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## SPECTRUM OF HIV-1 REVERSE TRANSCRIPTASE MUTATIONS SELECTED BY NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR TREATMENT IS GREATER THAN PREVIOUSLY REPORTED

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**BACKGROUND:** Mutations at 18 reverse transcriptase (RT) residues have been shown to reduce HIV-1 susceptibility to nucleoside reverse transcriptase inhibitors (NRTIs). However, many other RT mutations are typically found during sequencing of clinical HIV-1 isolates and the relationship of these other mutations to selective drug pressure is not known. We used a statistical approach to identify previously unreported RT mutations that might be selected by treatment with (NRTIs) and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs).

**METHODS:** We analysed HIV-1 subtype B RT sequences (determined by dideoxy sequencing and encompassing codons 1–240) from 1210 individuals with known antiretroviral treatment histories. To identify positions associated with drug therapy, we performed  $\chi^2$  tests of independence for an association between mutations and treatment. To investigate the relationship between the number of NRTIs and the prevalence of a mutation, we performed logistic regression in which the number of drugs was the independent variable and the presence or absence of mutation was the dependent variable. To correct for multiple hypothesis testing, we used the method of Benjamini and Hochberg with a false discovery rate of 0.01.

**RESULTS:** 267 sequences were from untreated individuals. 584 were from individuals receiving NRTIs (n=1–6) but no NNRTIs. 357 were from individuals receiving NRTIs and NNRTIs. 569 sequences were previously published; 641 were previously unpublished sequences done at Stanford University Hospital. Mutations at 26 positions were strongly associated with NRTI therapy, including known drug-resistance mutations

at 17 positions (41, 44, 62, 65, 67, 69, 70, 74, 75, 77, 116, 118, 151, 184, 210, 215, 219) and previously unreported mutations at nine positions (20, 39, 43, 203, 208, 218, 221, 223, 228). The drug-resistance mutation Y115F and mutations at the polymorphic positions 60, 64, 104, 122, 135, 196, 200, 207, 211 were associated with therapy before (but not after) correction for multiple comparisons. Of the nine previously unreported drug-associated mutations, all but the mutation at position 203 were positively correlated with the number of NRTIs received. Positions 20, 39, and 43 were polymorphic occurring in 4%, 4%, and 1% of untreated isolates; whereas positions 203, 208, 218, 221, 223, and 228 were non-polymorphic. The nine previously unreported mutations are likely to be compensatory because when they occurred (a total of 817 instances), they were almost invariably associated with known nucleoside resistance mutations (777/817, 95%). Fourteen NNRTI-resistance mutations were observed but no new associations between NNRTI therapy and other mutations were identified.

**CONCLUSION:** Besides the 18 known NRTI-resistance mutations, mutations at nine additional RT positions are strongly associated with NRTI therapy. These mutations appear to be accessory because they occur almost exclusively together with known drugresistance mutations.

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