Isla travir Selects for HIV-1 Variants in MT4-GFP Cells That Profoundly Reduce Replicative Capacity in Peripheral Blood Mononuclear Cells

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Background

Isla travir (ISL, MK-8591), a first-in-class Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI) With Multiple Mechanisms of Action

Activity Against A114S Variants Differentiates ISL (an NRTTI) From NRTIs

Figure 2A. Potency (IC50) of ISL and NRTIs Against RT Variants in PBMCs

- ISL displays similar or greater potency against A114S, M184V, and A114S/M184V compared to TDF, AZT, 3TC, and FTC against WT
- A114S has differential effects on susceptibility to the NRTIs
- A114S augmented resistance conferred by M184V

Figure 2B. Fold Change in IC50 From WT for ISL and NRTIs Against RT Variants in PBMCs

- Fold Change > Max
- In contrast to ISL, A114S maintained or increased susceptibility to the NRTIs
- A114S-containing viruses with reduced susceptibility to ISL have profound replicative capacity defects in PBMCs

Figure 3A. Potency (IC50) of ISL and TAMs Against Variants Encoding TAMs in MT4-GFP Cells (100% NHS)

- ISL remained comparable or more potent than the NRTIs against 4 TAMs
- Linear regression was performed during the phase with the largest increase in p24 for each virus to determine the R² value for each virus

Figure 3B. Fold Change in IC50 from WT for ISL and TAMs Against Variants Encoding TAMs in MT4-GFP Cells (100% NHS)

- A combination of 4 TAMs had a modest impact (+4-fold) on ISL potency
- A combination of 4 TAMs conferred +4-fold potency reductions to the tested NRTIs
- A114S mitigated resistance to TAMs caused by 4 TAMs but did not impact susceptibility to ISL

Figure 4A. Replicative Capacity of Viruses in MT4-GFP Cells

- All viruses replicated to some extent in MT4-GFP cells as monitored by GFP (data not shown) and p24

Figure 4B. Replicative Capacity of Viruses in PBMCs

- No replication was observed for A114S/M184V in PBMCs (R² = 1.08)
- M41L/A114S/M184V had decreased replicative capacity in PBMCs (~36% of WT)

Conclusions

- In resistance selection studies, M184I and M184V were the most common substitutions to emerge across multiple HIV subtypes
- With the exception of A114S, other substitutions observed during these studies had minimal effects on viral susceptibility alone or in combination with M184 substitutions
- A114S augmented resistance conferred by M184V but had minimal effect (2-fold) on its own
- Virus containing A114S in combination with M184V did not replicate in PBMCs
- The differential impact of A114S on ISL vs NRTIs is consistent with its distinct mechanism of action

References


Figure 1. Effect of Single-codon Substitutions on the Susceptibility of HIV-1 Subtype B to ISL in MT4-GFP Cells (100% NHS)

- M184I and M184V were the only single substitutions that conferred +2-fold shift in potency
- Only A114S (observed in 1 selection experiment at passage 38) in combination with M184V augmented resistance conferred by M184V by +2-fold
- A114S is exceedingly rare in clinical isolates
- 8 out of 139,609 people had A114S detected (Stanford HIV Drug Resistance Database)

Figure 2. Decreased Susceptibility of ISL and TAMs to Thymidine Analog Mutations (TAM)

- ISL remained comparable or more potent than the NRTIs against 4 TAMs
- Linear regression was performed during the phase with the largest increase in p24 for each virus to determine the R² value for each virus

Figure 3. Fold Change in IC50 from WT for ISL and TAMs Against Variants Encoding TAMs in MT4-GFP Cells (100% NHS)

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Figure 4. Replicative Capacity of Viruses in MT4-GFP Cells

- All viruses replicated to some extent in MT4-GFP cells as monitored by GFP (data not shown) and p24

Figure 5. Replicative Capacity of Viruses in PBMCs

- No replication was observed for A114S/M184V in PBMCs (R² = 1.08)
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Presented at HIV Drug Therapy, Glasgow 2020; October 5-8, 2020.

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