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NATURAL VARIATION OF INTEGRASE SEQUENCES FROM SUBTYPE B AND CRF02-AG HIV-1 ANTIRETROVIRAL-NAÏVE PATIENTS AND POSSIBLE EFFECT ON SUSCEPTIBILITY TO INTEGRASE INHIBITORS

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BACKGROUND: HIV-1 integrase (IN) is an essential enzyme required for viral replication and has great potential as a novel target for anti-HIV drugs. Raltegravir and elvitegravir are integrase inhibitors that are highly active in patients harbouring resistant viruses to other antiretroviral classes. Few data are available concerning the efficacy of these inhibitors on HIV-1 non-B subtype strains such as CRF02-AG, which is mainly prevalent in West Africa and is of increasing prevalence in Europe. The aim of this study was to examine IN sequences from HIV-1 subtype B and CRF02-AG antiretroviral-naïve patients for the presence of naturally occurring polymorphisms, and to search for a possible effect on IN structure and sensitivity to IN inhibitors caused by variations between these subtypes.

METHODS: The entire IN gene from 72 HIV-1 subtype B and 66 subtype CRF02-AG antiretroviral-naïve patients was amplified and sequenced. Naturally occurring polymorphisms and protein structures from both subtypes were compared. The possible effect on IN structure and sensitivity to IN inhibitors caused by variations between subtypes B and CRF02-AG was addressed within the context of a three-dimensional model of the HIV-1 IN complex.

RESULTS: The analysis of IN amino acid sequences showed that 13 positions (K/R14, V/I31, L/I101, T/V112, T/A124, T/A125, G/N134, I/V135, K/T136, V/I201, T/S206, L/I234 and S/G283) differed between subtypes B and CRF02-AG. As observed in the three-dimensional model of the pre-integration complex, these differences may affect the functional property of IN. Moreover, most variations are co-localized in three clusters: C1 (Leu101, Thr112, Gly134, Ile135 and Lys136), C2 (Val31, Thr124 and

Thr125) and C3 (Val201 and Thr206). Several variations of amino acids in HIV-1 IN subtype CRF02-AG could have a putative effect on IN inhibitor sensitivity. In particular, the cluster formed by Thr125, Thr124 and Val31 contains at least one residue, Thr125, which variation has been involved in resistance to the naphthyridine carboxamide L870,810 IN inhibitor.

CONCLUSION: These results suggest that virological response to IN inhibitors, according to the subtype, needs to be carefully studied in clinical trials. The fact that most variations were found in clusters suggests that some of them could be linked together through compensatory mechanisms.

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