

NATURALLY OCURRING POLYMORPHISMS IN HIV-1 INTEGRASE: RELATIONSHIP TO HIV SUBTYPE, INTEGRASE INHIBITOR RESISTANCE AND IMMUNE SELECTION

Tschochner M¹, Chopra A¹, Maiden T¹, Ahmad I¹, Fordham A¹, Mallal S¹,
John M¹

¹Centre for Clinical Immunology and Biomedical Statistics, Royal Perth
Hospital and Murdoch University, Perth, Western Australia

Integrase inhibitors have emerged as an important new class of antiretroviral agents. A number of resistance associated mutations have been described based on pre-clinical testing. In order to determine whether viral subtype or HLA-specific immune selection may contribute to baseline integrase inhibitor resistance, we examined the prevalence of naturally occurring polymorphisms in the integrase sequences of 202 HIV-1 infected patients in the Western Australian HIV Cohort, all of whom were naïve to integrase inhibitors. We further examined these changes in relation to HIV subtype, co-variation patterns and established associations with HLA alleles.

Integrase sequences obtained by bulk sequencing and 4-digit HLA class I genotypes determined by sequence based typing were examined at a codon-specific level. The subtypes of all samples were assigned on the basis of the genome wide sequences using the NCBI genotyping tool.

The subtype distribution in the cohort revealed 74.8% were subtype B, 4% C, 4.5% CRF01, 0.5% CRF02, 0.5% CRF06 and 15.8% inter-subtype recombinants. Residues E92, T97, F121, and Y143 were absolutely conserved, however at other sites the prevalence of resistance-associated mutations was as follows: E138K (1.2%), G140S (2.3%), V151I (2.9%), M154I (2.4%), N155S (0.6%), E157Q (3.6%), G163R (3.0%), Y226D (0.6%), D232N (0.6%). Several residues (51, 61, 74, 125, 147, 148, 153, 183 and 230) had some degree of polymorphism but none that were drug resistance-associated changes. No sequences contained the resistance associated T125K. However, an alternative polymorphism T125A occurred in 35.5% of sequences and was dominated by non-B subtype sequences (3% of sequences with T125 were non-B subtypes versus 62.3% with A125). Notably, this polymorphism corresponds to HLA-B*5701/-B*5703 and -B*5801 driven escape within the known SW10 epitope.

In a population-based cohort, most integrase residues previously associated with integrase inhibitor resistance are highly conserved across and within HIV-1 subtypes, in keeping with being sites of significant functional, catalytic or structural importance. T125A appears to be subtype-specific as well as a result of immune selection in individuals expressing HLA-B*57/5801. Otherwise, the low prevalence of natural polymorphism is consistent with the lack of overlap between evident immune and drug targets in the integrase gene.