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## THE DRUG RESISTANCE PROFILE OF TENOFOVIR: A STORY OF RESISTANCE AND RESENSITIZATION

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**OBJECTIVES:** Most recently, the new nucleotidic reverse transcriptase (RT) inhibitor tenofovir was approved by the FDA. This drug promises to be active against viral isolates with resistance to other nucleoside reverse transcriptase inhibitor (NRTI). Since the number of patients with NRTI drug resistance is increasing, the drug resistance profile of tenofovir should be characterized in more detail.

**METHODS:** Viral genotype and phenotypic resistance to tenofovir were obtained from 330 samples, which were derived from HIV-1-infected patients being treated at more than 20 clinical and outpatient centres in Germany. Twenty-eight of these samples exhibited NRTI multidrug resistance (6× aminoacid insertions and 2× deletions between RT 67–70, 20× Q151M complex). Viral clones with drug resistance-associated mutations at codons 41, 44, 70, 118, 184, 210, and 215, which were obtained by site-directed mutagenesis in different combinations, were also evaluated for tenofovir resistance. Bioinformatic analysis, including mutual information profiles and decision tree building, were applied to the dataset.

**RESULTS:** All samples with insertions between RT 67–70 proved to be resistant against tenofovir with a mean resistance factor (RF) of 15.0 (10.0–19.3). The samples with the deletion had 1.7- and 6.3-fold reduced susceptibility, respectively. Of the samples with Q151M, 12 samples were susceptible with a mean RF of 2.0 (0.9–3.3), whereas eight samples derived from three different patients exhibited a mean RF of 13.2 (9.3–17.0). These samples were different for the presence of K65R: none of the susceptible samples contained K65R, whereas this mutation was present in all except one of the resistant

samples ( $P < 0.0001$ , Fisher's exact test). This was still true if only samples of different patients were considered ( $P < 0.03$ , Fisher's exact test). Additionally, replacing of K65R by wild-type in one sample resulted in resensitization. Viral clones containing mutations associated with resistance to zidovudine were resistant to tenofovir (single mutants: 41>215>70; double mutants: 41+215>70+215>41+70; triple mutants: 41+210+215>41+70+215). This effect was (at least in part) resensitized by the additional presence of M184V. Mutations 44 and 118 did not show an effect on tenofovir resistance. Bioinformatic analysis confirmed the central role of mutations K65R and L210W for the prediction of tenofovir resistance.

**CONCLUSION:** Tenofovir resistance is associated with insertions between RT 67–70 as well as K65R in the presence of Q151M. Zidovudine mutations – in particular 41 and 215 – confer cross-resistance to tenofovir, which can be in part resensitized by M184V. This supports the conclusion that the parallel administration of tenofovir and lamivudine may be of clinical benefit in zidovudine-experienced patients.

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