Islatravir selects for HIV-1 variants in MT4-GFP cells that profoundly reduce replicative capacity in peripheral blood mononuclear cells

Diamond, Tracy [1] ; Ngo, Winnie [1] ; Xu, Min [2] ; Goh, Shih Lin [2] ; Rodriguez, Silveria [2] ; Lai, Ming-Tain [1] ; Asante-Appiah, Ernest [1] ; Grobler, Jay [1]

[1]Merck & Co., Inc., Infectious Disease and Vaccines, Kenilworth, NJ, USA ; [2]Merck & Co., Inc., Quantitative Biosciences, Kenilworth, NJ, USA

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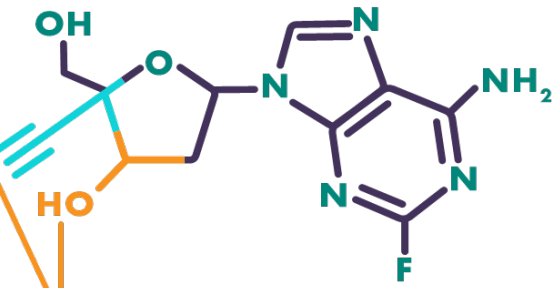
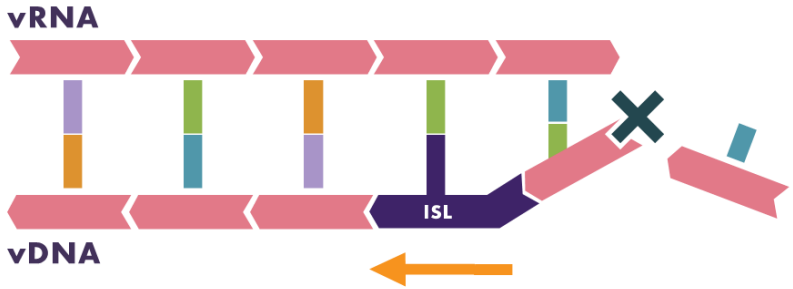
Islatravir (ISL, MK-8591), a First-in-Class Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI) with Multiple Mechanisms of Action



Translocation Inhibition
Due to the 4'-ethynyl Group

- Translocation inhibition prevents the opening of the nucleotide binding site
- Additional nucleotides cannot bind or be incorporated into the viral DNA
- Viral replication is inhibited

Delayed Chain Termination
Due to the 4'-ethynyl and 3'-hydroxyl Groups



- ISL incorporation changes the vDNA structure
- If translocation occurs and a nucleotide is added, the structural change prevents further nucleotide incorporation
- Viral replication is inhibited
- As such, ISL is not in the reverse transcriptase (RT) active site, and is no longer susceptible to resistance-conferring mutations

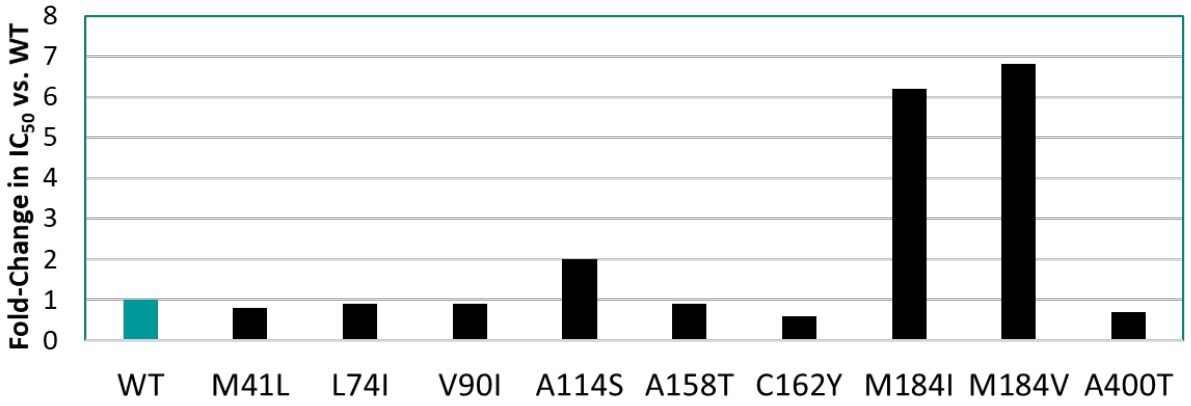
ISL is in clinical development for the treatment and prevention of HIV-1 infection.

