



EMERGENCE OF HIV-1 DRUG RESISTANCE DURING ANTIRETROVIRAL

Modeling a system with varying drug efficacy

BACKGROUND

- “There are currently four categories of antiretroviral drugs (ARV) including, “nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and entry/fusion inhibitors (EIs) (2028)”.
- All antiretroviral therapy’s (ART) use a combination of three or more drugs from two or more classes depending on the specific patient





MODEL I:

The pretreatment Model

THE MODEL- BACKGROUND

- In this model five state variables were used to model the interaction of the uninfected T-cells, the free virions of the drug-resistant and drug-sensitive strain, and cells infected by either the drug-sensitive strain and the drug-resistant strain. T represents the number of uninfected T cells. T_i is the concentration of cells productively infected by drug sensitive virus, T_r is the concentration of cells infected by drug-resistant virus, V_r/V_s are the concentration of drug resistant and the drug sensitive virus respectively(2031).



THE MODEL & THE PARAMETERS

Table 1: Parameter Definitions- See ARTICLE

Parameter	Value	Description
λ	$10^4 ml^{-1} day^{-1}$	Recruitment rate of the uninfected cells
d	$0.01 day^{-1}$	Death Rate of the uninfected cells
k_s	$2.4 * 10^{-8} ml^{-1} day^{-1}$	Infection rate of target cells by wild-type virus
k_r	$2.0 * 10^{-8} ml^{-1} day^{-1}$	Infection rate of target cells by drug-resistant virus
u	$3.0 * 10^{-5}$	Mutation rate into drug-resistant strain
δ	$1 day^{-1}$	Death rate of infected cells
N_s	3000	Burst size of drug-sensitive strain
N_r	2000	Burst size of drug-resistant strain
c	$23 day^{-1}$	Clearance rate of free virus.



THE MODEL- THE SYSTEM

Uninfected T cells $\frac{d}{dt}T(t) = \lambda - dT - k_s V_s T - k_r V_r T$

Infected T cells
Sensitive strain $\frac{d}{dt}T_s(t) = (1 - u)k_s V_s T - \delta T_s$

Sensitive Free
Virus $\frac{d}{dt}V_s(t) = N_s \delta T_s - c V_s$

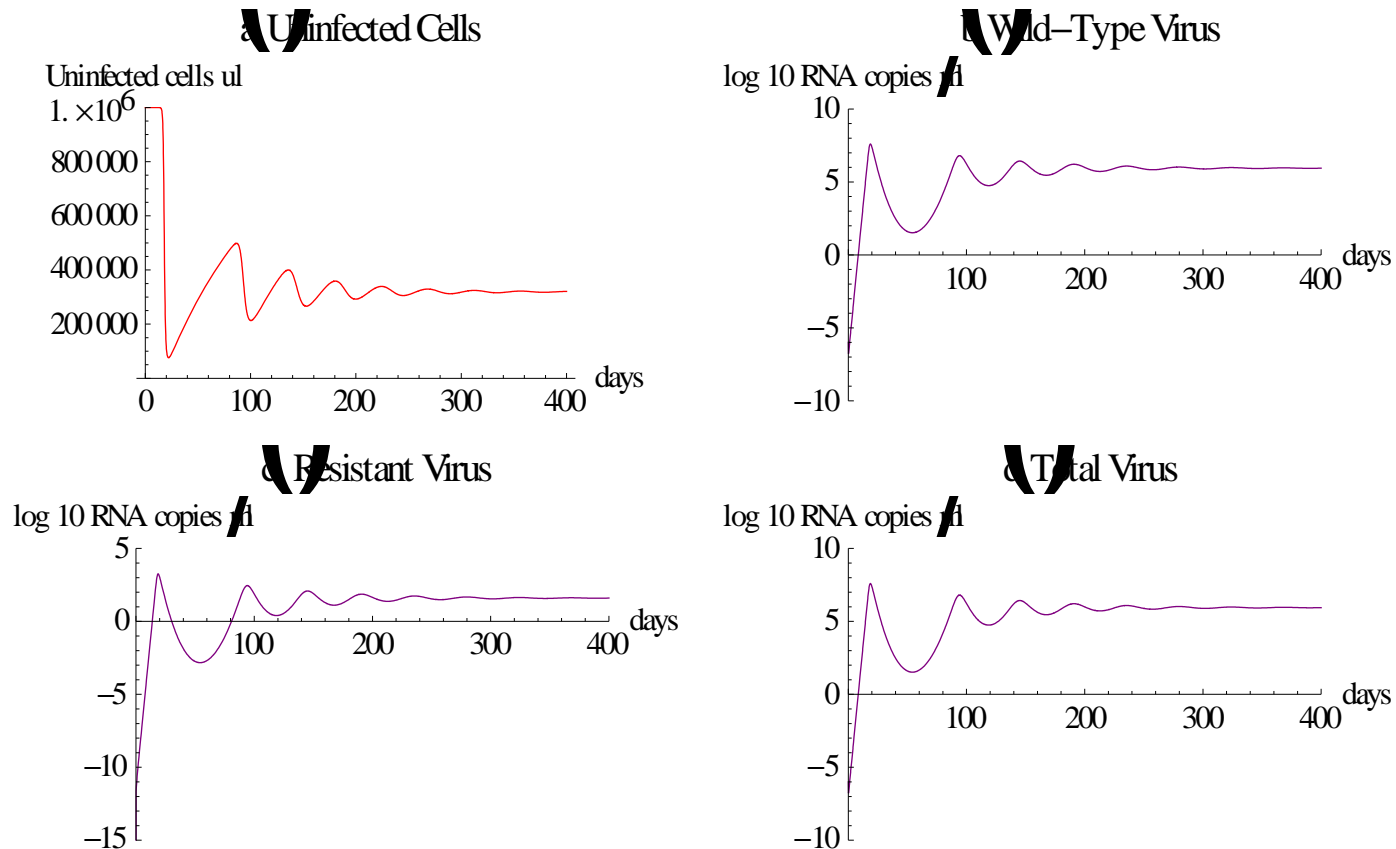
Infected T cells
Resistant Strain $\frac{d}{dt}T_r(t) = u k_s V_s T - k_r V_r T - \delta T_r$

