



## Analysis of Mutational Patterns Associated with Resistance to Tenofovir DF and Lopinavir/ritonavir

R. Boulmé<sup>1</sup>, O. Dugas<sup>2</sup>, P. Halfon<sup>3</sup>, R. Diaz<sup>4</sup> and J.C. Schmit<sup>1</sup>

1 CRP-Santé Luxembourg, Luxembourg, 2 Advanced Biological Laboratories, Paris, France, 3 Département de Virologie, Laboratoire Alphabio, Marseille, France and 4 Retrovirology Laboratory of the Federal University of São Paulo, SP, Brazil

**BACKGROUND OF STUDY** : In treatment-experienced HIV patients failing their regimen, new antiretroviral drugs are needed for continuous viral suppression. Two compounds became recently available: the protease inhibitor lopinavir boosted by ritonavir (LPV/r) is already commercialized in many countries and the nucleotide analogue reverse transcriptase inhibitor tenofovir disoproxil fumarate (tenofovir DF) (TDF) is in phase III trials.

**OBJECTIVE** : We report the prevalence of resistance-associated mutations and the deduced phenotypic resistance and cross resistance patterns for the two drugs from a routine clinical genotyping database. **DESIGN** : Reverse transcriptase (RT) and protease (PRO) sequences were analysed using the ViroScorer™, a previously described internet-based system ([www.ablnetworks.com](http://www.ablnetworks.com)). Resistance was estimated by the interpretation algorithm of the Centre Hospitalier de Luxembourg (CHL) which has been updated for TDF and LPV/r with mutations recently described by M. Miller for TDF (K65R, insertions at codon 69 (Ins69), T215Y/F and multiple thymidine associated mutations (TAM)), and V. Calvez / D. Kempf (mutation score for positions 10, 20, 24, 46, 53, 54, 63, 71, 82, 84 and 90) for LPV/r.

**RESULTS** : Three thousand one hundred forty (3140) sequences were available for the analysis: one thousand five hundred eighty-seven (1587) PRO and one-thousand five hundred fifty-three (1553) RT sequences, respectively. Multi-nucleoside resistance (MNR) RT genotypes (i.e. Q151M and associated mutations or Ins69) were observed in 2.4% of isolates. Forty-two (2.7%) RT sequences carried a Q151M mutation, sometimes without other MNR mutations. The prevalence of resistant or possible resistant viruses to RT inhibitors were estimated to be for zidovudine 13% for resistance and 31% for possible resistance, for lamivudine (24%;17%), for zalcitabine (9%;22%), for didanosine (10%;19%), for stavudine (5%;20%), and for abacavir (14%;4%), respectively. Prevalence of resistant or possible resistant viruses to PRO inhibitors were: for indinavir (IDV), 32% for resistance and 21% for possible resistance, for saquinavir (SQV) (18%;25%), for ritonavir (RTV) (31%;17%), for nelfinavir (NFV) (24%;31%), for amprenavir (APV) (25%;11%). Twelve percent (12%) of sequences were concomitantly resistant to IDV, SQV, RTV, NFV and APV. For LPV/r, we found 4% of sequences having a mutation score of 8 and more, and 11% with a score of 6-7 mutations. All lopinavir mutation scores  $\geq 8$  (4%) were also resistant to APV. For TDF, 1% were resistant (K65R mutation) and 11% were possible resistant (at least the mutation 215 with at least 3 or more TAM). No Ins69 was described.

**CONCLUSION** : Drug experienced patients could potentially benefit from TDF and LPV/r. An important number of isolates presenting a possible resistance to TDF were due to mutations T215Y/F and TAM which could be a limit for a broad use of this drug. Cross resistance from other drugs with LPV/r was limited possibly due to the high genetic barrier necessary for LPV/r resistance.

## Abstracts