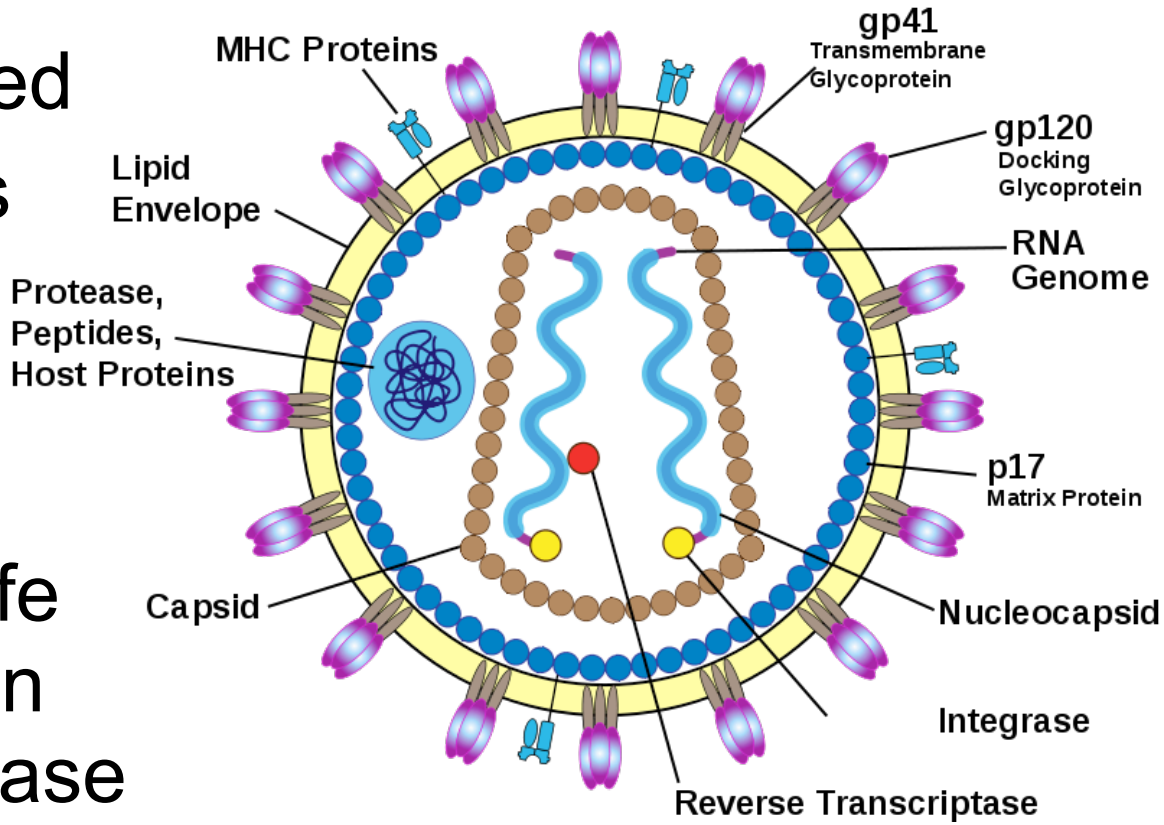
Outline

- Biology of HIV and drug resistance
- Mathematical model of induction therapy
- Impulsive differential equations
- Determining resistance thresholds
- Calculating the length and number of drug holidays
- Comparison with clinical results
- Implications.

HIV/AIDS

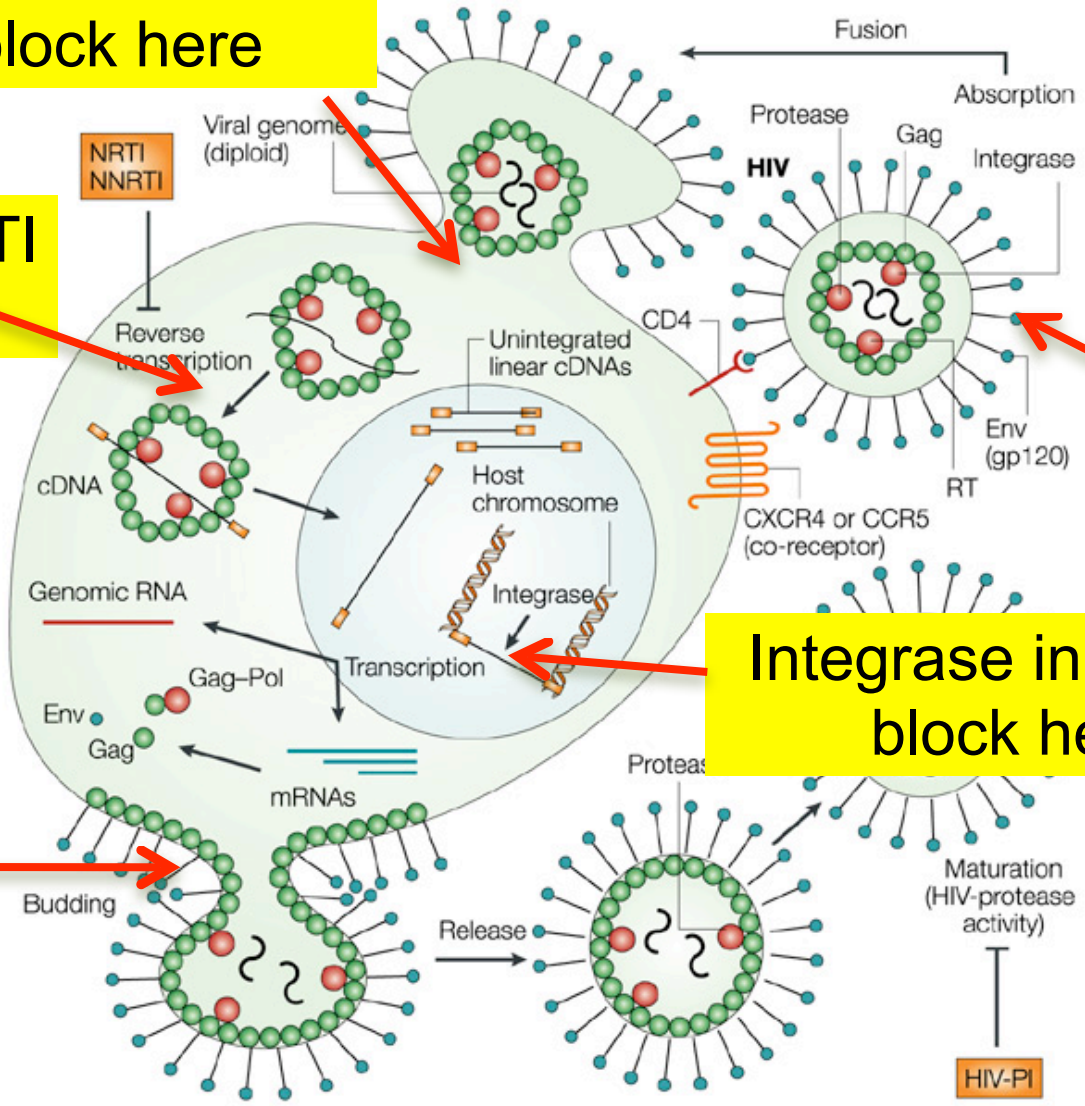
- 33 million infected
- Infection causes a depletion of $CD4^+$ T cells
- No cure
- Drugs prolong life (RTIs, PIs, fusion inhibitors, integrase inhibitors).



RTI=reverse transcriptase inhibitors
PIs=Protease inhibitors

Fusion inhibitors block here

NRTI and NNRTI block here



HIV

Integrase inhibitors block here

PIs block here.

NRTIs=nucleoside reverse transcriptase inhibitors
NNRTIs=nonnucleoside reversetranscriptase inhibitors
PIs=protease inhibitors

Nature Reviews | Cancer

Adherence

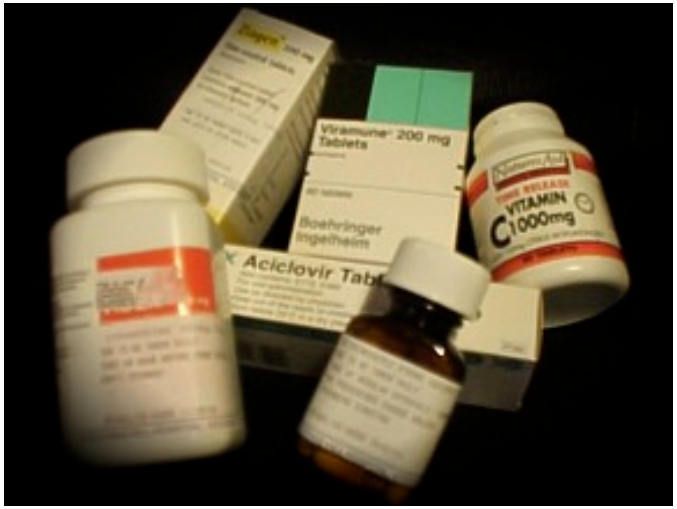
- Studies have shown that 40-60% of patients are less than 90% adherent to their drugs
- Adherence also decreases over time
- Lack of adherence promotes the development of drug-resistant mutations.

