A Comparison of Present and Future Integrase Inhibitors
Used in the Treatment of HIV-1

Student Presenter: Meredith Phelps
Project Advisor: Craig Woodard

Human immunodeficiency virus (HIV) compromises the body’s ability to fight disease and infection. Since the mid-1990s, treatments for HIV have been a cocktail of medications comprised mainly of a number of protease inhibitors\(^1\). This treatment was a breakthrough, but patients of this regiment developed resistance to the medications. Current drug therapies are HIV integrase (IN) inhibitors, which block the strand-transfer step in the multi-step process that allows the double stranded viral DNA to be irreversibly incorporated into the host DNA. Recent drugs, such as Raltegravir and Elvitegravir, showed great potential, but mutations in HIV integrase soon rendered these drugs ineffective\(^2\). The most recent integrase inhibitor, Dolutegravir, was approved to treat HIV-infected individuals who have developed tolerance towards previous integrase strand transfer inhibitor (INSTI) therapies. Current research is now aimed at trying to develop second-generation integrase inhibitors that have higher efficacy at targeting mutations of IN that confer resistance to current drug therapies.

In this literature review, the potency of Dolutegravir towards cells harboring Raltegravir-resistant IN mutants is compared with the latest synthesized drugs, 1-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxamide-containing HIV-1 IN inhibitors. Results showed that the newly synthesized drugs showed a greater efficacy in strand transfer (ST) inhibition in cells containing different IN mutants, specifically Y143R, N155H, and the double mutant, G140S/Q148H than Dolutegravir\(^3\). The new inhibitors also showed lower cytotoxic concentrations than Dolutegravir, which could mean that these second-generation IN inhibitors could have fewer side effects than current IN inhibitors. The new IN inhibitors, unlike current antiretroviral drugs, contain a hydroxlamide group that can function as a high affinity metal-chelating group, which could explain their increased potency towards ST inhibition\(^3\).