Islatravir and Ulonivirine Create a Combination With a High Barrier to Resistance In Vitro

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Background

Islatravir (ISL) is an investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI) in clinical development in combination with ulonivirine (ULO), a non-nucleoside reverse transcriptase inhibitor (NNRTI), for once-weekly oral treatment of HIV-1. Resistance selection studies were performed in vitro to assess the barrier and pathways for the emergence of resistance to the combination.

Methods

In vitro resistance selection was performed with ISL and ULO alone or in combination (ISL+ULO) at multiples of each compound's potency (IC50) against wild-type (WT) HIV-1. Selection was initiated with WT HIV-1 or a variant encoding reverse transcriptase (RT) M184I in 96-well plates. Wells were assessed for viral breakthrough (VBT) after 12 passages, and breakthrough viruses were genotyped in RT. Viral clones encoding emergent mutations were produced and phenotyped in MT4-GFP cells.

Results

VBT with ISL occurred up to 8X IC50 (WT) and 16X IC50 (M184I). With ULO, VBT occurred up to 16X IC50 (WT) and 8X IC50 (M184I). With ISL+ULO, there was no VBT above 1X IC50 with WT, and VBT occurred in 2/8 wells at 2X IC50 with M184I.

Emergent mutations with WT were primarily M184I (ISL) and V106A (ULO). With M184I virus, ULO selected E138K and M230I/L. With ISL+ULO, V108I/M184I (WT) and E138K/M184I (M184I virus) predominated.

ISL showed a 6.2-fold potency reduction against M184I but retained WT potency against ULO-associated variants. ULO retained WT potency against M184I but showed reduced potency against ULO-associated variants (e.g., V106A, E138K, M230I/L). Against the ISL+ULO-selected variants (V108I/M184I and E138K/M184I), both compounds showed only mild potency reductions.

Conclusions

ISL+ULO suppressed VBT more effectively than either agent alone and showed complementary resistance profiles, with expected activity against selected variants at clinical exposures. These data support continued clinical development of ISL+ULO as a once-weekly oral HIV-1 regimen.

Disclosure of interest:

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