Factors associated with early virological response to etravirine in NNRTI experienced HIV-infected patients

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645

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Abstract

Background: Etravirine (ETR, TMC125) is a next-generation NNRTI that demonstrated activity against NNRTI-resistant HIV-1 in the DUET-1 and 2 studies and has been recently approved in several countries. The aim of this study was to identify factors associated with virological response (VR) to ETR-containing regimens in NNRTI-experienced patients.

Methods: We analyzed 243 treatment-experienced patients receiving an ETR-containing regimen. VR was defined as a decrease of at least 1.5 log10 copies/ml and/or HIV-1 RNA < 50 copies/ml at month 2 (M2). Patients who had at least one genotypic resistance test before the introduction of ETR, including also historical genotypes, were included in the analysis. A mutation was considered as present if it was detected in at least one -previous genotype (patients had a median of 4 genotypes). The impact of baseline HIV-1 RNA, CD4 cell count, 57 NNRTI resistance mutations, Genotypic Sensitivity Score (GSS) for PI, and associated antiretrovirals on the VR to ETR regimen was also investigated.

Results: Among the 243 patients, median baseline HIV-1 RNA was 4.4 log10 copies/ml (IQR, 3.7 to 4.9) and median CD4 was 175 cells/mm3 (IQR, 69 to 312). Patients had been previously exposed to a median of 6, 1 and 5 NRTIs, NNRTI and PIs, respectively. Overall, 81.9% of patients achieved a VR. Patients used for the first time T20, DRV and RAL in combination with ETR in 10%, 49% and 61% of the cases, respectively. Factors associated with a better VR were the number of new drugs associated with ETR (p<0.0001) and the use of RAL, DRV or T20 for the first time in combination with ETR. Although the number of previous NNRTI received was not associated with VR to ETR, the previous use of NVP rather than EFV was associated with a poorer response (77% vs. 91%, p=0.03). There was no difference in VR between patients receiving an active PI and those receiving non active PI or no PI (85% vs. 80%). The following NNRTI mutations were associated with a decreased VR: Y181V, V179I, V106I, Y188L and E138A. The K103N mutation had no effect and was even associated with a better VR to ETR.

Conclusions: ETR showed a great potency in NNRTI experienced patients in combination with other active drugs that not necessarily include a boosted PI. The K103N mutation had no impact on the VR to ETR.

Objective

The aim of this study was to identify factors associated with virological response (VR) to etravirine (ETR)-containing regimens in NNRTI-experienced patients.

Patients and methods

Inclusion criteria: treatment-experienced patients with baseline HIV-1 RNA >100 copies/ml and receiving ETR in their antiretroviral treatment during at least 3 months.

Virological methods:
RT and protease resistance genotypic analysis were determined from baseline plasma samples.

Statistical methods:
Virological response (VR) was defined as a decrease of at least 1.5 $\log_{10}$ copies/ml and/or HIV-1 RNA < 50 copies/ml between month 2 and month 3.
Association between 57 NNRTI resistance mutations (list of 57 NNRTI mutations according to Vingerhoets et al. IHDRW 2008. abst. 24) and VR was studied using Fisher's exact test. All past genotypic resistance tests were taken into account: a mutation was considered as present if it was detected in baseline genotype or in at least one previous genotype (patients had a median of 4 genotypes, IQR (2-6)).
The impact of baseline HIV-1 RNA, CD4 cell count, past NNRTI used, Genotypic Sensitivity Score (GSS) for PI, and the number of new drugs associated with ETR for the first time on the VR to ETR regimen was also investigated.
Multivariate analysis (logistic model) was performed to search for independent predictive factors associated with VR to ETR.

Results

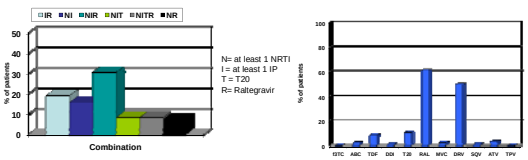
Baseline characteristics of patients

N =243 patients

- Male	82%
- Subtype B	89%
- HIV RNA (log copies/ml)*	4.4 (3.7-4.9)
- CD4 (cells/mm3)*	175 (69-312)
- Previous treatment:	
Antiretroviral drugs (n)*	13 (11-15)
NRTIs (n)*	6 (5-7)
PIs (n)*	5 (4-6)
NNRTIs (n)*	1 (1-2)
T20 (%)	60%
RAL (%)	12%

* Median (IQR)

ARV associated to ETR



Main type of ARV combination associated to ETR

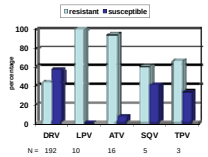
- Most frequent NRTIs: F/3TC= 63%, TDF = 49%, ABC = 21%
- Most frequent PI: DRV = 79%
- T20 = 23%, RAL = 73%

