POSTER 50

CHARACTERIZATION OF T69 INSERTION MUTANT IN HIV-1 SUBTYPE C WITH PARTIAL SUPPRESSION OF VIREMIA DURING NRTI THERAPY

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Background: Amino acid insertions at codon 69 (T69ins) of reverse transcriptase (RT) have been associated with phenotypic resistance to nucleoside RT inhibitors (NRTIs), reduced replication capacity, and uniformly poor response to NRTI therapy. T69ins generally consist of two or more amino acids and have to date been described in subtype B. Here we report T69ins in subtype C HIV-1, which maintained low HIV-RNA levels during NRTI therapy.

Methods: Records from HIV natural history protocols at the NIH Clinical Center were reviewed; CD4, HIV-1 RNA (bDNA) HIV-1 Genotypic (TRUGENE) and phenotypic (Phenosense) studies were analyzed.

Results: A 31 year old Caucasian man with HIV-1 infection of 15 years duration with a history of unprotected heterosexual sex in Europe, Africa, and United States. He had been treated with mono and dual NRTI regimens, and subsequently with protease inhibitor and non-nucleoside RT inhibitor-based therapy. On evaluation, he had persistent HIV-1 RNA (1338 copies/ml) on AZT+3TC+abacavir therapy,with stable CD4 cell counts (653 cells/µl). Genotyping (in duplicate) revealed HIV-1 subtype C with RT mutations:D67G, K70R, M184V, K219Q. In addition, a three nucleotide duplication was identified between positions 69 and 70 (5'ACT ACT AGA 3') resulting in a threonine insertion. Phenotyping revealed elevated IC50s for all regimen components (AZT:157-fold, 3TC:max, abacavir:9.4-fold), and a marked decrease in replication capacity (13%). The patient decided to interrupt ART; unexpectedly, viral RNA increased nearly 10-fold (11820 copies/mL) within three wks of discontinuation. Repeat genotyping revealed D67D/G, K70R M184M/V, K219K/Q; T69ins was not detected.HIV-1 RNA remained elevated (70,000 copies/ml) over 3 years off therapy; subsequent genotyping noted only K70R mutation.

Conclusions: To our knowledge, this is the first report of T69ins in subtype C. Partial suppression of T69ins by AZT+3TC+abacavir is unexpected and suggests NRTI may provide a residual benefit in treatment experienced subtype C-infected patients with this insertion, either by a residual antiviral activity or by selection of a poorly replicating virus.