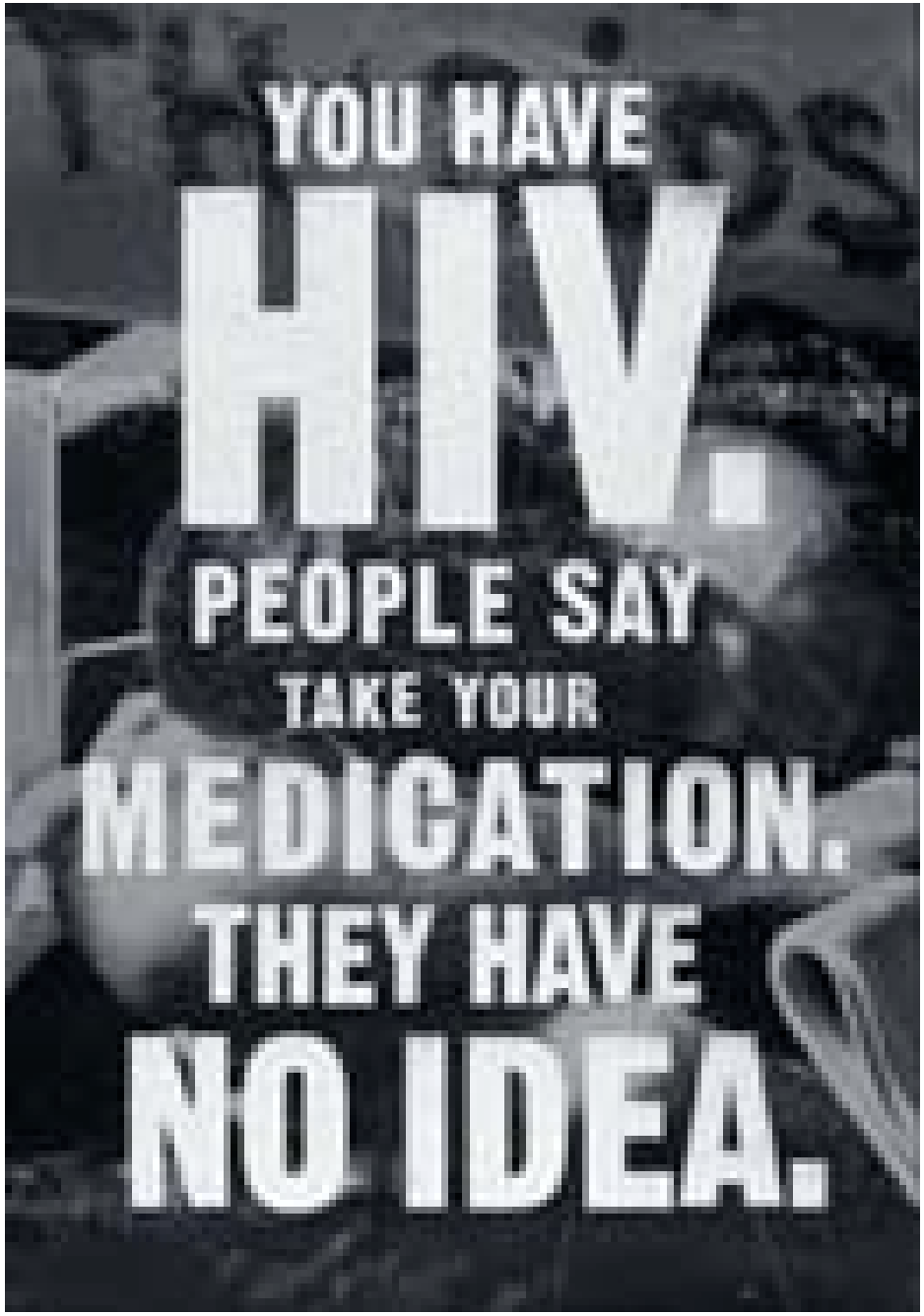
Drug holidays

"Drug holidays" are extended breaks from the drugs. They may occur due to:

- lifestyle factors
- relief from side effects
- economic implications

  (especially in the developing world).




YOU HAVE
H.I.V.
PEOPLE SAY
TAKE YOUR
MEDICATION.
THEY HAVE
NO IDEA.

Induction Therapy

- New HIV/AIDS treatment regime that hopes to benefit patients by decreasing drug resistance and reducing the overall number of drugs that must be taken
- Two phases:
  - Induction phase: Period of intensified antiretroviral therapy
  - Maintenance phase: Long-term regimen
- The induction phase lasts about six months.

RTI=reverse transcriptase inhibitors
PIs=Protease inhibitors

Adherence to Induction Therapy

- Since induction therapy has a higher chance of pill fatigue than maintenance therapy, it is likely that patients will take some holidays during this period
- If a holiday occurs at the end, induction therapy finished too early, which isn't acceptable
- However, a few breaks in the middle may be acceptable...

  ...assuming subsequent therapy was undertaken to control the virus.

Research Questions

For all PI-sparing drugs, how long can a drug holiday be?

How many doses must be taken after a holiday to return drug levels to before?

How many drug holidays can be taken during the entire induction phase?

PI sparing drugs=reverse transcriptase inhibitors, fusion inhibitors, integrase inhibitors

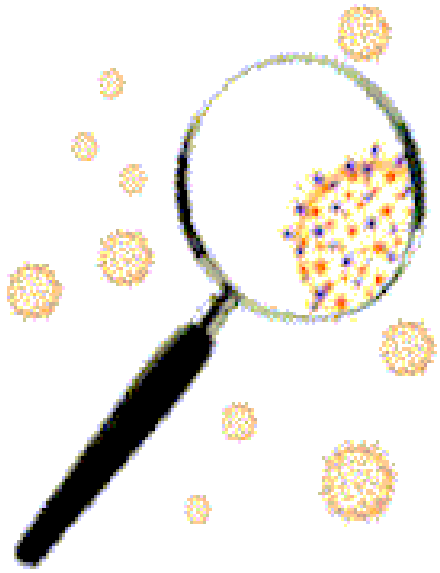
Modelling Drug Therapy

We assume two strains of the virus:

1. The wild-type strain will dominate in the absence of drugs
2. There is also a mutant strain that is a less efficient competitor, but more resistant to the drugs.

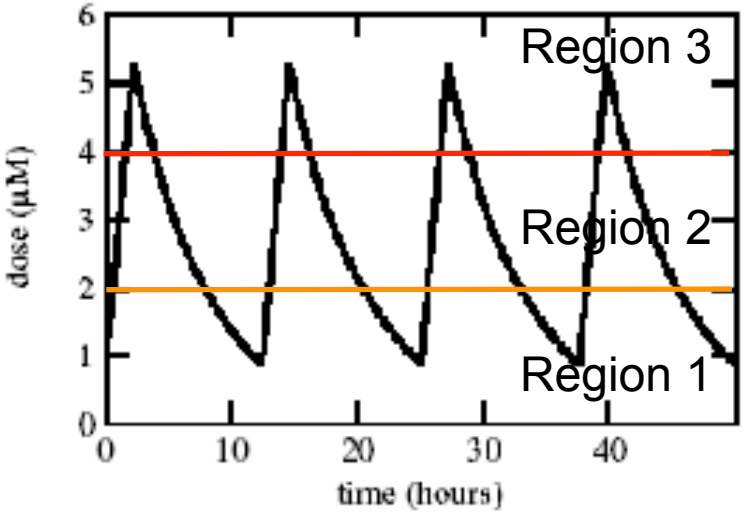
The basic idea

- Resistant mutants are not impervious to the drugs
- Rather, “resistance” confers a degree of resistance to the drugs
- Thus, if drug concentrations in the cell were sufficiently high, then even the mutant would be controlled.



Drug dependence

- As drug levels fall, the wild-type strain is controlled, but the mutant may take hold
- When the drug falls to trough levels, the wild-type strain can regain its advantage
- The amount of drug will determine how and when one, the other or neither strain gains dominance.

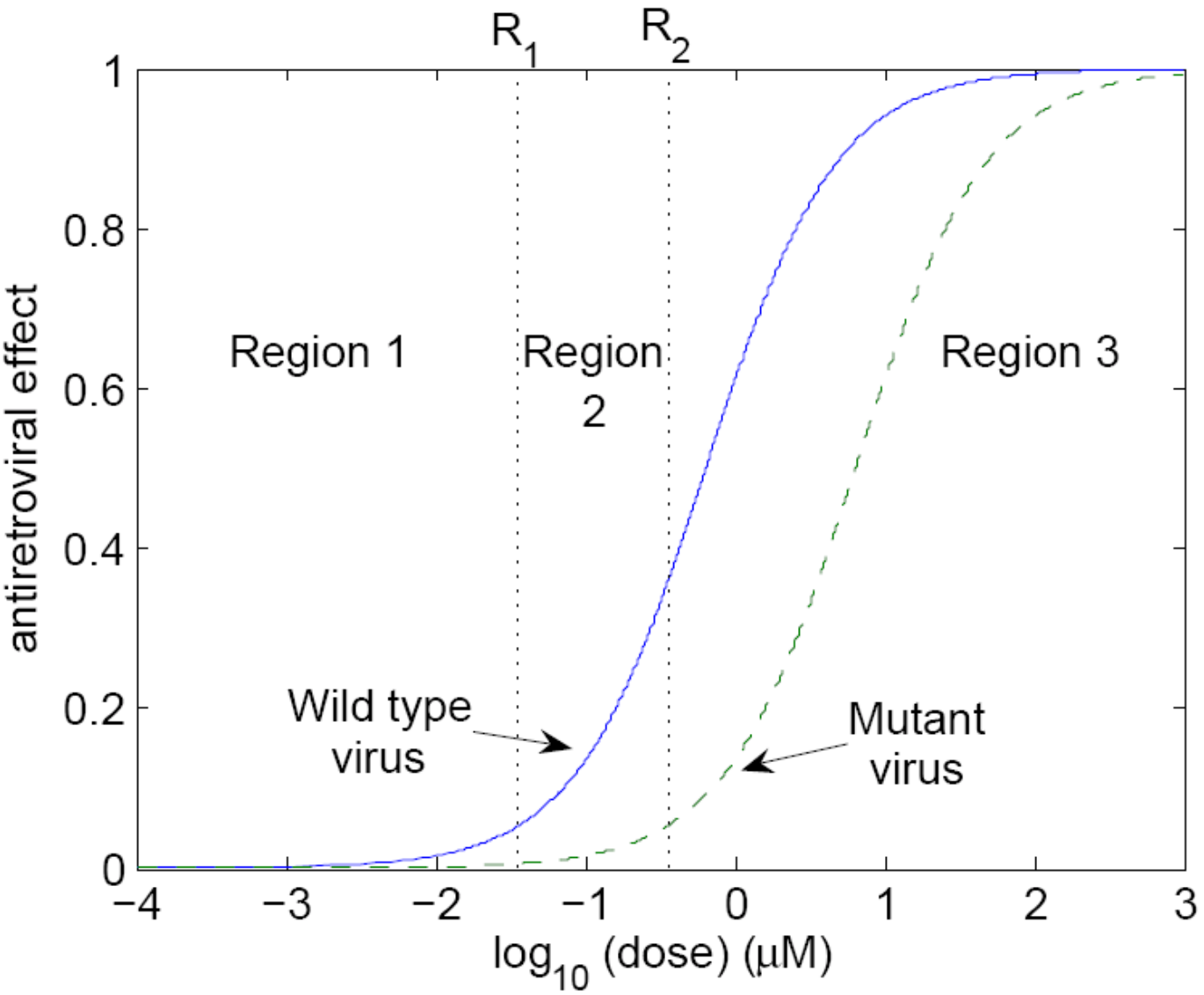


The three regions

We consider three drug regimes:

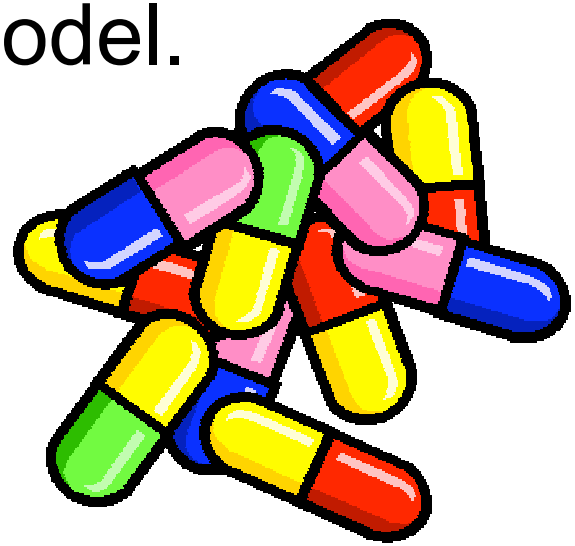
- Region 1 (low): drugs are not sufficient to inhibit either strain
- Region 2 (medium): drugs will inhibit the wild type, but not the mutant
- Region 3 (high): drugs will inhibit both strains.

