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HIGH PREVALENCE OF THE K65R MUTATION IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED BATSWANA PATIENTS TREATED WITH DDI/D4T-BASED REGIMENS

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BACKGROUND: Although the K65R substitution can cause extensive cross-resistance among currently used NRTIs, this mutation has been observed relatively rarely among subtype B infected individuals who received antiviral drugs. Increases in the frequency of K65R in western countries are attributed to extensive tenofovir use in recent years. These observations led us to evaluate the incidence of K65R in Botswana patients who received ARV therapy in the context of both first and second line regimens provided by the National Antiretroviral Treatment Program.

METHODS: We analysed the reverse transcriptase (RT) genotypes of subtype C isolates from 23 Botswana individuals who experienced treatment failure, i.e. rising viral loads and diminishing CD4 counts, while on combination regimens that included didanosine (ddI) and stavudine (d4T). Ten of these individuals had initiated treatment with ddI/d4T-based regimens while 13 had started therapy with zidovudine (ZDV)/3TC/NVP or ZDV/3TC/EFV prior to switching to ddI and/or d4T containing regimens.

RESULTS: Seven of the 23 patients who failed ddI-based regimens possessed the K65R substitution after a median exposure to combination ddI/d4T of only eight months (range 4–18 months). Four of these patients developed K65R while still on ddI/d4T at the time of genotyping. Three of the seven patients developed only K65R, while four others also developed Q151M, F116Y, and S68G. The association of K65R/M184V was seen in two patients who had experienced both ddI/d4T and ZDV/3TC-based regimens. In contrast, 8 of 13 patients who received 3TC/ZDV as initial therapy mostly developed thymidine-associated mutations (TAMs) e.g. M41L, D67N, K70R, T215Y/F and 219E/Q, while 5 of

13 had no NRTI resistance. The presence of TAMs in patients who first experienced ZDV/3TC may explain the non-emergence of K65R while subsequently receiving ddI/d4T, due to presumed antagonism among these mutations.

CONCLUSIONS: In summary, the K65R substitution may emerge at a higher frequency in individuals infected with subtype C viruses who experienced treatment with ddI/d4T. In view of widespread ARV access in sub-Saharan countries, these findings establish a degree of concern in regard to the possibility that certain mutations, such as K65R, may emerge more rapidly in viruses of subtype C.

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