M184V and M184I are a common resistance pathway in vitro across subtypes and combinations are required to further reduce potency

- Resistance was always associated with M184I or M184V across subtype A (92W026), B (R8), and C (93MW959) viruses

- Other substitutions were observed ≤2 of 48 selection experiments
  - Substitutions Observed in 2 experiments – V90I
  - Substitutions Observed in 1 experiment - E36K, E36D, M41L, L74I, V75A, A114S, A158T, C162Y, K166R, G196R, H221Y, A400T

- M184I and M184V were the only single substitutions that conferred >2-fold shift in potency

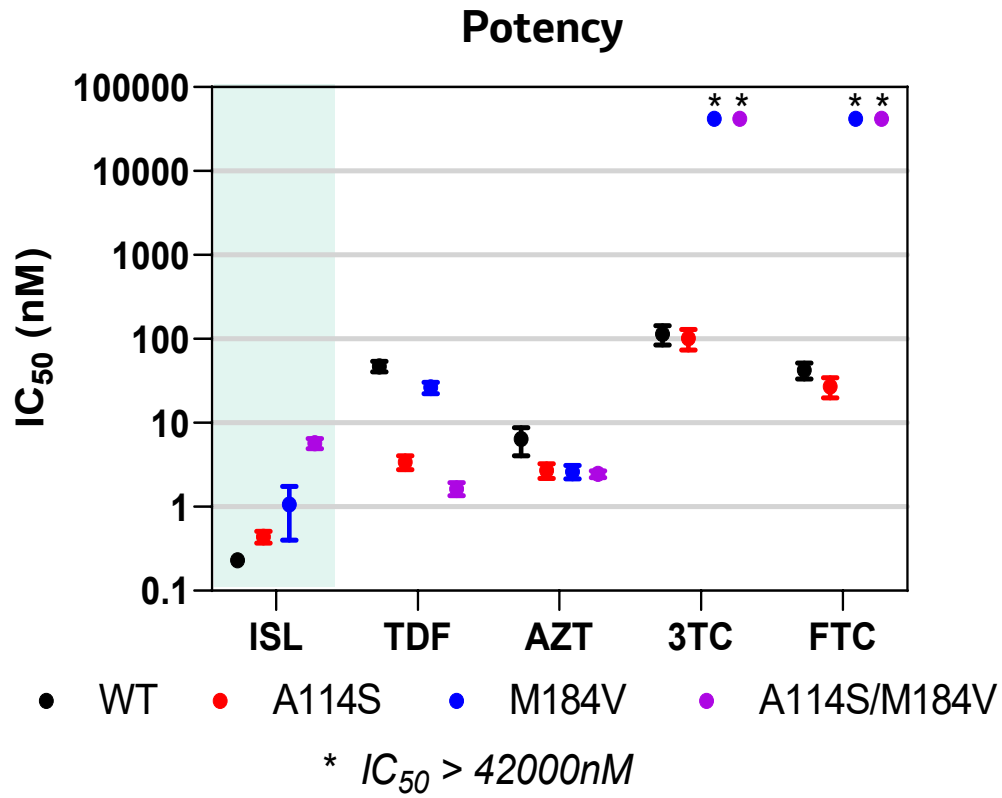


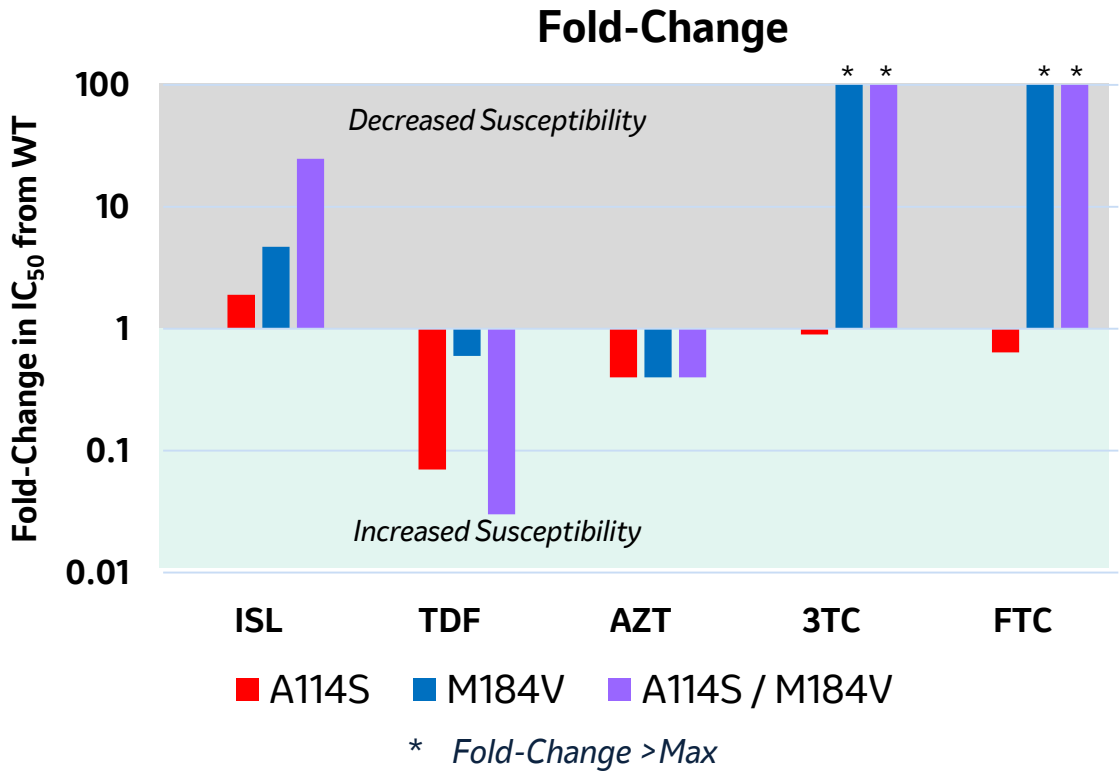
- Only A114S (observed in 1 of 48 selection experiments at passage 38) in combination with M184V augmented resistance conferred by M184V by >2-fold

- A114S is exceedingly rare in clinical isolates

  - 8 out of 139,609 people had A114S detected [Stanford HIV Drug Resistance Database (Rhee et al. 2003)]