The region thresholds

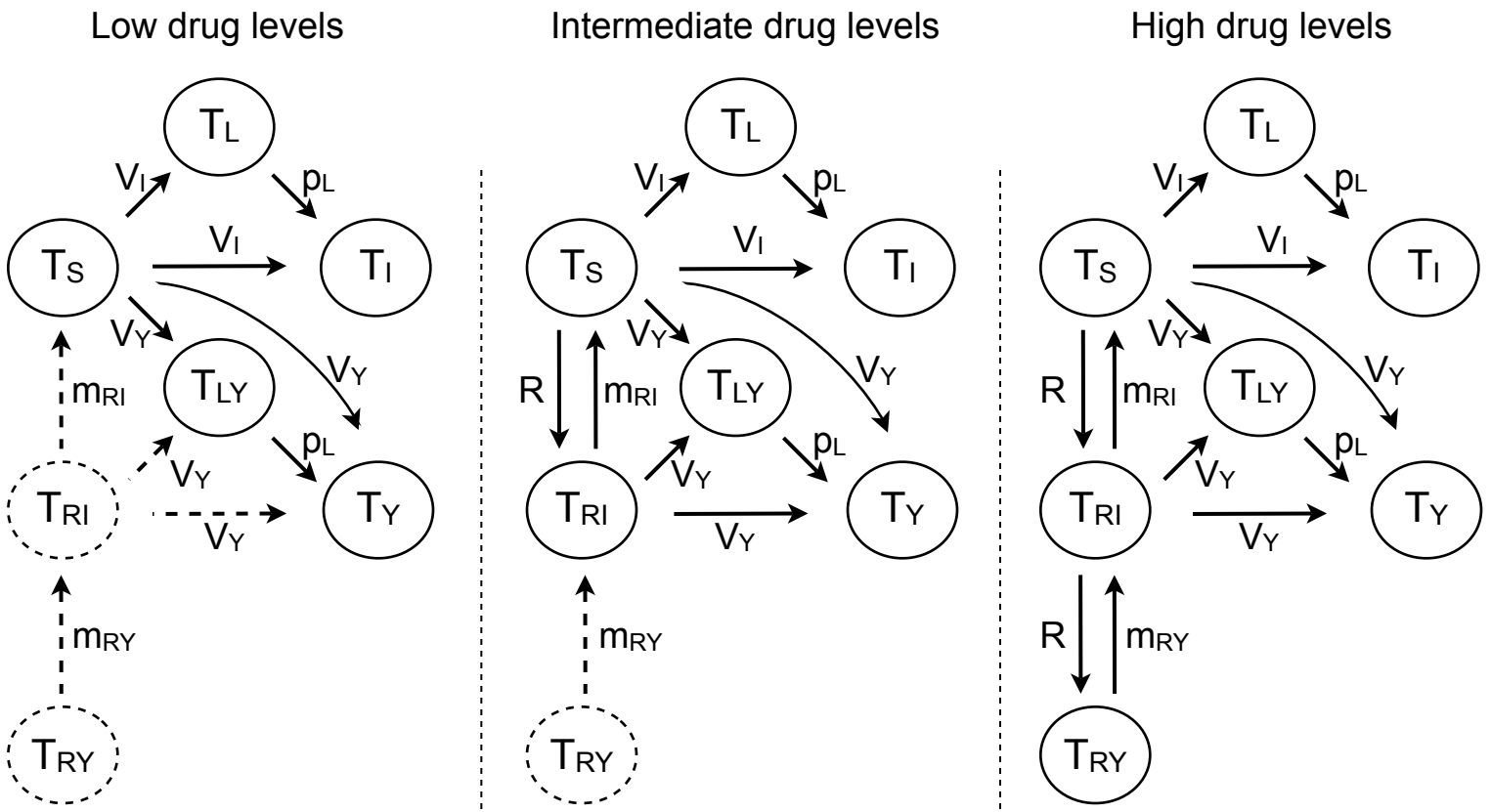


The model itself changes

- Within each regime, the model itself will be different
- We have three models, connected by the drug behaviour
- Thus, as the drug levels change, so too does each model.



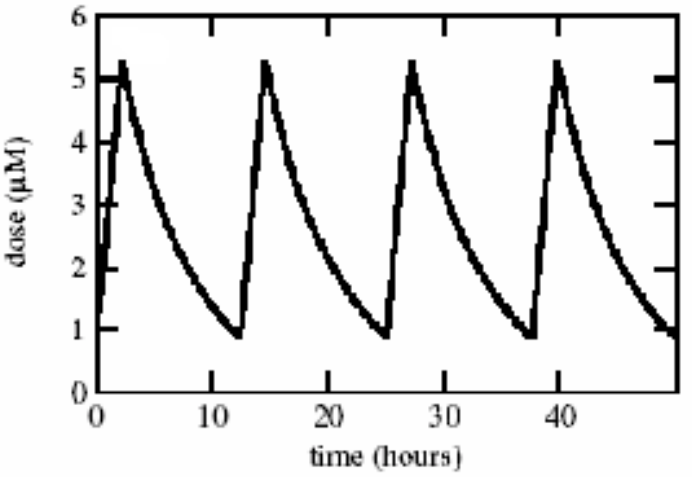
The Model - Flow Chart

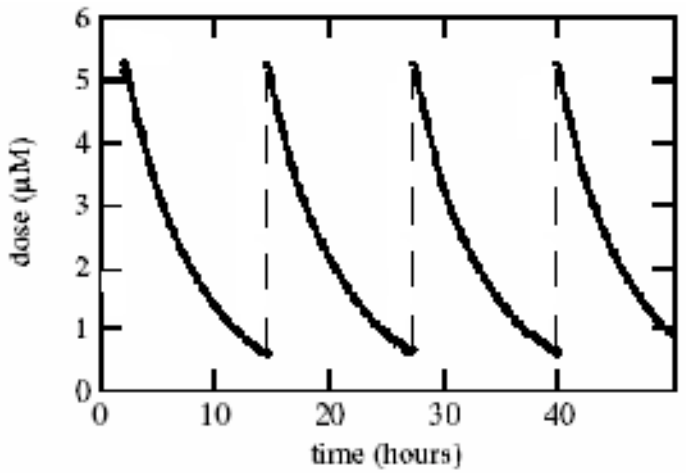


V_I=wild-type virus *V_Y=mutant virus* *V_{NI}=noninfectious* *T_S=Susceptible T cells*
T_I=Infected (wild type) *T_Y=Infected (mutant)* *R=drug* *T_L=Latently infected (wild type)*
T_{RY}=Highly inhibited *T_{RI}=Intermediate inhibited* *m_j=waning rates* *T_{LY}=Latently infected (mutant)*

Impulsive Differential Equations

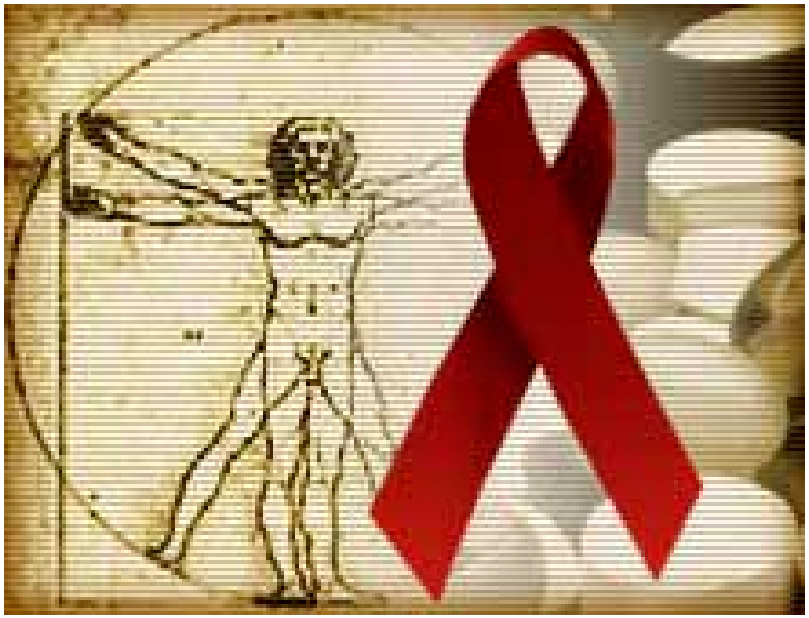
- Assume drug effects are instantaneous
- That is, the time-to-peak is assumed to be negligible
- Impulsive differential equations provide an adequate mathematical model of evolutionary processes that suddenly change their state.





Putting it together

- The model thus consists of a system of ODEs (virus and T cells) together with an ODE and a difference equation (drugs).



