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LOSS OF RALTEGRAVIR SUSCEPTIBILITY IN TREATED PATIENTS IS CONFERRED BY MULTIPLE NON-OVERLAPPING GENETIC PATHWAYS

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BACKGROUND: The HIV-1 integrase mutations N155H, Q148R/H/K and Y143R/C reduce susceptibility to the integrase inhibitor raltegravir and have been identified in patients failing raltegravir-containing treatment regimens. Whether these primary resistance mutations occur individually or in combination is not fully understood and the susceptibility of viruses containing secondary mutations only has not been well-characterized. To address these important questions we have explored the susceptibility and replication capacity (RC) of viruses containing primary and/or secondary mutations by analyzing individual clones isolated from raltegravir treated patients.

METHODS: Raltegravir susceptibility was characterized using the PhenoSenseTM and GeneSeqTM HIV integrase assays. Samples included HIV-1 populations from patients enrolled in the BENCHMRK Phase III trials, molecularly cloned integrase sequences derived from 11 trial patients and a series of site-directed mutants (SDMs) containing the N155H, Q148R/H/K, E92Q and G140S/A mutations, separately or in combination.

RESULTS: In patients treated with raltegravir, mutation N155H was selected independently from mutations at position Q148. No virus population examined by clonal analysis harboured single variants containing mutations at both positions. Reduction in raltegravir susceptibility was associated with primary mutations and, in a small number of cases, secondary mutations alone. Clonal analysis revealed variants containing E92Q in combination with N155H but not with Q148 mutations. G140A/S was found in combination with Q148 mutations but not N155H. Individual variants containing E92Q in the absence of N155H were identified and displayed reduced raltegravir susceptibility. In general, secondary mutations enhanced resistance conferred by primary mutations. SDMs demonstrated that E92Q and N155H, in combination, reduced susceptibility to raltegravir much more than either mutation alone. Similar observations were found using SDMs containing combinations of G140A/S with Q148

mutations, except G140S and Q148K together, which interestingly, suppressed resistance conferred by Q148K alone. Both N155H and Q148 mutations reduced RC while the addition of secondary mutations improved or reduced RC depending on which primary mutation was present.

CONCLUSIONS: This is the first study that demonstrates the selection of distinct resistance pathways in raltegravirtreated patients using clonal analysis. Combinations of drug resistance mutations differentially affected raltegravir susceptibility and RC depending on the patterns of mutations that were selected.

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