

POSTER 35**MODELING THE DEVELOPMENT OF RESISTANCE TO ANTIRETROVIRAL DRUGS WITH LARGE GENETIC BARRIERS: TIMING THE FAILURE OF TIPRANA VIR**Pankhuri Arora¹ and Narendra M. Dixit^{1,2}¹Department of Chemical Engineering, and ²Bioinformatics Center, Indian Institute of Science, Bangalore, 560012, Karnataka, India

The recently approved inhibitors of HIV-1 protease (PIs), tipranavir and darunavir, offer large genetic barriers to resistance and exhibit antiviral activity against strains resistant to other PIs. The new PIs thus increase options for second-line therapy and present promising weapons to avert the failure of current antiretroviral therapies. Treatment strategies that maximize the impact of the new PIs, however, are yet to be established. A key limitation is the poor understanding of the process by which HIV surmounts large genetic barriers to resistance. We develop a mathematical model that describes HIV dynamics under the influence of a PI with a given genetic barrier and predicts the waiting time for the emergence of genomes that carry the requisite mutations to overcome the genetic barrier of the drug. We apply our model to describe the development of resistance to tipranavir in *in vitro* passage experiments. Remarkably, model predictions of the times of emergence of different mutant genomes with increasing resistance to tipranavir are in excellent agreement with experiments: Genomes carrying 2, 3, 5, and 6 resistance mutations were first observed experimentally in passages 16, 33, 39, and 49, respectively. The genome with 6 mutations exhibited >10 fold resistance to tipranavir. Our model predicts the emergence of these genomes in passages 14, 29, 44, and 49, respectively, indicating that our model captures the dynamics of the development of drug resistance during HIV infection accurately. Our model thus enables timing the failure of antiretroviral drugs. Further, model predictions provide insights into the roles of underlying evolutionary processes, such as recombination, in the development of resistance and suggest guidelines for drug design: Drugs that offer large genetic barriers to resistance with resistance sites tightly localized on the viral genome and exhibiting positive epistatic interactions maximally inhibit the emergence of resistant genomes. When the distinction between different viral genomes is ignored, our model reduces to the basic model of HIV dynamics, which captures viral load changes in patients accurately. Our model may thus be applied to describe the development of drug resistance *in vivo* and identify treatment strategies that impede the failure of current antiretroviral therapies.

Acknowledgement: This work was supported by the National Institutes of Health grant AI065334.