The model in Region 1 (low drugs)

$$
\begin{aligned}
\frac{dV_I}{dt} &= n_I\omega T_I - d_V V_I - r_I T_S V_I \\
\frac{dV_Y}{dt} &= n_I\omega T_Y - d_V V_Y - r_Y T_S V_Y - r_Y T_{RI} V_Y \\
\frac{dV_{NI}}{dt} &= n_I(1-\omega)(T_I + T_Y) - d_V V_{NI} \\
\frac{dT_S}{dt} &= \lambda - r_I T_S V_I - r_Y T_S V_Y - d_S T_S + m_{RI} T_{RI} \\
\frac{dT_I}{dt} &= (1-\psi) r_I T_S V_I - d_I T_I + p_L T_{LI} \\
\frac{dT_{LI}}{dt} &= \psi r_I T_S V_I - d_S T_{LI} - p_L T_{LI} \\
\frac{dT_Y}{dt} &= (1-\psi) r_Y T_S V_Y - d_I T_Y + (1-\psi) r_Y T_{RI} V_Y + p_L T_{LY} \\
\frac{dT_{LY}}{dt} &= \psi r_Y T_S V_Y - d_S T_{LY} - p_L T_{LY} + \psi r_Y T_{RI} V_Y \\
\frac{dT_{RI}}{dt} &= -r_Y T_{RI} V_Y - (d_S + m_{RI}) T_{RI} + m_{RY} T_{RY} \\
\frac{dT_{RY}}{dt} &= -(d_S + m_{RY}) T_{RY}
\end{aligned}
$$

V_I=wild-type virus
V_Y=mutant virus
V_{NI}=noninfectious
T_S=Susceptible T cells
T_I=Infected (wild type)
T_Y=Infected (mutant)
T_{LI}, T_{LY}=Latently infected
T_{RI}=Intermediately inhibited T_{RY}=Highly inhibited R=drug
λ=lymphic source
d_j=clearance rates
m_j=waning rates
$n_I\omega$=# infectious virions
r_I=wild type infection rate
r_Y=mutant infection rate
ψ=latently infected proportion

The model in Region 2 (intermediate drugs)

$$
\begin{aligned}
\frac{dV_I}{dt} &= n_I\omega T_I - d_V V_I - r_I T_S V_I \\
\frac{dV_Y}{dt} &= n_I\omega T_Y - d_V V_Y - r_Y T_S V_Y - r_Y T_{RI} V_Y \\
\frac{dV_{NI}}{dt} &= n_I(1-\omega)(T_I + T_Y) - d_V V_{NI} \\
\frac{dT_S}{dt} &= \lambda - r_I T_S V_I - r_Y T_S V_Y - d_S T_S + m_{RI} T_{RI} - r_P T_S R \\
\frac{dT_I}{dt} &= (1-\psi) r_I T_S V_I - d_I T_I + p_L T_{LI} \\
\frac{dT_{LI}}{dt} &= \psi r_I T_S V_I - d_S T_{LI} - p_L T_{LI} \\
\frac{dT_Y}{dt} &= (1-\psi) r_Y T_S V_Y - d_I T_Y + (1-\psi) r_Y T_{RI} V_Y + p_L T_{LY} \\
\frac{dT_{LY}}{dt} &= \psi r_Y T_S V_Y - d_S T_{LY} - p_L T_{LY} + \psi r_Y T_{RI} V_Y \\
\frac{dT_{RI}}{dt} &= -r_Y T_{RI} V_Y - (d_S + m_{RI}) T_{RI} + m_{RY} T_{RY} + r_P T_S R \\
\frac{dT_{RY}}{dt} &= -(d_S + m_{RY}) T_{RY}
\end{aligned}
$$

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λ=lymphic source
d_j=clearance rates
m_j=waning rates
$n_I\omega$=# infectious virions
r_I=wild type infection rate
r_Y=mutant infection rate
ψ=latently infected proportion
r_P=drug uptake rate

The model in Region 3 (high drugs)

$$
\begin{aligned}
\frac{dV_I}{dt} &= n_I\omega T_I - d_V V_I - r_I T_S V_I \\
\frac{dV_Y}{dt} &= n_I\omega T_Y - d_V V_Y - r_Y T_S V_Y - r_Y T_{RI} V_Y \\
\frac{dV_{NI}}{dt} &= n_I(1-\omega)(T_I + T_Y) - d_V V_{NI} \\
\frac{dT_S}{dt} &= \lambda - r_I T_S V_I - r_Y T_S V_Y - d_S T_S + m_{RI} T_{RI} - r_R T_S R \\
\frac{dT_I}{dt} &= (1-\psi) r_I T_S V_I - d_I T_I + p_L T_{LI} \\
\frac{dT_{LI}}{dt} &= \psi r_I T_S V_I - d_S T_{LI} - p_L T_{LI} \\
\frac{dT_Y}{dt} &= (1-\psi) r_Y T_S V_Y - d_I T_Y + (1-\psi) r_Y T_{RI} V_Y + p_L T_{LY} \\
\frac{dT_{LY}}{dt} &= \psi r_Y T_S V_Y - d_S T_{LY} - p_L T_{LY} + \psi r_Y T_{RI} V_Y \\
\frac{dT_{RI}}{dt} &= -r_Y T_{RI} V_Y - (d_S + m_{RI}) T_{RI} + m_{RY} T_{RY} + r_R T_S R - r_Q T_{RI} R \\
\frac{dT_{RY}}{dt} &= -(d_S + m_{RY}) T_{RY} + r_Q T_{RI} R
\end{aligned}
$$

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λ=lymphic source
d_j=clearance rates
m_j=waning rates
$n_I\omega$=# infectious virions
r_I=wild type infection rate
r_Y=mutant infection rate
ψ=latently infected proportion
r_R, r_Q=drug uptake rates

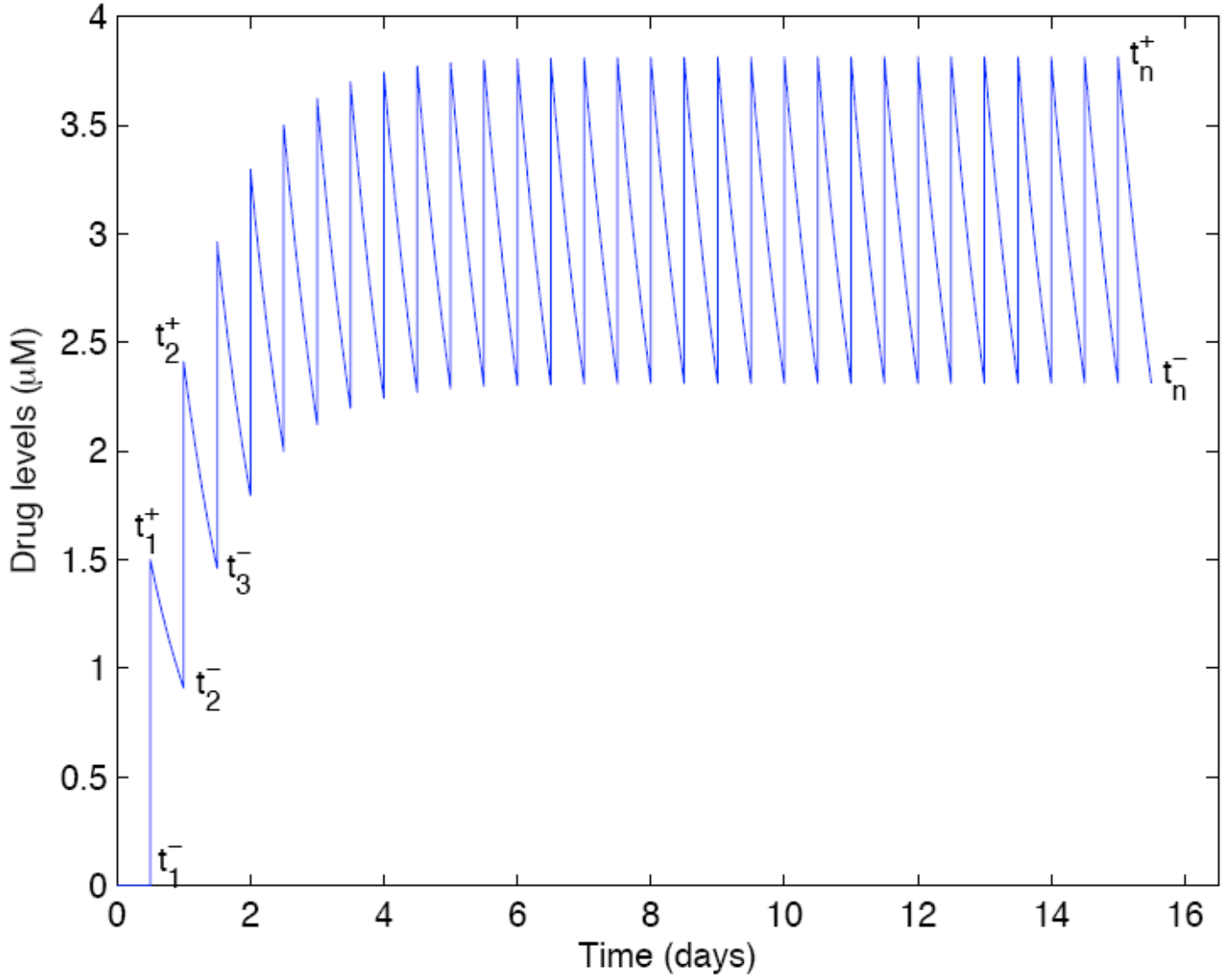
…with the (impulsive) dynamics of the drugs:

$$\frac{dR}{dt} = -d_R R \qquad t \neq t_k$$

$$\Delta R = \begin{cases} R^i & \text{if a dose is to be taken} \\ 0 & \text{if no dose is to be taken.} \end{cases}$$

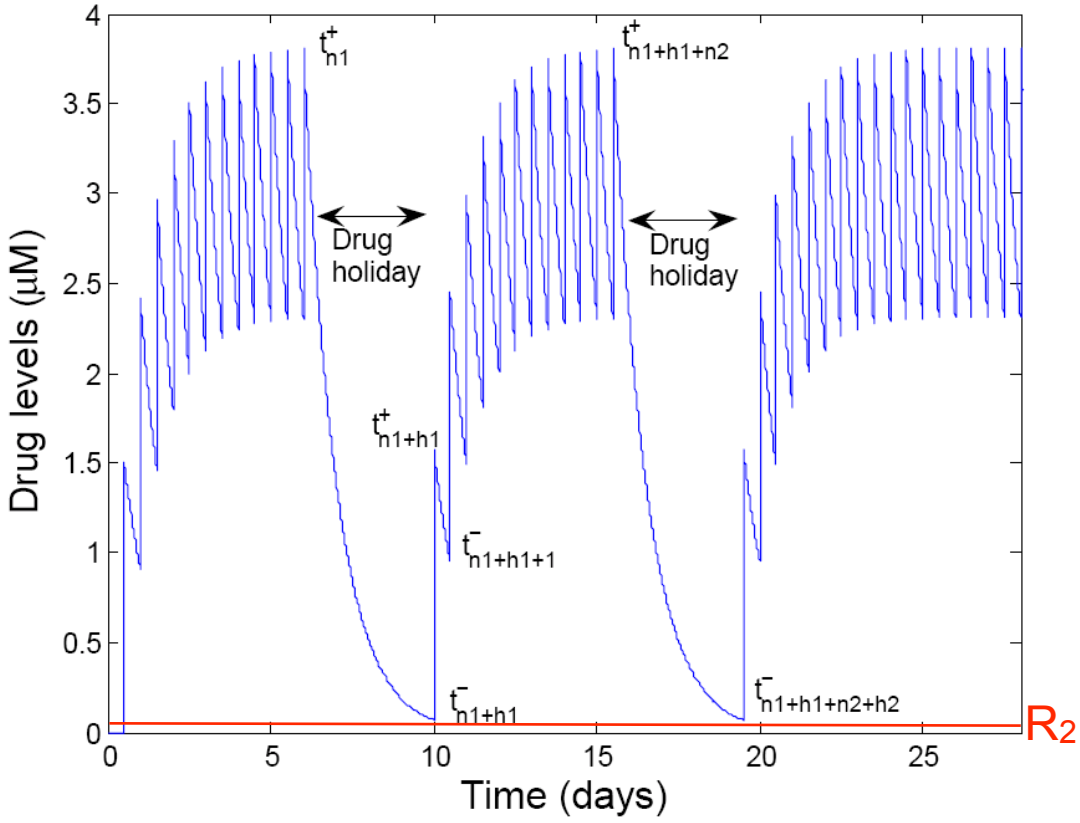
R=drug
d_R=decay rate
R^i=dosage
t_k=impulse time

Perfect adherence



Imperfect Adherence to Drug Therapy

- As long as the drug concentration level does not drop below R_2, there is sufficient amount of drug to control both viral strains
- Drug holidays can be taken, and the number of doses that can be missed in order to stay over R_2 can be calculated.

