1107-92-225 **Alison L Hill*** (alhill@fas.harvard.edu), **Stefany Moreno-Gamez**, **Daniel IS Rosenbloom**, **Mark Freeman**, **Pleuni Pennings** and **Martin A Nowak**. *Viral evolution in heterogeneous host environments.* Preliminary report.

Antiviral therapies can dramatically reduce the mortality of viral infections, but they remain vulnerable to drug resistance. Here I will discuss how temporal and spatial heterogeneity in drug levels within infected individuals can promote the evolution of antiviral resistance. Firstly, I will show how models that incorporate time-varying drug efficacy, due to both pharmacokinetics and pharmacodynamics, can explain patterns of resistance and the effects of suboptimal patient adherence. During combination therapy, this variation can lead to times when only a single drug reaches a therapeutic concentration, and this "temporal monotherapy" promotes resistance. Secondly, I will discuss how periodic fluctuations in drug levels may lead to the evolution of "cryptic" resistance, whereby instead of directly avoiding a drug target, a virus may adapt to synchronize its lifecycle with the pattern of drug treatment. Thirdly, I will present results demonstrating how the evolution of multi-drug resistance can occur rapidly when individual drugs within a combination do not penetrate effectively into certain regions of the body. Even small areas of mismatched drug coverage can create situations of "spatial monotherapy" that allow mutations to accumulate in a stepwise fashion. (Received January 15, 2015)