A QSP Model of HIV to understand and predict virological failure from antiretroviral use

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Background: A remarkable proportion of HIV patients experience virological failure despite plasma drug concentrations being multiple times higher than the 90% efficacy threshold.

Objectives: Elaborate a mathematical model that can replicate the observed relationship between antiretroviral drug use and the proportion of patients experiencing virological failure; and better understand the pathogenesis of drug resistance in vivo.

Methods: The most up-to-date knowledge in immune physiology, antiretroviral pharmacology and viral kinetics was incorporated into a model that describes the processes linking drug use to treatment effect. In parallel, we obtained data from the literature which relates the patients' drug adherence level to virological failure. The model was used to run numerical experiments simulating the collection of this virological failure data.

Results: In silico results are consistent with clinical observations for treatment with efavirenz, efavirenz in association with tenofovir and emtricitabine, or boosted darunavir. In particular, the limited lymph node drug penetration can account for a large proportion of cases of virological failure and drug resistance for these drugs.

Conclusions: Our findings suggest that the main cause of virological failure can be attributed to insufficient drug exposure in one or more physiological compartments hosting a large number of CD4+ T-cells infections. It further suggests that a high drug concentration inside lymph node T-cells is desirable, although not observed for many current drugs. Since a limited amount of information is required by the model, it can be of use in the process of drug discovery and to guide clinical treatment strategies.