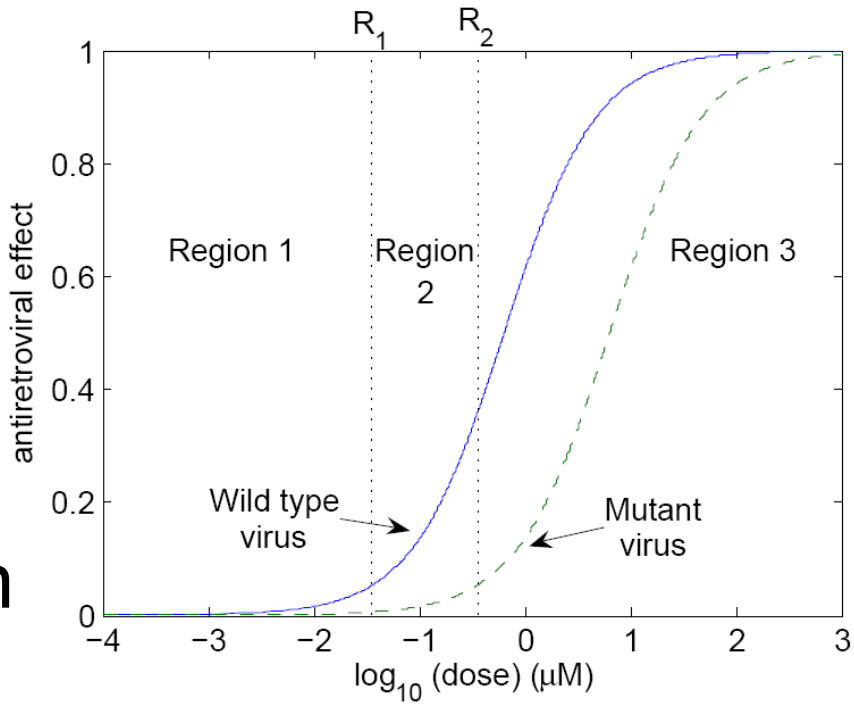


How to determine R_1?

- Define R_1 by

$$\frac{R_1}{R_1 + \mathrm{IC}_{50}} = \frac{R_2}{R_2 + n\mathrm{IC}_{50}}$$

where *n* is the degree of n-fold resistance conferred by the mutation



- eg for 10-fold resistance, you need 10 times as much drug to have the same effect
- Thus $R_1 = R_2/n$.

R_1=Region 1 threhsold
R_2=Region 2 threshold

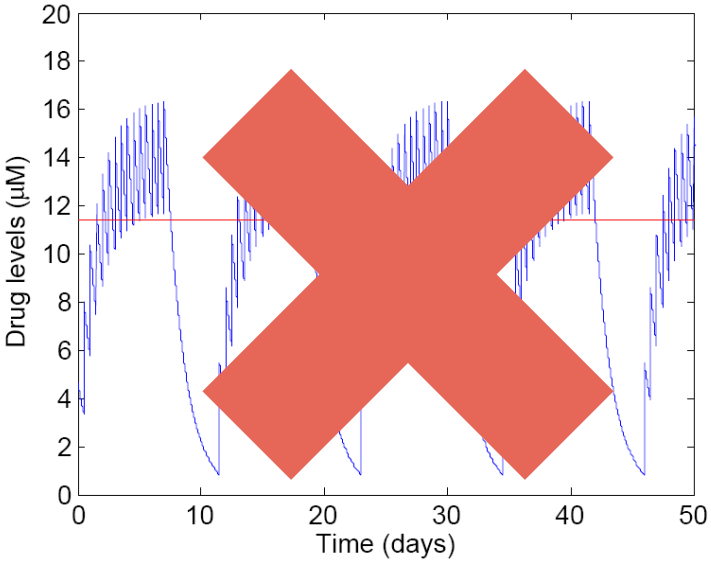
How to determine R_2?

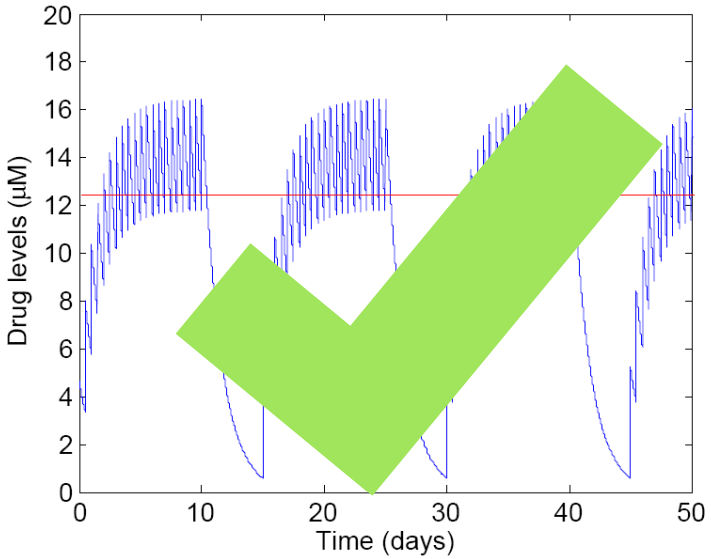
- $V_Y(0)>0$ and $V_Y'(0)<0$, so the resistance viral load is initially decreasing
- The resistance viral load either reaches a minimum at time t* or it decreases indefinitely (in which case we can define t* arbitrarily)
- Define $R_2=R(t^*)$
- Thus R_2 is reached when resistance stops decreasing and starts increasing
- This guarantees that resistance has not emerged at time t*.

V_Y=mutant virus
R_2=Region 2 threshold

An additional condition

- The mean drug concentration must be larger than the trough value when no drug holiday is taken
- This ensures that drugs are maintained at sufficiently high levels over the length of the entire induction phase.

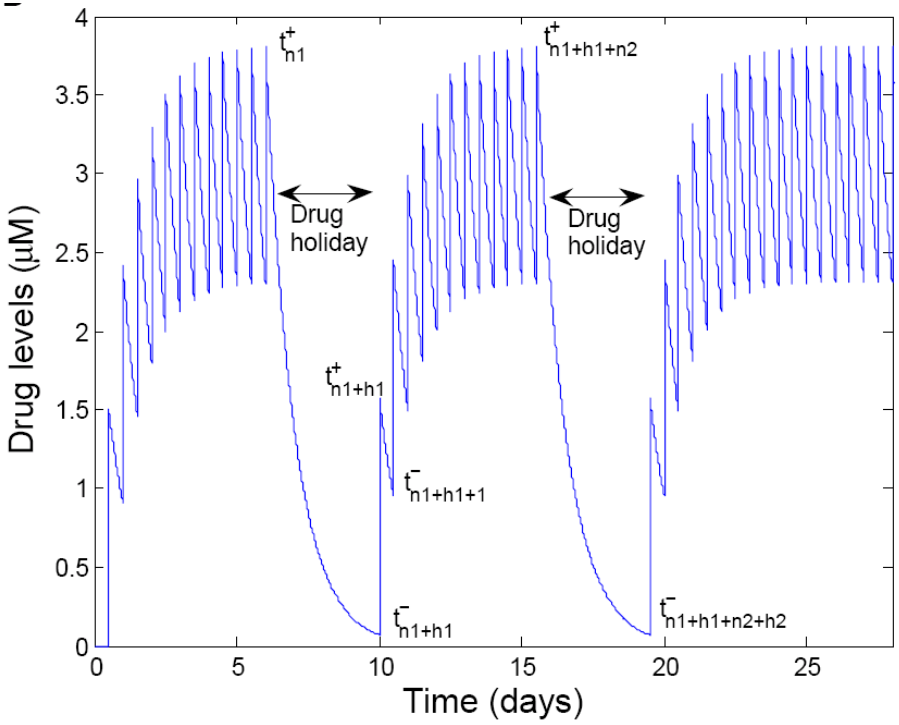




Imperfect adherence

We need to determine:

- n_1, the number of doses to be taken initially
- h_1, the number of doses that can be safely missed during the drug holiday
- n_2, the number of doses needed to return to high drug levels
- k, the number of doses that must be taken at the end so that the induction phase ends at high levels.

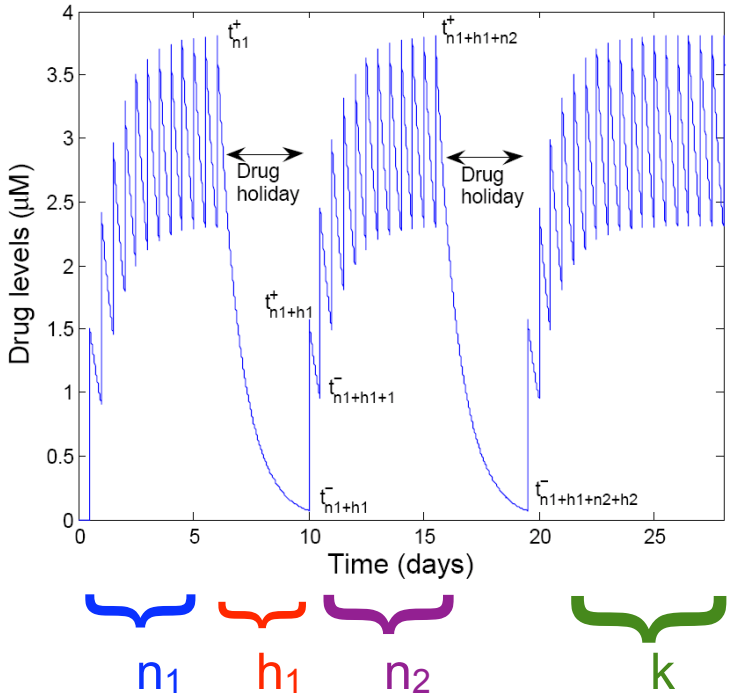


Taking the first n_1 doses

- To be within ε_1 of the periodic orbit, we require

$$n_1 > \frac{1}{d_r \tau} \ln \left[\frac{R^i}{\epsilon_1 (1 - e^{-d_r \tau})} \right] - 1$$

where ε_1 is chosen to ensure the mean drug concentration is sufficiently high over the entire induction period.



