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TRACKING HIV-1 INTEGRASE POLYMORPHISMS FROM THE PRE-ANTIRETROVIRAL THERAPY ERA UP TO THE INTRODUCTION OF INTEGRASE INHIBITORS

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BACKGROUND: More than 40 HIV integrase (IN) gene mutations are associated with resistance to integrase inhibitors (INI). Identification of baseline mutations and defining IN polymorphisms in treatment-naïve patients will assist in understanding and/or predicting INI drug resistance pathways. Genetic and functional proximity of replication enzymes IN, reverse transcriptase (RT) and protease (PRO) may result in non-INI antiretroviral therapy (ART) leading to changes in the IN gene. To explore these issues we analysed the IN gene of subtype B virus obtained during the pre-ART and pre-INI eras.

METHODS: Baseline IN nucleotide and amino acid polymorphisms were analysed in 71 clinical specimens collected from patients during 1982–1985, before the introduction of ART. IN sequences were compared with those obtained from 127 diagnostic specimens, collected from ART-naïve patients, after the introduction of ART but before INI were available (2001–2003). Both nucleotide and amino acid variation was examined to evaluate evolutionary trends using MEGA 4.0.

RESULTS: The nucleotide polymorphism rates in pre-ART and pre-INI groups were 28% and 47% ($P < 0.05$), whereas amino acid polymorphism rates (288aa) were 22% and 47%, respectively ($P < 0.05$). Q148H/K/R and N155H were not detected in either group; however, we identified five other INI-resistance-associated mutations in pre-ART samples (V151I: 5.6%, M154I: 2.8%, K156N: 4.2%, T206S: 1.4% and S230N: 2.8%). In contrast, many more mutations were detected in pre-INI group (L74M/I: 3.2%, T97A: 0.8%, T112I: 6.3%, E138K: 1.6%, V151I: 0.8%, S153A: 0.8%, M154I: 9.4%, K156N: 3.1%, V165I: 0.8%, I203M: 4.7%, S230N: 9.4% and V249I: 0.8%). The V72I and V201I mutations were identified as common polymorphisms in both groups with their frequencies increasing over time (V72I pre-ART versus pre-INI: 52.1% and 78.0%; V201I pre-ART versus pre-INI: 16.9% and 37.8%). Phylogenetic analysis revealed significant genetic distance differences between the two groups, driven predominantly by synonymous mutations.

CONCLUSIONS: The HIV-1 IN gene is intrinsically polymorphic with some INI-resistance-associated mutations present in samples collected in the pre-ART era. Increasing levels of nucleotide and amino acid sequence polymorphisms over time may be due to the influence of ART. Further characterization of these observations is ongoing.

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