ARV used for the first time in combination with ETR

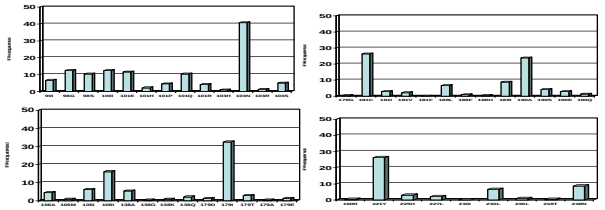
Results

Baseline genotypic characteristics

Susceptibility to PIs used in combination with ETR according to (www.hivfrenchresistance.org)



Prevalence of NNRTI mutations among the list of 57 NNRTI mutations* (Vingerhoets et al. IHDRW 2008. abst. 24)



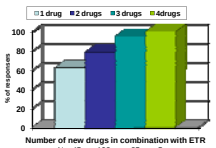
*Mutations among the list of 57 that were not detected in the population studied: 101N, 103T, 179F, 188C, 190C, 227C, 318F, 348I, 348T

Virological response to ETR at month 2-3

- **199/243 (81.9%) patients were responders**

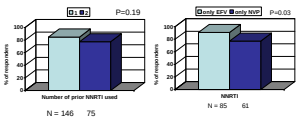
Factors associated to VR to ETR

Number of drugs received for the first time among DRV, RAL, T20 and Etravirine



Trend P<0.0001

Impact of prior use of NNRTI



Although the number of previous NNRTI received in the past was not associated with VR to ETR, among patients exposed to only one NNRTI, the previous use of NVP rather than EFV was associated with a poorer response (77% vs. 91%, p=0.03). In these patients who received only NVP or EFV before the use of ETR, the number of NNRTI mutations was not statistically different.

Mutations among the list of 57 NNRTI mutations associated with a negative (black) and a positive (red) impact on VR (the other mutations had no impact or were absent at baseline)

	Responders N (%)		
Position	Wild type	Mutation	p-value
Y181V	198/238 (83%)	1/5 (20%)	0.00415
K103N	110/144 (76%)	89/99 (90%)	0.00694
V179I	142/164 (87%)	57/79 (72%)	0.00784
V106I	190/228 (83%)	9/15 (60%)	0.03477
Y188L	189/228 (83%)	10/16 (63%)	0.04800
E138A	191/230 (83%)	8/13 (62%)	0.06415

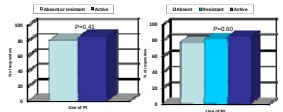
Patients harboring viruses with K103N mutation compared with patients not harboring the K103N mutation :
- had less NNRTI mutations (p=0.054)
- were more frequently exposed to EFV in the past (p=0.004)
- were less frequently exposed to NVP in the past (p=0.008)
- had no difference regarding the number of new drugs received

The best VR to ETR observed in patients with K103N mutation was not associated with the number of new drugs received in combination with ETR.

Although Y181C was not associated to VR, we compared patients harboring viruses with Y181C mutation with patients not harboring the Y181C mutation :
- had more NNRTI mutations (p<0.0001)
- were NOT more frequently exposed to EFV in the past
- were more frequently exposed to NVP in the past (p=0.001)
- received a lesser number of new drugs (p=0.05)

Factors not associated to VR to ETR

- Baseline HIV RNA
- Baseline CD4 cell count
- Use of boosted PI in associated treatment to ETR



There was no difference in VR between patients receiving an active PI and those receiving non active PI or no PI (85% vs. 80%)

- Among the 17 ETR RAMs defined by Vingerhoets et al. in the ETR weighted mutation score, Y181I and Y181V had the highest weight, followed by L100I, K101P, Y181C and M230L. In our analysis, although all these mutations were present in the dataset, only Y181V had a negative impact on VR to ETR.

Multivariate analysis

Four variables were retained in the final multivariate model. Of note the variable indicating past exposure to EFV only or past exposure to NVP only could not be included in the model due to monotonic likelihood

Variables	Odds Ratio	95%CI	P-value
Receiving 3 or 4 new drugs* vs. only ETR	7.79	2.5-34	<0.0001
Y181V	0.055	0.005-0.63	0.0013
K103N	2.30	1.03-5.1	0.04
E138A	0.24	0.06-0.9	0.027

* ETR is included in the 3 or 4 new drugs

Conclusions

In this population of NNRTI experienced patients, ETR showed a great potency. Factors associated with a better VR to ETR were the number of new drugs (among RAL, DRV or T20) associated for the first time in combination with ETR and the presence of K103N. The use of a boosted PI in the combined regimen to ETR was not associated to a better VR, suggesting that the key issue is the use of active drugs whatever the therapeutic class. Previous exposure to NVP rather than EFV was associated to a poorer VR. Mutations Y181V and E138A were independently associated to poor VR, whereas no effect on VR was observed with Y181C. The positive impact of K103N mutation on ETR VR should be further investigated, and especially the type of mutations associated to K103N that could explain an hypersensitivity to ETR, such as NRTI mutations.

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