d_r=drug waning rate
τ=period R^i=dosage

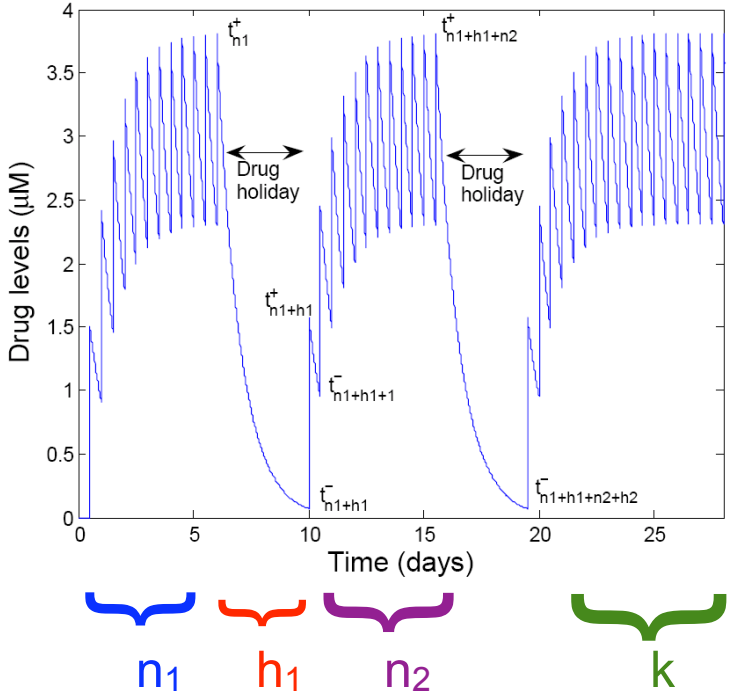
Missing h_1 doses

- To avoid Region 2 after h_1 doses have been missed, we require

$$h_1 < \frac{1}{d_r \tau} \ln \left[\frac{R^i}{R_2} \left(\frac{1 - e^{-(n_1+1) d_r \tau}}{1 - e^{-d_r \tau}} \right) \right]$$

- The number of doses that must be taken following a drug holiday satisfies

$$n_2 > \frac{1}{d_r \tau} \ln \left[\frac{R^i e^{-d_r \tau} - R_2 (1 - e^{-d_r \tau})}{\epsilon_2 (1 - e^{-d_r \tau})} \right].$$



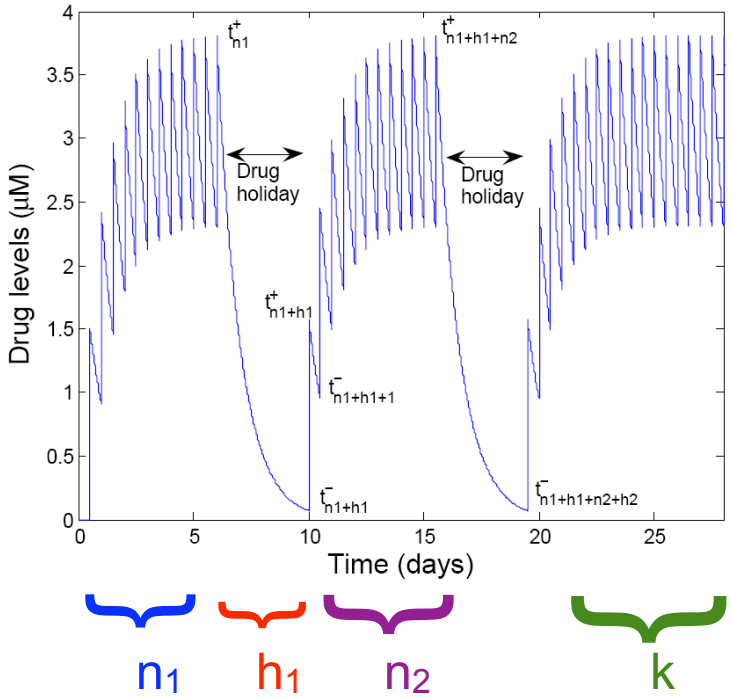
d_r=drug waning rate τ=period
R2=Region 2 threshold R^i=dosage

Straightforward formulas

- If the tolerance is the same, then $h_1=h_2=...$

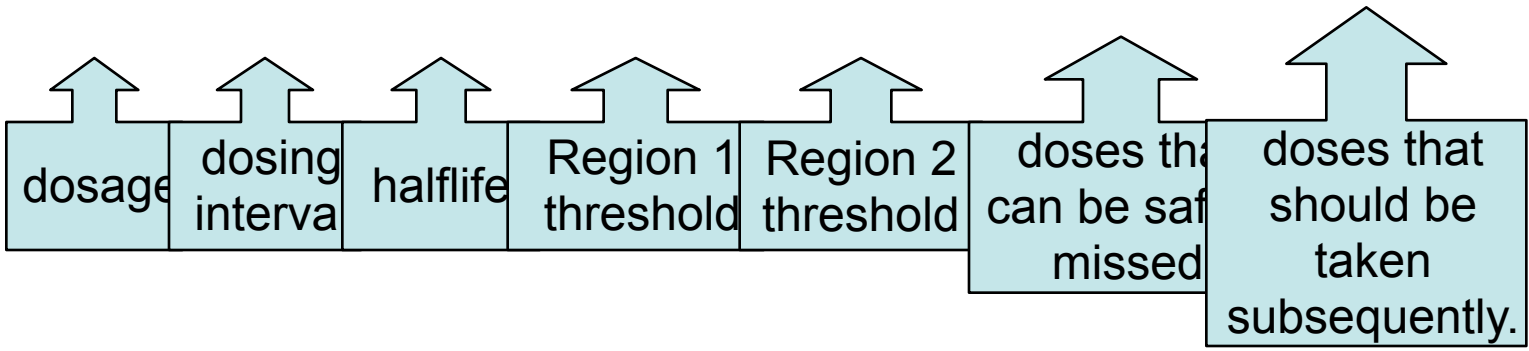
  (ie all drug holidays have the same length)
- Furthermore, $n_2=n_3=...=k$

  (ie all dosing intervals after a drug holiday are equal, including the final one)
- The formulas for h_i and n_j are straightforward and can be understood by policymakers.



Results

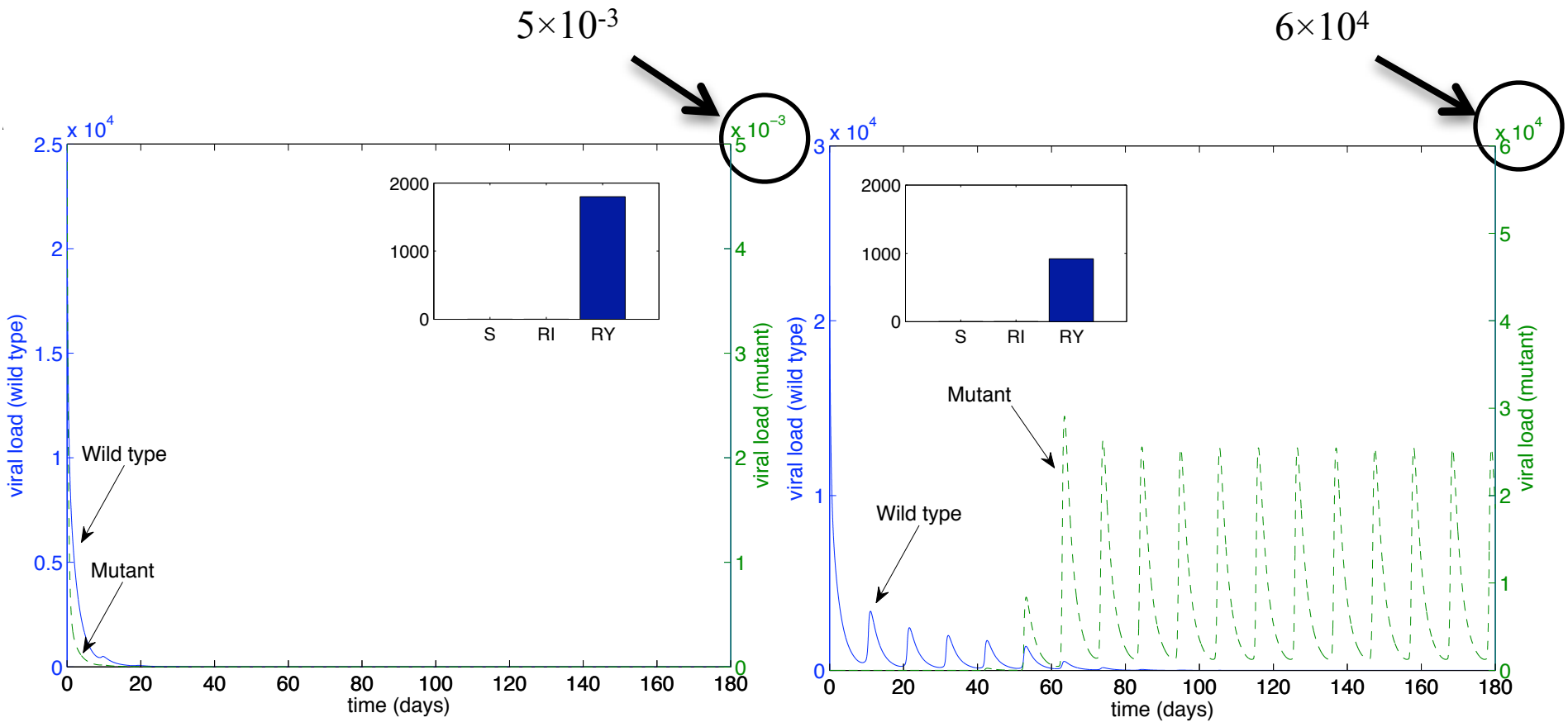
Drug (units)	R^i (μM)	τ (days)	$T_{1/2}$ (hours)	R_1 (μM)	R_2 (μM)	missable days (max)	subsequent days (min)
Abacavir (ABC)	12	1/2	15	$10^{-1.0269}$	$10^{-0.0269}$	3	7
Didanosine (ddI)	4.65	1/2	25	$10^{-1.2218}$	$10^{-0.2218}$	5	7.5
Emtricitabine (FTC)	7.2	1	39	$10^{-0.9788}$	$10^{0.0212}$	6	17
Lamivudine (3TC)	6	1/2	20	$10^{-1.1249}$	$10^{-0.1249}$	3.5	8.5
Stavudine (d4T)	2.144	1/2	7.5	$10^{-1.6383}$	$10^{-0.6383}$	1	2.5
Tenofivir (TDF)	1.184	1	60	$10^{-1.5229}$	$10^{-0.5229}$	10	24
Zidovudine (ZDV)	4.24	1/3	7	$10^{-1.6021}$	$10^{-0.6021}$	1.33	2.67
Delavirdine (DLV)	26.6	1/3	5.8	$10^{-1.4559}$	$10^{-0.4559}$	1.67	2.67
Efavirenz (EFV)	12.9	1	45	$10^{-0.8356}$	$10^{0.1644}$	9	22
Nevirapine (NVP)	7.5	1/2	27	$10^{-1.0088}$	$10^{-0.0088}$	5	12.5



Example

- A patient is taking the triple-drug cocktail FTC (emtricitabine), ddI (didanosine) and EFV (efavirenz), can have
  - FTC: 6 days off, 17 subsequently on
  - ddI: 5 days off, 7.5 subsequently on ← *First drug to reach R_2*
  - EFV: 9 days off, 22 subsequently on
- Therefore, during an 180 day induction period, a patient can have 13 holidays, each of which are 5 days long, followed by 7.5 days of strict therapy
- [7.5+(5+7.5)×13+7.5=177.5<180].

