Resistance Associated Mutations to Etravirine (TMC-125) in Antiretroviral Naive Patients infected with non-B HIV-1 subtypes

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Abstract

Background: Susceptibility to etravirine (ETR), a second generation non-nucleoside reverse transcriptase inhibitor (NNRTI), is dependent on the type and number of NNRTI resistance-associated mutations (RAMs). Studies have shown that some HIV-1 subtypes may have natural polymorphisms described as ETR RAMs. This study addresses the prevalence of ETR RAMs in treatment-naive patients infected with HIV-1 non-B subtypes and its potential impact on ETR susceptibility.

Methods: The prevalence of ETR RAMs was studied in 726 antiretroviral naive patients infected with non-B HIV-1 subtypes. ETR genotypic resistance was investigated according to ANRS and Stanford algorithms. NNRTI phenotypic susceptibility of samples with at least one ETR RAMs was measured. Phenotypic tests were done with a phenotypic assay (Antivirogram, Virco BVBA, Mechelen, Belgium). Fold changes (FC) in IC50 cut-off for normal susceptible range were 6.0, 3.3 and 3.2 for nevirapine, efavirenz and ETR, respectively.

Results: 75/726 (10.3%) of 726 sequences harbored Y181C and/or V179I in case of one ETR RAMs. This genetic profile is not considered to be resistant to ETR according to Stanford algorithm.

• Two samples with only one ETR RAM (mutations V179I and/or K101E) were not associated with increased ETR resistance.

The overall prevalence was 10% and this had a limited impact on ETR susceptibility.

Only 3 cases were associated with phenotypic resistance to ETR and in 2/3 cases this was in a context of Y181C transmitted drug resistance. Our results also show that V179I mutation could have an impact on ETR FC only in combination with some specific mutations such as E138A and that the concomitant presence of Y181C and H221Y, which is not considered as an ETR RAM, dramatically increases ETR FC suggesting that the role of H221Y, alone and in combination, on ETR resistance should be further investigated.

Conclusions

Phenotypic study

Characteristics of patients (n = 726)

Prevalence of ETR RAMs in non-B subtypes

Distribution of HIV-1 subtypes

Distribution of ETR RAMs in non-B subtypes

Phenotypic results were available for 20 clinical samples harboring at least one ETR RAM.

• Mutations V90I, A98G, K101E, V106I and E138A alone were not associated with increased ETR resistance.

• Two samples with only one ETR RAM (mutations V179I and/or K101E) were not associated with an increase (> 3.2-fold) in the ETR IC50.

This genetic profile is not considered to be resistant to ETR according to ANRS and Stanford algorithms.

• One sample with 2 ETR RAMs was associated with an increase (> 3.2-fold) in the ETR IC50.

This genetic profile is not considered to be resistant to ETR according to ANRS algorithm and intermediate resistant according to Stanford algorithm.

Patients and methods

**Patients:** HIV-1 seropositive individuals infected with non B subtype were eligible for this study if they had never been exposed to antiretroviral drugs before the time of sampling. Briefly, samples were collected at time of HIV diagnosis or before the start of antiretroviral treatment. In total, 726 patients were included from the following centers (no. of patients): CESAC, Centre d’Écoute, de Soins, d’Animation et de Conseils in Bamako, Mali (163); Nianankoro Fomba Hospital in Ségou, Mali (118); Pitié-Salpêtrière Hospital in Paris, France (192); Bichat Claude Bernard Hospital in Paris, France (192); and Saint-Antoine Hospital in Paris, France (71). For each patient a single HIV-1 sequence was used.

**Virological methods:** RT sequences were determined by bulk sequencing. We studied the prevalence of ETR RAMs according to the latest international AIDS Society (IAS)-USA panel list (www.inserm.fr, last update in December 2008) V90I, A98G, L100I, K101E, K101H, K103N, V106I, E138A, E138K, V179D, V179F, V179I, Y181C, Y181F, Y181V, G190A, G190S, and M230L. In case of presence of ETR RAMs, resistance genotypic tests were interpreted according to the last version of Agence Nationale de Recherches sur le SIDA (ANRS) (www.hivfranceResistance.org) and Stanford algorithms. (http://www.hivfranceResistance.org/barclay/stanfordLab/antivirogram/_showSequenceForm.jsp) .

Samples with at least one ETR RAMs were tested for phenotypic susceptibility to nevirapine (NVP), efavirenz (EFV) and ETR. Phenotypic tests were done with a commercial phenotypic assay (Antivirogram, Virco BVBA, Mechelen, Belgium). Fold changes (FC) in IC50 cut-off for normal susceptible range were 6.0, 3.3 and 3.2 for NVP, EFV and ETR, respectively. The definitions for resistance are those as defined by Virco: below these values samples were considered within normal susceptible range and above these values, samples were considered above normal susceptible range or resistant.