

Prevalence of etravirine (ETR; TMC125) resistance-associated mutations in a large panel of clinical isolates

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Abstract

Background

ETR is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with demonstrated activity against NNRTI-resistant HIV-1. Patients in the DUET trials whose viruses contained ≥ 3 TMC125 Resistance Associated Mutations (RAMs; V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S) at baseline had a response comparable to that of the overall placebo group. The likelihood of a response to ETR was estimated by determining the prevalence of each ETR RAM and the frequency of various combinations in a large number of samples received for routine clinical resistance testing (RCRT).

Methods

A total of 226,491 samples were submitted to Virco for RCRT from January 1999 to June 2007. Samples were defined as NNRTI-resistant if they carried at least one NNRTI IAS-USA mutation (September 2006) or if the predicted fold change in EC_{50} for any currently approved NNRTI was greater than the respective vircoTYPE (vT) biological cut-off (BCO).

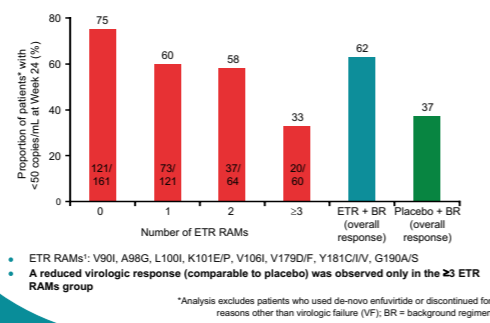
Results

89,113 and 95,019 samples, respectively, met the definition of having NNRTI resistance according to the IAS-USA mutation list or vT BCO. Forty percent of isolates with NNRTI resistance, defined by the IAS-USA list, contained no ETR RAMs, while 36.7%, 16% and 7.3% harbored 1, 2, and ≥ 3 ETR RAMS, respectively. In the same subset (n=89,113), the ETR RAMs occurring most frequently were Y181C (27.6%), G190A (21.1%), K101E (8.9%), L100I (7.6%), V90I (6.9%), A98G (6.4%), G190S (4.3%) and V106I (3.5%). The other five ETR RAMs had a prevalence of $< 3\%$. Among all NNRTI-resistant samples with two ETR RAMs (n=14,258) the most frequent combinations were: Y181C+G190A (27.1%), K101E+G190A (12.5%) and V90I+Y181C (7.0%). While the proportion of NNRTI-resistant samples with ETR RAMS declined over time (69.9% in the first semester in 1999 to 54% in the first semester in 2007) and the prevalence of some ETR RAMS changed (Y181C declined from 44.9 to 20.7%, V106I increased from 2.1 to 4.8%), the ratio between isolates with 1, 2, or ≥ 3 ETR RAMS remained relatively constant ($\sim 5:2:1$). Similar results were observed in samples with NNRTI resistance defined by the vT BCO (n=95,019).

Objectives

- To study the prevalence of each ETR Resistance Associated Mutation (RAM) and the frequency of various combinations in a large number of samples received for routine clinical resistance testing (RCRT)
- To study the prevalence of ETR RAMs over time

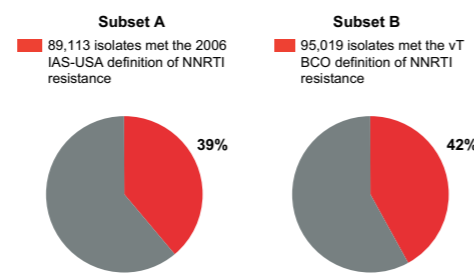
Response (< 50 copies/mL) at Week 24 in the DUET studies according to number of baseline ETR RAMs



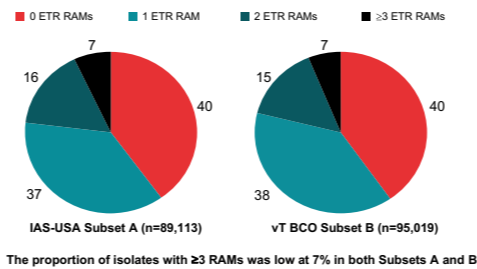
Methods

- 226,491 samples were submitted to Virco for RCRT from January 1999 to June 2007
 - samples from clinical trials (including DUET) were excluded
- Samples were defined as NNRTI resistant if
 - they carried at least one NNRTI IAS-USA mutation (IAS-USA September 2006) (Subset A)
 - the predicted fold-change in EC_{50} (FC) for any currently approved NNRTI (excluding ETR) was greater than the respective vircoTYPE HIV-1 (vT) biological cut-off (BCO) (Subset B)
- ETR RAMS¹
 - V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S
- The prevalence reported is in a broad patient population

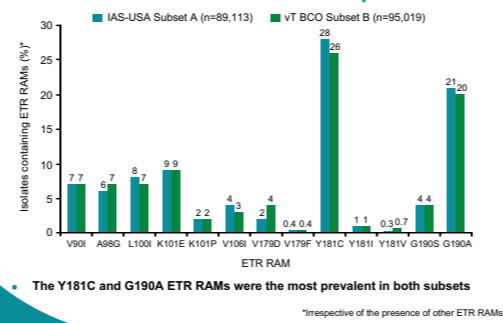
Results



Proportion of isolates with 0, 1, 2, or ≥ 3 ETR RAMs among two subsets of NNRTI-resistant samples



Percentage of isolates containing each ETR RAM* among two subsets of NNRTI-resistant RCRT samples



Most frequent combinations of ETR RAMs among NNRTI-resistant RCRT samples* with two or three ETR RAMs