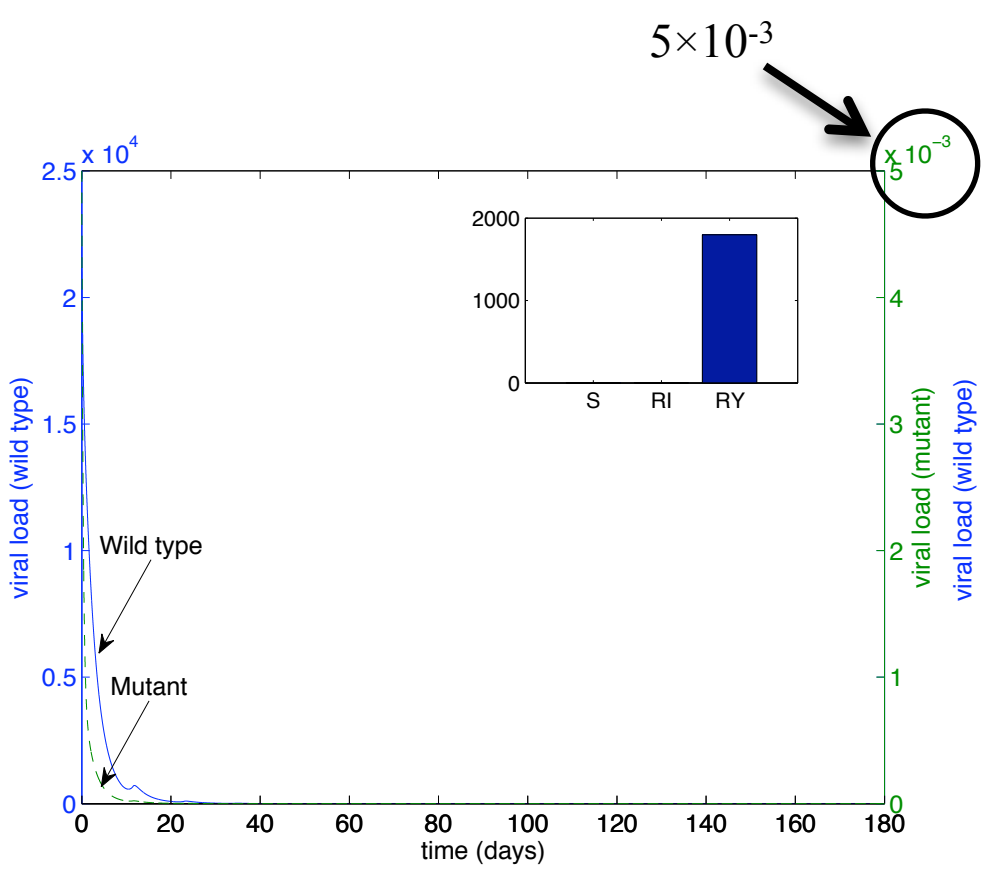
Abacavir (ABC)



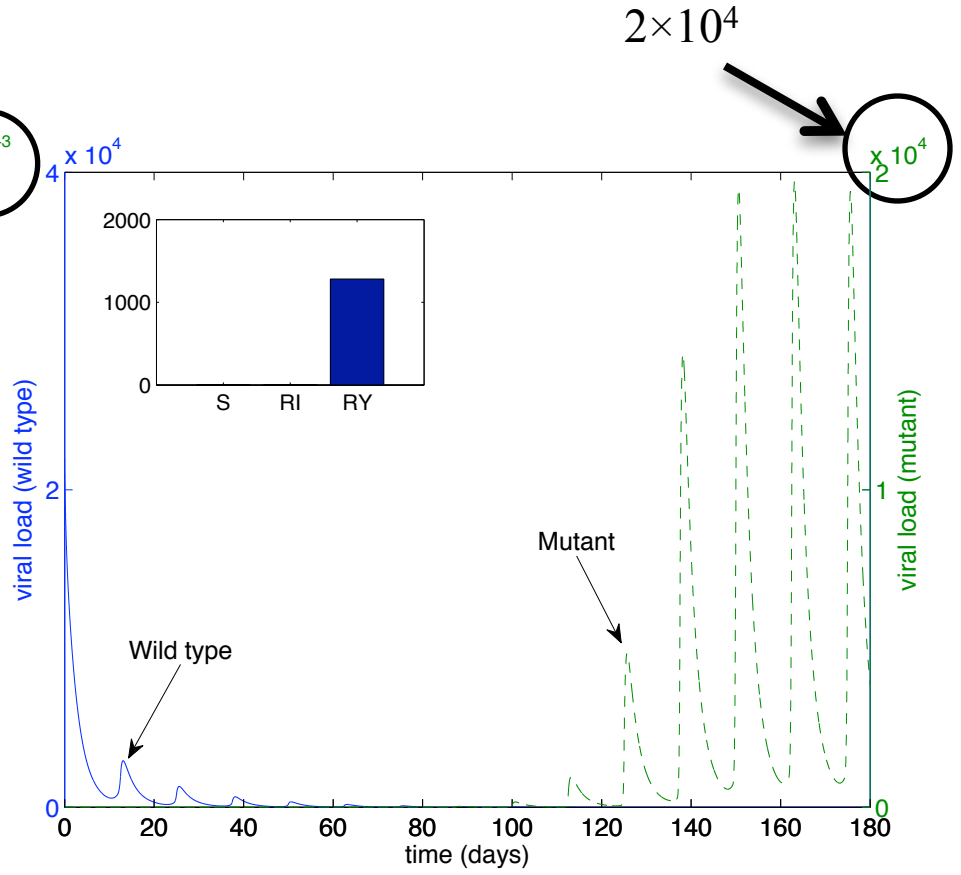
Taking the prescribed drug holidays

Missing one extra dose during each holiday

Lamivudine (3TC)

