Effects of HIV-1 Immune Selection on Susceptability to Integrase Inhibitor Resistance

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Abstract

Objectives: Integrase inhibitors have emerged as an important new antiretroviral agent. We examined polymorphisms in integrase sequences from 342 antiretroviral-naïve individuals from the Western Australian and Swiss HIV Cohort Studies, to examine site-specific interactions between HIV-1 subtype, human leukocyte antigen (HLA)-associated immune selection and integrase inhibitor resistance.

Methods: Standard bulk sequencing and sequence based typing were used to generate integrase sequences and 4-digit HLA genotypes. Viral residues were examined with respect to published drug resistance mutations and a reference dataset of CD8 T-cell escape mutations. Elispot-assays were performed for functional analysis of predicted epitopes.

Results: In both predominantly subtype-B cohorts, twelve of 38 sites that mediate integrase inhibitor resistance were absolutely conserved including the primary resistance mutations. There were 18 codons with non-primary drug resistance associated substitutions at rates up to 58.8%. V72I and V201I, were the most common resistance mutations and isoleucine was associated for both with a significantly higher viral load than valine (p=0.025, mean delta log VL=0.21 at codon 72, p=0.00003, mean delta log VL=0.39 at codon 201). Five viral residues were potentially subject to dual drug and HLA associated immune selection in which both selective pressures either drove the same amino acid substitution (codons 72, 157, 163) or HLA alleles were associated with an alternative polymorphism that would alter the genetic barrier to resistance (125 and 193) (Tab.1).

Tab.1

human leukocyte antigen allele	epitope	epitope position in integrase	amino acid position in integrase	non-adapted	adapted	drug resistance associated mutation
A*0206	HLEGKVILV	67 - 75	72	V	I	I
B*5701, B*5703, B*5801	STTVKAACWW	123 - 132	125	T	A	K
A*3303	ELKKIIGQVR	157 - 166	157	E	Q	Q
A*3303	ELKKIIGQVR	157 - 166	163	G	E/A	A, E, Q, T, R
B*2705	KRKGGIGGY	186 - 194	193	G	E	R

The common polymorphism T125A increased the mutational barrier to the resistance mutation T125K and was both characteristic of non-subtype-B and associated with carriage of HLA-B*57/*5801.

Conclusions: In an antiretroviral-naïve population-based cohort, primary integrase inhibitor resistance mutations were not detected in keeping with these being sites of significant functional, catalytic or structural importance. Viral polymorphisms due to immune selection and/or associated with non-subtype-B and particular HLA alleles may alter the genetic barrier to some non-primary resistance associated mutations.