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ANALYSIS OF DOSE RESPONSE CURVES IN DRUG RESISTANT HIV

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Treatment with highly active antiretroviral therapy (HAART) has clearly reduced morbidity and mortality in the millions of people infected with HIV-1. However, the selection of drug resistant variants of the virus in patients on HAART is one of the barriers that prevent therapy from being effective. Previous pharmacological studies from our lab using a single round infectivity assay have shown that the dose response curves of different HIV drugs have slope values (m) that are characteristic of the class of drugs to which they belong. In this study, we examine, in addition to other pharmacological parameters such as IC_{50} , how this slope parameter is altered in viral clones that bear drug resistance mutations. Dose response curves were generated to characterize the behavior of virus bearing single mutations in reverse transcriptase, protease and integrase. Using measured slope values, IC_{50} measurements and fitness of virus, we calculated the instantaneous inhibitory potential (IIP) of individual drugs against resistant virus. From our analysis, in comparison to wild-type, NRTI mutants appear to have a generally decreased slope and increased IC_{50} ; PI mutants appear to maintain IC_{50} values similar to wild-type while showing a decreasing slope, and InSTI mutants appear to maintain slope while IC_{50} values increased. As expected, drug resistance mutations result in a reduced drug IIP. This analysis provides insight into selection pathways of drug resistant variants and sheds light on the mechanisms by which different classes of HIV drugs inhibit viral replication. Work on fusion inhibitors and NNRTI is ongoing.