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

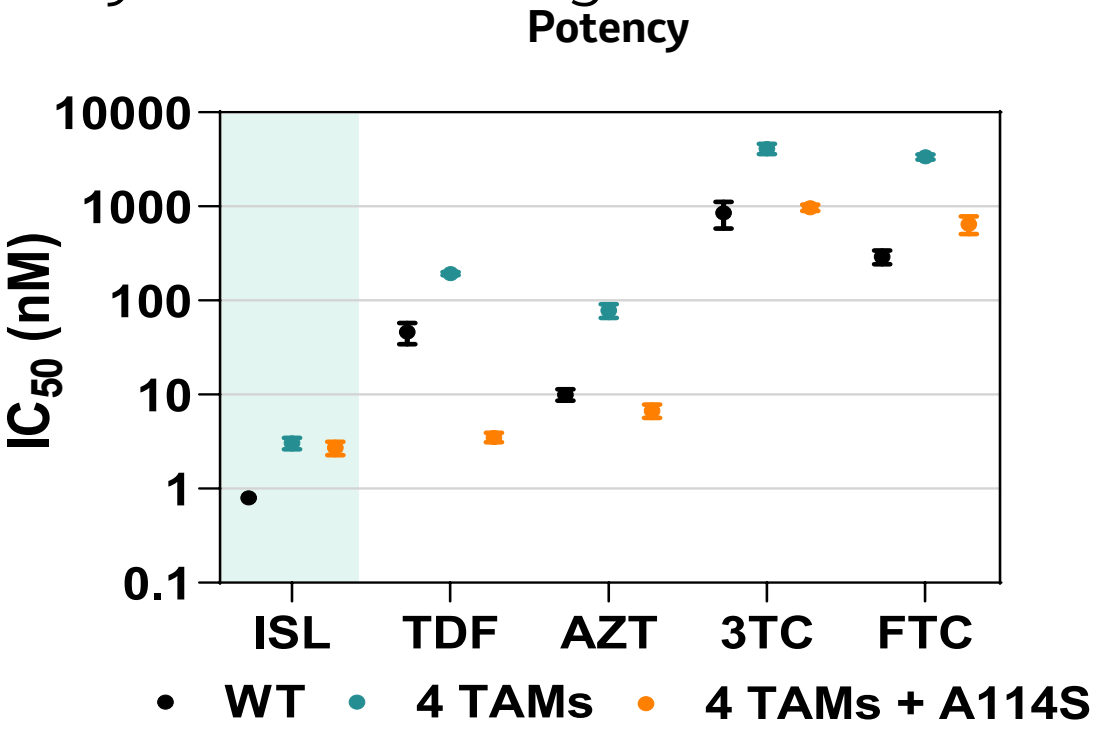


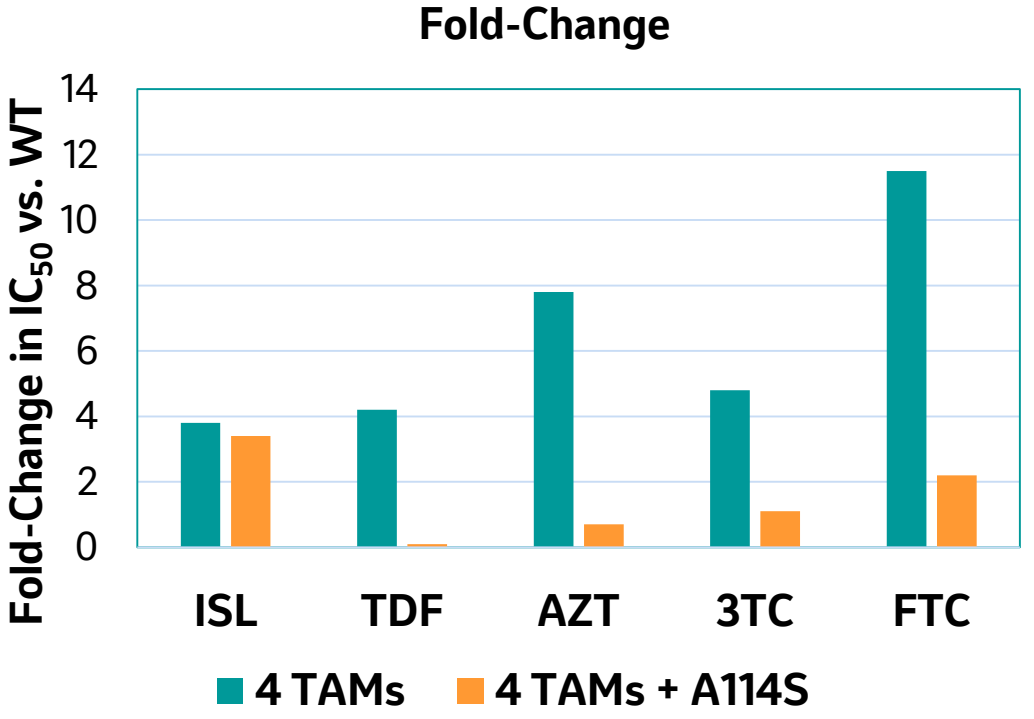


- ISL displayed similar or greater potency against A114S, M184V, and A114S/M184V compared to TDF, AZT, 3TC, and FTC against WT
- In contrast to ISL, A114S maintained or increased susceptibility to the NRTIs

Assay = PMBCs/10% Normal Human Serum; AZT = zidovudine; TDF = tenofovir disoproxil fumarate; 3TC = lamivudine; FTC = Emtricitabine

A114S has Differential Effects on Susceptibility of ISL and NRTIs to Thymidine Analog Mutations (TAMs)





- ISL remained comparable or more potent than the NRTIs against 4 TAMs

- 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 NRTIs caused by 4 TAMs but did not impact susceptibility to ISL

Assay = MT4-GFP Cells/10% NHS; 4 TAMs = D67N/K70R/T215F/K219Q

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
- A114S-containing viruses have profound replicative capacity defects
  - All viruses replicated to some extent in MT4-GFP cells as monitored by GFP
  - No replication was observed for A114S/M184V in PBMCs (Replicative Ratio = 1.08)
  - M41L/A114S/M184V had decreased replicative capacity in PBMCs (~36% of WT)
- The differential impact of A114S on ISL vs NRTIs is consistent with its distinct mechanism of action