Resistant Free
Virus $\frac{d}{dt}V_r(t) = N_r \delta T_r - c V_r$

- 5 state variables , solved using NDSolve in Mathematica



FIGURE 1: SIMULATION OF UNINFECTED T CELLS AND VIRAL LOADS OF BOTH WILD - TYPE AND DRUG - RESISTANT STRAIN FOR THE PRETREATMENT MODEL



Pretreatment Model



STEADY STATE- DIFFERENT TYPES

infection free steady state ($E = (T, T_s, V_s, T_r, V_r)$).

$$E_0 = \left(\frac{\lambda}{d}, 0, 0, 0, 0 \right)$$

$$T^*_{s} = \frac{[(1-u)\sigma - 1][(1-u)R_s - 1]\lambda}{(\sigma - 1)(1-u)R_s\delta} > 0$$

$$T^*_{r} = \frac{[(1-u)R_s - 1]\sigma u \lambda}{(\sigma - 1)(1-u)R_s\delta} > 0$$

$$E_r = \left(\frac{c}{k_r N_r}, 0, 0, \frac{(R_r - 1)dc}{k_r N_r \delta}, \frac{(R_r - 1)d}{k_r} \right)$$

$$E_c = \left(\frac{c}{(1-u)k_s N_s}, T^*_{s}, \frac{N_s \lambda}{c} T^*_{s}, T^*_{r}, \frac{N_r \lambda}{c} T^*_{r} \right)$$

The reproduction ratios for the 2 strains

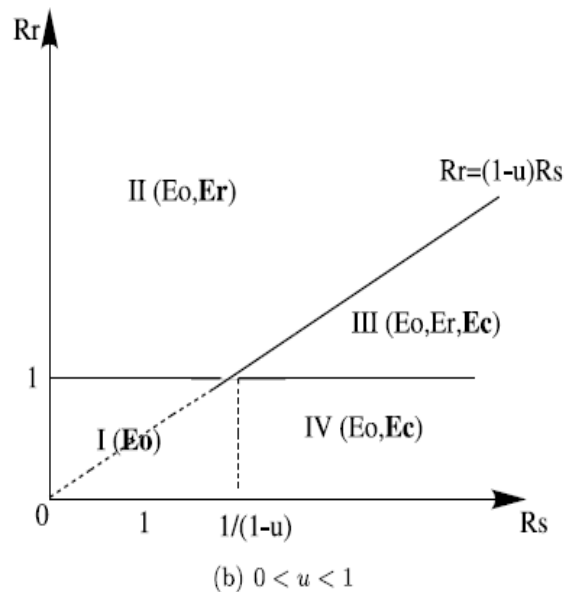
$$R_s = \frac{k_s N_s \lambda}{dc}$$

$$R_r = \frac{k_r N_r \lambda}{dc}$$



STABILITY AROUND EQUILIBRIUM POINTS

- Wanted to look at stability around equilibrium points (for each steady state)



Region	Steady State Type	Eigen Values	Stability
1	E_o	-23.9415, -23.8743, -.125658, -0.0584758, -0.01	Stable
2	E_o	-24.6886, -24.53, 0.688578, 0.529964, -0.01	Unstable
2	E_r	-24., -23.9038, -.0999629, -0.00317635 + 0.0214559 \square , -0.00317635-0.0214559 \square	Stable
3	E_c	-24., -23.4073, -0.592689, -0.00504257 + 0.00788028 \square , -0.00504257-0.00788028 \square	Stable
3	E_o	-25.092, -23.8743, 1.09198, -0.125658, -0.01	Unstable
3	E_r	-25.3776, -24., 1.37766, -0.00930277, -.000731919	Unstable
4	E_c	-24., -23.4073, -0.592689, -0.00504257 + 0.00788028 \square , -0.00504257-0.00788028 \square	Stable
4	E_r	-25.3776, -24., 1.37766, -0.00930277, -0.000731919	Unstable

