Attainment of Higher Efavirenz Plasma Levels Allow to Regain Complete Virus Suppression in Patients Carrying NNRTI Resistance mutations.

González de Requena D, Gallego O*, Briones C*, Jiménez-Nácher I, and Soriano V*.
Service of Pharmacy and *Infectious Diseases. Instituto de Salud Carlos III

BACKGROUND

- Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) exert a potent activity against HIV-1, although the development of single mutations at critical sites within the reverse transcriptase gene can reduce or even annul their activity. In this regard, the genetic barrier for efavirenz (EFZ) seem to be greater than for nevirapine (NVP).
- It is general believe that cross-resistance between the current available NNRTIs is quite prominent and does not allow their use sequentially.
- Response to EFZ-based regimens has been linked to the attainment of plasma drug concentrations above 1μg/ml.

OBJECTIVES

In this study we have examined whether the response to EFZ could be preserved in patients experiencing an early virological failure under NVP-containing regimens, and the influence of EFZ plasma levels in response.

METHODS

- 40 patients who showed their first confirmed detectable plasma viral load (VL) > 50 HIV-RNA cop/ml after being undetectable for at least 3 months under a NVP-triple combination (400 mg/24h) were selected.
- All were compliant with its medication.
- NVP was replaced by EFZ keeping the same two-nucleoside backbone.
- Genotyping and NVP plasma concentrations at the time of failure were examined.
- EFZ plasma concentrations and virological outcome 3 months after the rescue intervention were performed

RESULTS

Characteristics at the time of NVP first virological failure

	Median (range)
• Time on NVP (months)	7.4 (3-15)
• CD4+ count (cells/μl)	471(180-1073)
• Viral load (HIV-RNA copies/ml)	4313 (72-45148)

Genotipic analisys at the time of viral rebound

25 of 31(80%) subjects for whom genetic material could be amplified and sequenced harboured one or more mutations linked to NNRTI resistance (codons 103, 181, or 190)

Virological outcome at 3 months

•Overall, 17/40 (43%) subjects regained undetectable VL or showed VL reductions > 1 log after replacing NVP by EFZ.

•5 of 6 (83.3%) subjects lacking NNRTI-resistant mutations reached undetectable VL with EFZ. In contrast, only 2 of 25 (8%) carrying mutant viruses achieved <50 HIV-RNA copies/ml (p<0.01)

Virologic response	Outcome at 3 months	
	N (%)	CD4+*
No response	23 (57.5)	- 44
> 1 log reduction	5 (12.5)	
Undetectable VL (< 50 cop/ml)	12 (30)	+ 54

*P <0.05

NVP plasma levels at the time of viral failure

Mean NVP trough concentrations at the time of viral rebound was 3,6 μg/ml [95% CI (2.6-4.1)

Patients lacking NNRTI resistance mutations had lower NVP plasma concentrations at the time of virological rebound (1.16 vs. 3.63; p=0.06)

EFZ plasma levels at 3 months

	C_{12h} (95%IC) (μg/ml)
TOTAL (n=37)	2.28 (1.6-2.9)
RESPONDERS	2.63 (1.4-3.8)*
NON RESPONDERS	1.99 (1.2-2.7)*

P=0.3

Resistance mutations, EFZ plasma levels and response to therapy

EFV RESISTANCE MUTATIONS WITH EXPERT ADVICE	Resistance (μg/ml[95% IC])	Non resistance (μg/ml[95% IC])	p
RESPONDERS	4.3 (0.4-8.2)	1.96 (0.33-3.5)	0.05
NON RESPONDERS	2.18 (0.88-3.47)	1.93 (0.8-3)	0.3

•Overall, 33% of subjects with EFZ plasma levels above 2 μg/ml showed virological response even in the presence of EFZ associated mutations (p=0.02)

CONCLUSIONS

More than 40% of subjects experiencing early virological failure with NVP can be rescued with EFZ.

The genotypic profile at the time of virus rebound can help to predict which patients may benefit from this intervention.

NVP plasma levels seems to play an important role in the development of NNRTI mutant strains.

Therapeutic drug monitoring of EFZ plasma concentrations may permit to adapt therapy and obtain response even in patients carrying NNRTI associated mutations maintaining EFZ levels above 2 μg/ml

e-mail: danifarre@hotmail.com.

Suggested references: - González de Requena, Nuñez M, Jimenez Nacher *et al*. Does an increase in Nevirapine Plasma Levels Allow to reach complete virological suppression in subjects with early virological failure? HIV Clinical Trials 2002 (*in press).* -González de Requena D, Núñez M, Jiménez-Nácher I *et al.* Liver toxicity caused by Nevirapine. AIDS 2002;16:290-291.-Nuñez M, González de Requena D, Jimenez-Nácher I, *et al.* Higher efavirenz plasma levels correlate with development of insomnia. JAIDS 2001;28:399.-.Marzolini C, Talenti A, Decosterd L, *et al.* Efavirenz plasma levels can predictc treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS 2001;15:71-5 .-Veldkamp A, Gerrit J, Lange J, *et al.* High exposure to nevirapine in plasma is associated with an improved virological response in HIV-1 infected individuals. AIDS 2001;15:1089-95.