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Keywords: antiviral, NNRTIs, diarylpyrimidine

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Sir,

Etravirine, formerly TMC-125, is a diarylpyrimidine with potential activity against HIV-1 resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs).1 The DUET 1 and 2 trials have evaluated the safety and efficacy of etravirine in treatment-experienced HIV-1-infected patients with documented genotypic evidence of NNRTI resistance. Etravirine (200 mg twice daily) showed significantly higher rates of virological response and increased CD4 counts over the placebo control group at 24 weeks. Moreover, the safety and tolerability of etravirine was generally comparable to placebo.2,3 Information on etravirine resistance is still scarce. Preliminary analyses from the DUET trials have identified 13 mutations associated with decreased virological response to etravirine: V90I, A98G, L100I, K101E, K101I, V106I, V179D, V179F, Y181F, Y181C, Y181I, Y181V, Y188L, G190A and G190S.4

We have examined retrospectively the prevalence of etravirine-associated resistance mutations in all HIV drug resistance tests performed since January 1999 until May 2007 for antiretroviral-experienced individuals with plasma HIV-RNA >1000 copies/mL in a reference HIV laboratory located in Madrid, Spain. Prior treatment history and drugs taken at the time of failure were recorded in a case report form for each sample. Only NNRTI-experienced patients were selected for this analysis.


References

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Prevalence of etravirine (TMC-125) resistance mutations in HIV-infected patients with prior experience of non-nucleoside reverse transcriptase inhibitors

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We have examined retrospectively the prevalence of etravirine-associated resistance mutations in all HIV drug resistance tests performed since January 1999 until May 2007 for antiretroviral-experienced individuals with plasma HIV-RNA >1000 copies/mL in a reference HIV laboratory located in Madrid, Spain. Prior treatment history and drugs taken at the time of failure were recorded in a case report form for each sample. Only NNRTI-experienced patients were selected for this analysis.

A total of 1470 genotypes corresponding to distinct NNRTI-experienced patients were recorded during the study period. Of them, 66.9% (n = 983) belonged to patients who had received efavirenz and 58.5% (n = 860) to subjects treated with nevirapine. Up to 25.4% (n = 373) had been exposed to both NNRTIs. The mean number of NNRTI resistance mutations was 1.08 ± 1.07 using the list recently reported by Tambuyzer et al.\(^5\) and 0.87 ± 0.9 using the last IAS-USA panel list.\(^6\) Overall, 38.3% (n = 563) of specimens did not harbour any NNRTI resistance mutation. The prevalence of each of the etravirine-associated resistance mutations is recorded in Figure 1. Overall, there was a low prevalence of etravirine-associated resistance mutations. The most prevalent mutations were Y181C and G190A, with a frequency of 17.5% and 15.3%, respectively. Changes K101P, V106I, Y181I, Y181V and G190S were the less frequently found, with a rate ≤2.5% in all instances. Mutations L100I, V179D and V179F were not found, and the last of these seems to have the most pronounced impact on etravirine susceptibility.\(^4\)

In the DUET trials, the presence of ≥3 etravirine-associated resistance mutations was required to substantially impair the virological efficacy of the drug. Among the 1470 genotypes examined in our study, only 4.6% (n = 68) had ≥3 etravirine-associated resistance mutations. In contrast, most patients (63.1%) did not harbour any etravirine-associated resistance change, 22.2% had only one, 10.1% had two, 4% had three and only 0.6% had four or more. Mutations V90I, A98G, K101E, Y181C and G190A were the most frequently recognized in the subset of this population with ≥2 NNRTI-associated resistance mutations, with a frequency of 18.9%, 17.1%, 39.2%, 68.7% and 67.3%, respectively.

The mean number of etravirine-associated resistance mutations was significantly higher in patients with prior exposure to nevirapine than efavirenz (0.66 ± 0.92 versus 0.43 ± 0.78; P < 0.001). Moreover, mutations Y181C, K101E and G190A were significantly more prevalent in nevirapine-than efavirenz-treated patients (23.7% versus 8.7%; P < 0.001; 8.1% versus 5.2%; P = 0.037; and 17.7% versus 12%; P = 0.003, respectively). The total number of NNRTI-associated resistance mutations (B = 0.59; 95% CI: 0.56–0.62) and prior nevirapine exposure (B = 0.103; 95% CI: 0.02–0.182) were independently associated with a higher number of etravirine-associated resistance mutations. Conversely, current failure on efavirenz was associated with a lower number of etravirine-associated resistance mutations (B = −0.22; 95% CI: −0.3 to −0.13).

Although mutations Y181C, K101E and G190A were more prevalent in patients who had failed nevirapine than efavirenz, mutation K103N, which is not associated with etravirine resistance, was more frequently found in patients who had failed efavirenz than nevirapine (54.3% versus 26.2%; P < 0.001). Therefore, the overall low prevalence of etravirine-associated resistance mutations seen in our study might be in part explained by the more frequent use of efavirenz than nevirapine in our population.

In summary, a low prevalence of etravirine-associated resistance mutations was observed in a large database of genotypic tests derived from NNRTI-experienced patients tested outside clinical trials. Therefore, the vast majority of NNRTI-experienced patients should benefit from etravirine rescue therapy, although our results suggest that patients who have failed efavirenz might be more prone to respond than those previously treated with nevirapine.

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### Transparency declarations

None to declare.

### References


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**Figure 1.** Prevalence of etravirine (TMC-125) resistance mutations in 1470 NNRTI-experienced HIV-infected patients.