity increased from 52·5% to 68·8% after the inclusion of etravirine ($P = 0·022$).

The 75th percentiles for the viral load values were 115·0 RNA copies/mL before taking etravirine versus 22·8 RNA copies/mL

Table 2. Pharmacotherapy characteristics of the study population

	HAART without etravirine	Etravirine-based HAART	*P*
Number of doses per day *n* (%)			
1	40 (50)	57 (71·3)	0·002
2	40 (50)	23 (28·7)	
Number of agents active against HIV *n* (%)			
1	17 (21,3)	0 (0)	0·048
2	24 (30)	51 (63·7)	
3	24 (30)	17 (21·3)	
4	15 (18·8)	12 (15)	
Combination of antiretroviral drugs * *n* (%)			
a	31 (38·8)	51 (63·8)	0·031
b	23 (28·8)	0 (0)	
c	26 (32·5)	29 (36·3)	

*a: Nucleoside reverse transcriptase inhibitor in combination with a non-nucleoside reverse transcriptase inhibitor.
b: Nucleoside reverse transcriptase inhibitor in combination with a protease inhibitor.
c: Others.

Table 3. Correlation between the complexity index and the patients' perceived complexity

	Pearson's correlation	R^2	P
The entire simple	0·594	0·353	0·0005
Subgroups			
High difference between the complexity index before and after the introduction of etravirine to HAART	0·696	0·485	0·0005
Low difference between the complexity index before and after the introduction of etravirine to HAART	0·397	0·157	0·009

after etravirine was introduced. The median differences between the previous and current viral load were statistically significant (P = 0·003). Qualitatively, the percentage of patients with an undetectable viral load increased from 56·3% to 73·8% after etravirine was introduced (P = 0·009).

The median number of CD4-positive lymphocytes was 480·0 cells/μL in patients without etravirine versus 538·5 cells/μL in those taking the drug. The median difference between the current and previous CD4-positive counts was 75·5 (95% CI: 36 to 119, P = 0·0005).

After the introduction of etravirine to HAART, the number of adherent patients increased from 52 patients (65%) to 65 (81·3%), P = 0·002.

Table 3 shows a positive correlation between the complexity index and the patients' perceived complexity. The correlation increased as the difference between the complexity index before and after the introduction of etravirine to HAART grew.

DISCUSSION

Our study shows that the addition of etravirine to HAART leads to a significant reduction in the complexity index and patients' perceived complexity of their treatment regimen, as well as better adherence to treatment.

Despite the complexity of HAART regimens for patients with HIV disease, little is known about its impact on treatment adherence. Stone *et al.*[19] examined the complexity of antiretroviral regimens by assessing administration instructions and dosing frequency. Their results indicated that patients whose regimens included a more complex medication were more likely to become non-adherents. Similar conclusions can be drawn from the work of Paterson *et al.*[20], which reports a significantly greater adherence to twice-daily dosing versus three times daily. In contrast, regimen complexity was not a significant predictor of adherence in the study of Gao *et al.*[21] However, none of the previous studies have used a reliable and valid method to quantify the complexity of HAART in HIV patients. Most importantly, our study is the first one to confirm the potential of etravirine to simplify strategies leading to improvement in adherence. Our results show a stronger correlation between the complexity index and the patients' perceived complexity of their treatment regimen when the differences in the complexity of the previous and the current treatment are greater. Thus, the complexity index in daily practice may result in a greater response in patients with more complex treatments.

The main limitation is that the complexity index only incorporates antiretroviral medications. However, in addition to antiretroviral regimens, HIV-infected patients often take prophylactic therapy for opportunistic infections or other concomitant drugs to counteract the adverse effects induced by HAART. Non-antiretroviral treatment can add significant complexity to the antiretroviral regimen depending on the specific instructions for taking it. Thus, the complexity conferred by concomitant drugs is not considered in the complexity index analysed in this study. Another limitation of this study is the use of pharmacy refill records for measuring HAART adherence, because indirect methods could lead to an overestimation. To overcome this possible bias, patients were considered adherents when their drug intake was higher than 95%. Nevertheless, according to current literature[22], a 90% threshold would be enough to achieve desirable outcomes. This limitation could have been resolved with the utilization of a second method to assess adherence. Finally, the VAS related to previous HAART treatment was completed at least 6 months after patients had finished the treatment, so perceived complexity may not be exact.

One important area for future research is the development and validation of a complexity index that incorporates not only antiretroviral medication, but also the most frequent drugs used in HIV-infected patients, such as antifungal and antibacterial medications.

Although the assessment of viral load and CD4+ T-cell count after 1 month of etravirine treatment is too early to evaluate the effect of the new drug, the data obtained are promising. Therefore, another issue for future work could be to assess the efficacy of the treatment for a longer period.

Failure of HAART therapy is considered a risk factor for increasing viral load, disease progression and death.[23–25] For this reason, the antiretroviral regimen complexity index should be used in daily practice in order to provide drug therapy management.[26] This tool will allow us to identify patients who need more care from healthcare professionals.

WHAT IS NEW AND CONCLUSION

Adding etravirine to antiretroviral therapy reduces patients' perceived complexity of their treatment regimen and the complexity index value. Simplification of antiretroviral regimens increases medication adherence. The regimen complexity calculation may be useful in daily practice for identifying patients at a higher risk of becoming non-adherents.

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