Combinations of ETR RAMs	Frequency (%)
Two ETR RAMs (n=14,919)	
Y181C + G190A	27
K101E + G190A	13
V90I + Y181C	7
A98G + Y181C	7
K101E + G190S	4
Three ETR RAMs (n=5,370)	
K101E + Y181C + G190A	34
A98G + Y181C + G190A	12
K101E + Y181C + G190S	9
V90I + Y181C + G190A	7
V106I + Y181C + G190A	4

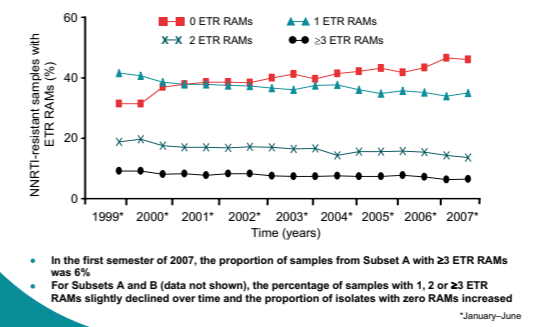
• For two ETR RAMs, the combination of Y181C and G190A occurred most frequently
• For three ETR RAMs, the combination of K101E, Y181C and G190A was most frequently observed
*NNRTI-resistant according to both defined criteria. Samples from patients in DUET were excluded

Most frequent combinations of two and three ETR RAMs and response (< 50 copies/mL) in pooled DUET* data

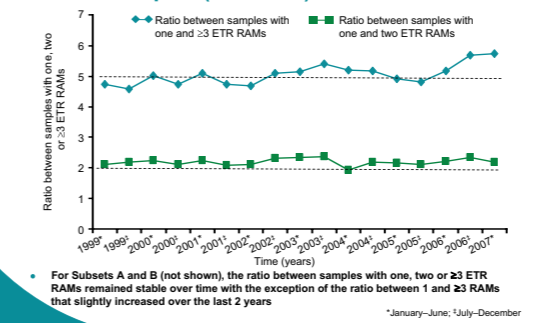
Combinations of two ETR RAMs (n=63)	Frequency (%)	Responders (< 50 copies/mL at Week 48) (%)
Y181C + G190A	46	59
K101E + G190A	8	80
Combinations of three ETR RAMs (n=36)		
K101E + Y181C + G190A	39	57
A98G + Y181C + G190A	11	0

• The same top two combinations of two and three ETR RAMs were observed in the routine clinical samples and patients enrolled in the ETR arm of the DUET studies
Overall placebo response = 41%
*Non-VF excluded population (n=401), excluding enfuvirtide de-novo patients. Remaining combinations occurred in $< 5\%$ of patients

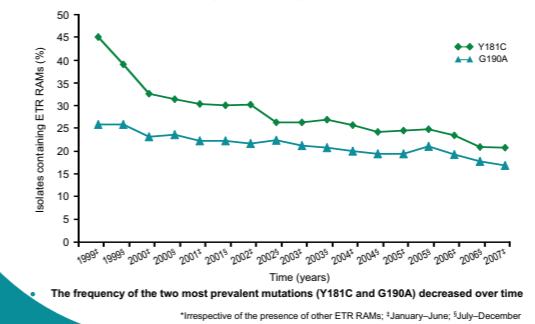
Percentage of samples with 0, 1, 2, ≥ 3 or ETR RAMs among NNRTI-resistant RCRT samples (Subset A) over time



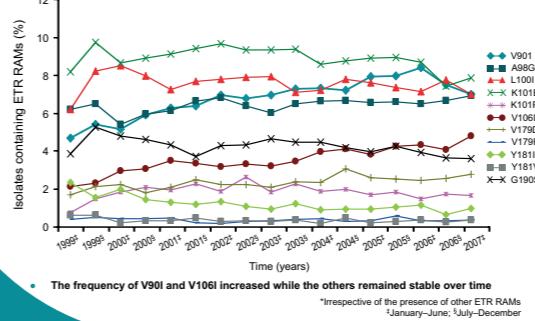
Ratio between isolates with 1, 2, or ≥ 3 ETR RAMs among NNRTI-resistant RCRT samples (Subset A) over time



Percentage of isolates containing the ETR RAMs* Y181C or G190A among NNRTI-resistant RCRT samples (Subset A) over time



Percentage of isolates containing other ETR RAMs* among NNRTI-resistant RCRT samples (Subset A) over time



Conclusions

- Among samples submitted for routine clinical resistance testing, a total of 39% and 42% of clinical isolates in Subset A and B, respectively, demonstrated NNRTI resistance
 - of the 89,113 (Subset A) and 95,019 (Subset B) clinical isolates with known NNRTI resistance submitted to Virco for routine clinical resistance testing, only 7% harbored ≥ 3 ETR RAMs
- The prevalence of NNRTI resistant samples with no ETR RAMs in both Subsets A and B increased over time
- Prevalence of the two most frequent ETR RAMs (Y181C and G190A) decreased over time in Subsets A and B
- The ETR RAMs associated with the highest impact on response in the DUET studies¹ (V179D, V179F, Y181V and G190S) exhibited some of the lowest prevalence rates among routine clinical resistance testing samples, ranging from 0.4% (V179F) to 4% (G190S), and were rarely observed among the top five combinations of two mutations
- The response rates in DUET patients harboring the two most frequent combinations of ETR RAMs was higher than the response observed in the overall placebo arm (59%, 80% vs 41%)
- These data suggest that the coexistence of ≥ 3 ETR RAMs, which is associated with a diminished virologic response to ETR, is infrequent even in patients with evidence of resistance to first-generation NNRTIs

Reference

- Vingerhoets J, et al. IHDRW 2007. Abstract 32.

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