Graph b from paper

The Eigenvalues that I calculated





MODEL II

Post treatment with RTIs and PIs

THE MODEL- THE SYSTEM

Uninfected T cells $\frac{d}{dt}T(t) = \lambda - dT - k_s(1 - \varepsilon^s_{RT})V_sT - k_r(\varepsilon^r_{RT})V_rT$

Infected T cells
Sensitive strain $\frac{d}{dt}T_s(t) = (1 - u)k_s(1 - \varepsilon^s_{RT})V_sT - \delta T_s$

Sensitive Free
Virus $\frac{d}{dt}V_s(t) = N_s(1 - \varepsilon^s_{PI})\delta T_s - cV_s$

Infected T cells
Resistant Strain $\frac{d}{dt}T_r(t) = uk_s(1 - \varepsilon^s_{RT})V_sT + k_r(1 - \varepsilon^r_{RT})V_rT - \delta T_r$

Resistant Free
Virus $\frac{d}{dt}V_r(t) = N_r(1 - \varepsilon^r_{PI})\delta T_r - cV_r$



Drug Efficacy is added

COMPARING DIFFERENT DRUG EFFICACY FOR THE SENSITIVE STRAIN

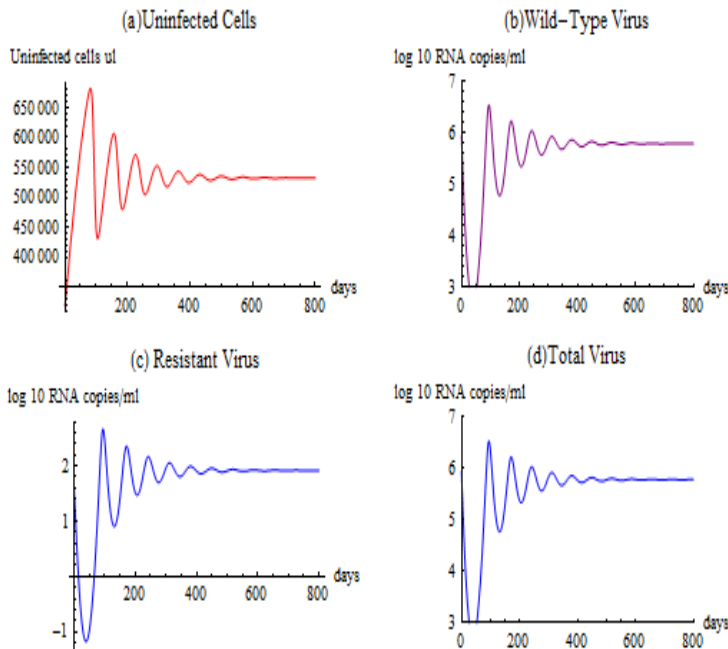


Figure 3 : Time evolution of uninfected T cells and both strains of virus of model $E_{srt}=.4$

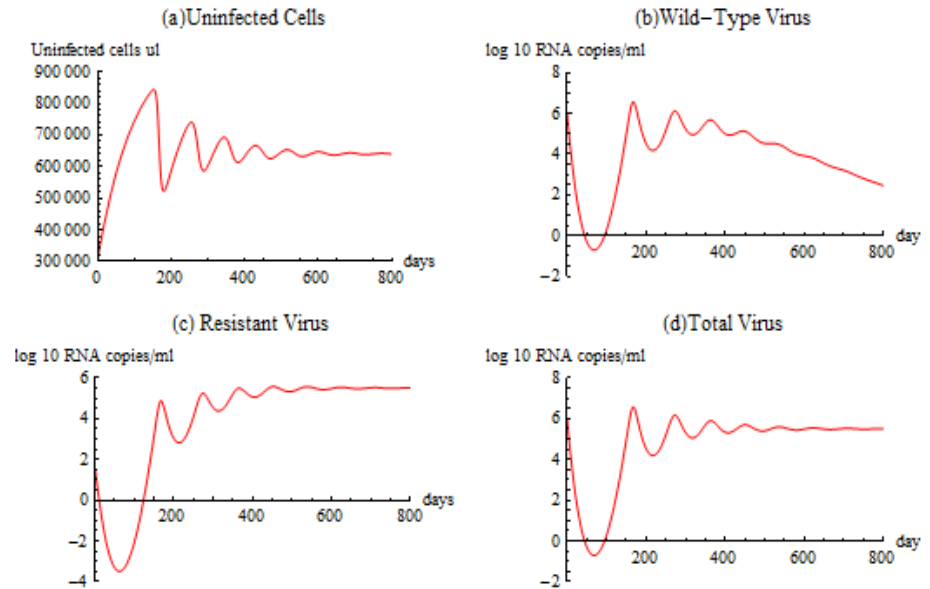


Figure 4 : Graphs with the $E_{srt} = .51$. Has a strong influence on which strain survives. Here, the resistant strain population rises and the Wild - type declines.

Drug efficacy influenced the sensitive population- declines and the resistant strain increases.



CONCLUSIONS

- Raising the drug concentration puts a selection pressure for the resistant strain that was not there in the pretreatment model (wild type dominates)
- Need to use multiple drugs in order to prevent the rise of the resistant strain.
- Questions?

