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ORAL COMMUNICATION

Virology and pharmacology across the spectrum of HIV treatment

OC 19 The in vitro genetic barrier to resistance of lenacapavir is not affected by viral subtype or heavy treatment exposure

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ABSTRACT

Background: Lenacapavir (LEN) is a HIV-1 capsid inhibitor currently approved for the use in heavily-treatment experienced (HTE) people with HIV (PWH). Mutations associated with resistance to LEN were identified at positions 56, 66, 67, 70, 74, 105 and 107 of the p24 coding region. To further characterize the mechanisms of resistance to LEN, this in vitro study aimed to evaluate LEN susceptibility and genetic barrier in B and non-B subtypes derived from therapy naïve (TN) and HTE PWH.

Materials and Methods: Twenty-six NL4-3 based recombinant viruses harbouring clinically derived GAG-PR region were generated from plasma samples collected from TN (n=15) and HTE PWH enrolled in the Italian PRESTIGIO registry (n=11). LEN half maximal inhibiting concentration (IC50) was measured through a TZM-bl cell line-based assay and fold-change (FC) susceptibility values were calculated with respect to the IC50 value of the NL4-3 wild type strain. In vitro resistance selection (IVRS) experiments were performed by exposing MT-2 cells infected with recombinant viruses and the NL4-3 control to increasing concentrations of LEN. Cultures were stopped when viral breakthrough was observed at approximately 100X LEN IC50 (2.56 nM) or after 105 days from the start of IVRS experiments. Sanger sequencing of the p24 coding region was performed at each viral breakthrough to detect emerging mutations. Statistical analyses were performed with GraphPad Prism version 9.0.0.

Results: None of the viruses harboured known LEN resistance mutations. Baseline susceptibility to LEN

was comparable between HTE vs. TN (median FC 0.9 [IQR 0.3-1.6] vs. 1.6 [0.6-3.0], p=0.253, Mann-Whitney test) and between B (n=12) vs. non-B (n=14; 3 CRF02_AG, 3 F1, 1 each A1, C, D, G, CRF01_AE, CRF06_cpx, CRF40_BF, URF D/B) subtypes (median FC 0.7 [0.2-2.2] vs. 1.6 [0.7-2.5], p=0.141). By Kaplan-Meier survival analysis, the time to viral breakthrough was comparable among both B vs. non-B subtypes and HTE vs. TN PWH at approximately 10X (p=0.112 and p=0.551, respectively, log-rank test) and 100X LEN IC50 (p=0.226 and p=0.382, respectively). Known LEN resistance mutations emerged in 25/27 cultures including N74D (n=7), Q67H/R/K+N74D (n=6), Q67H/K+T107N/S (n=6), , N74D+T107N/D (n=3), Q67H+K70R+T107N (n=2), Q67H+K70R (n=2), and Q67H (n=1), while in two cases no emergent mutations were identified when the cultures were stopped after 105 days at 10x LEN IC50. In addition, the non-polymorphic aminoacid substitutions F169L (with Q67H+T107TN), V86M (with Q67H+K70R) and E213D (with Q67H+T107N) were detected in three distinct cases each. The patterns of emerging mutations were equally distributed among B and non-B subtypes.

Conclusions: In this study, the genetic barrier to resistance to LEN was not affected by viral subtype, previous failures to other ARV classes or long-time exposure to antiretroviral therapy. The frequent detection of emerging mutations in IVRS experiments indicates a low genetic barrier to resistance.