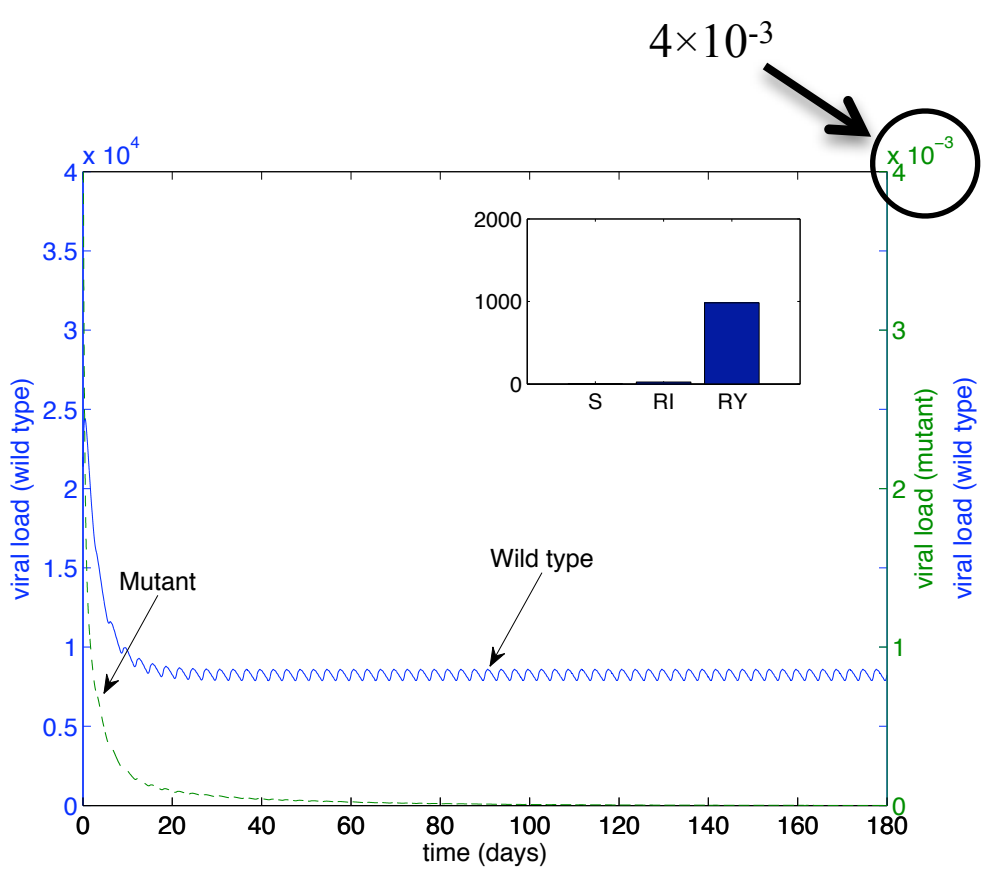


Taking the prescribed drug holidays

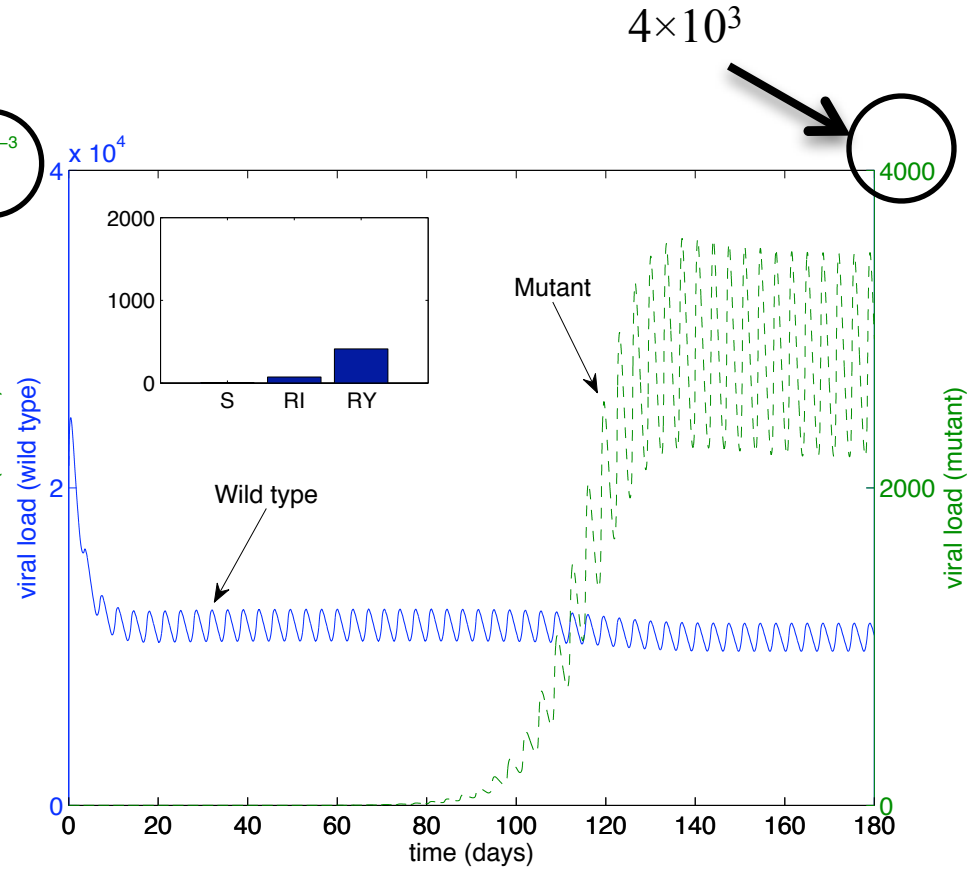


Missing one extra dose during each holiday

Stavudine (d4T)

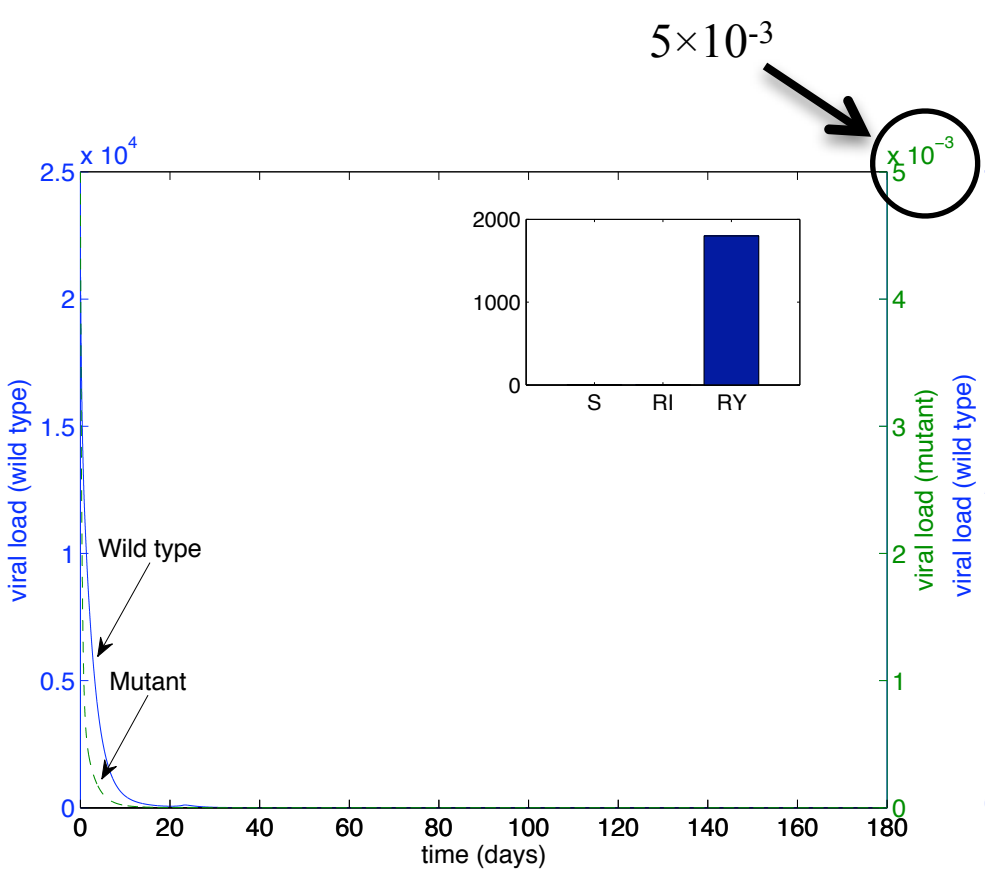


Taking the prescribed drug holidays

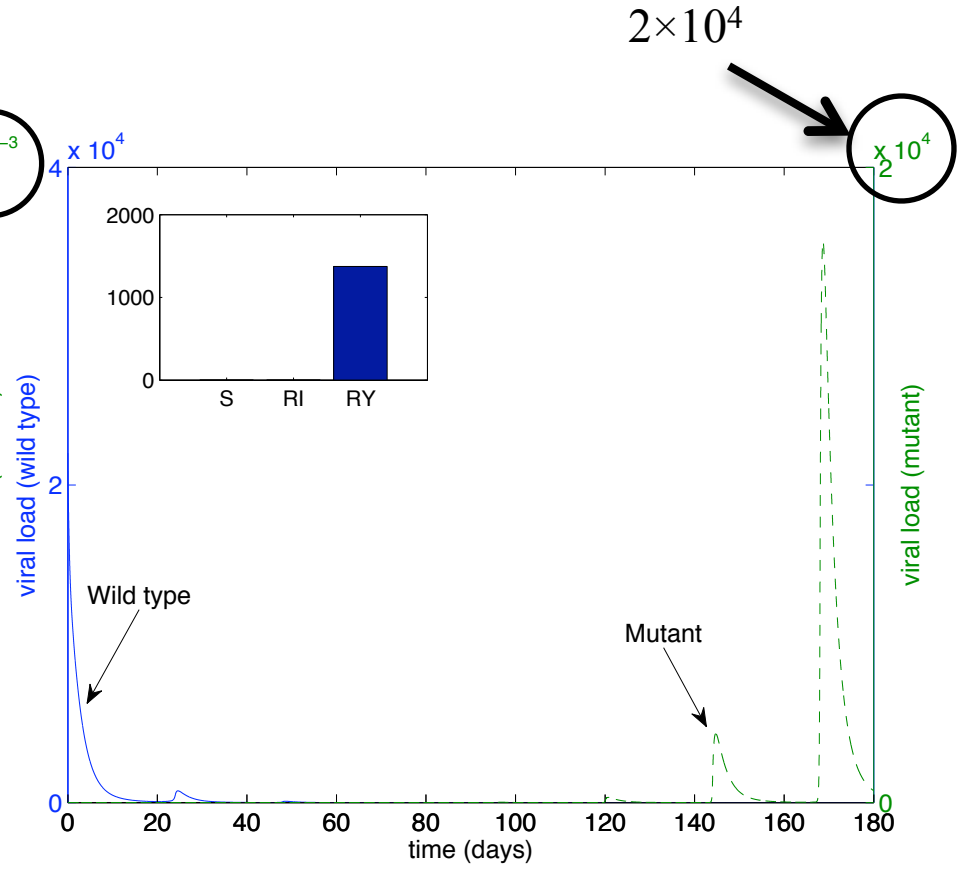


Missing one extra dose during each holiday

Emtricitabine (FTC)

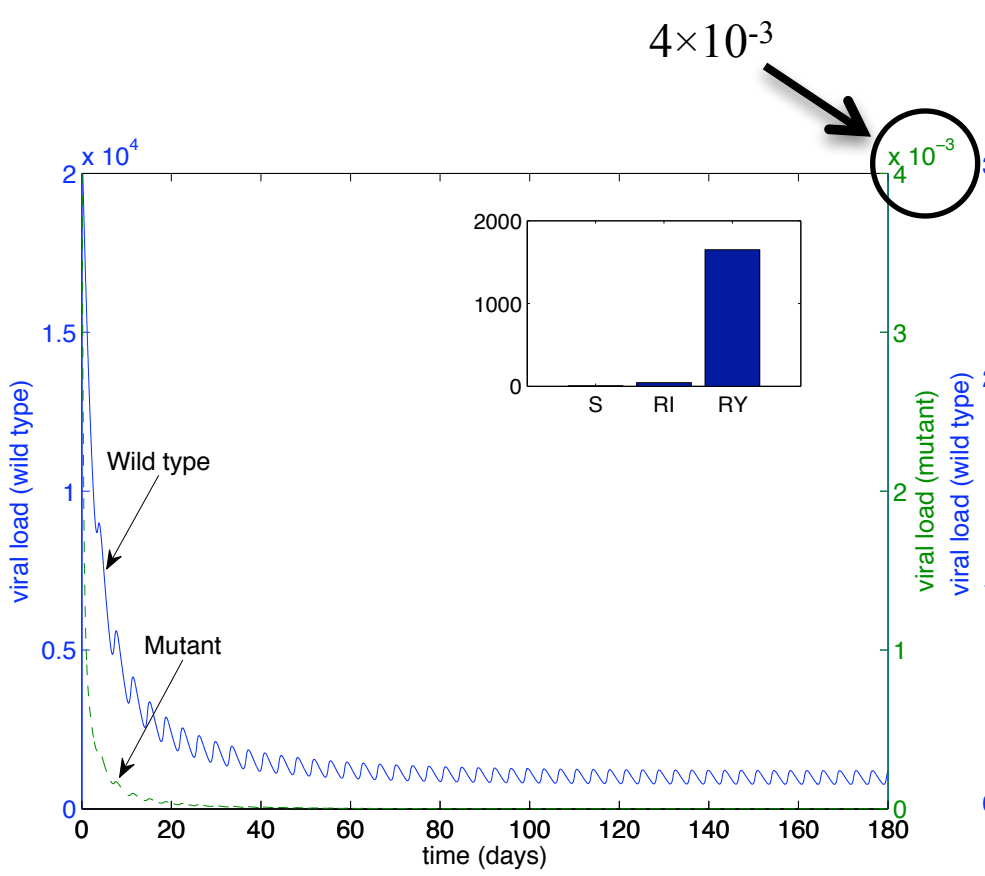


Taking the prescribed drug holidays

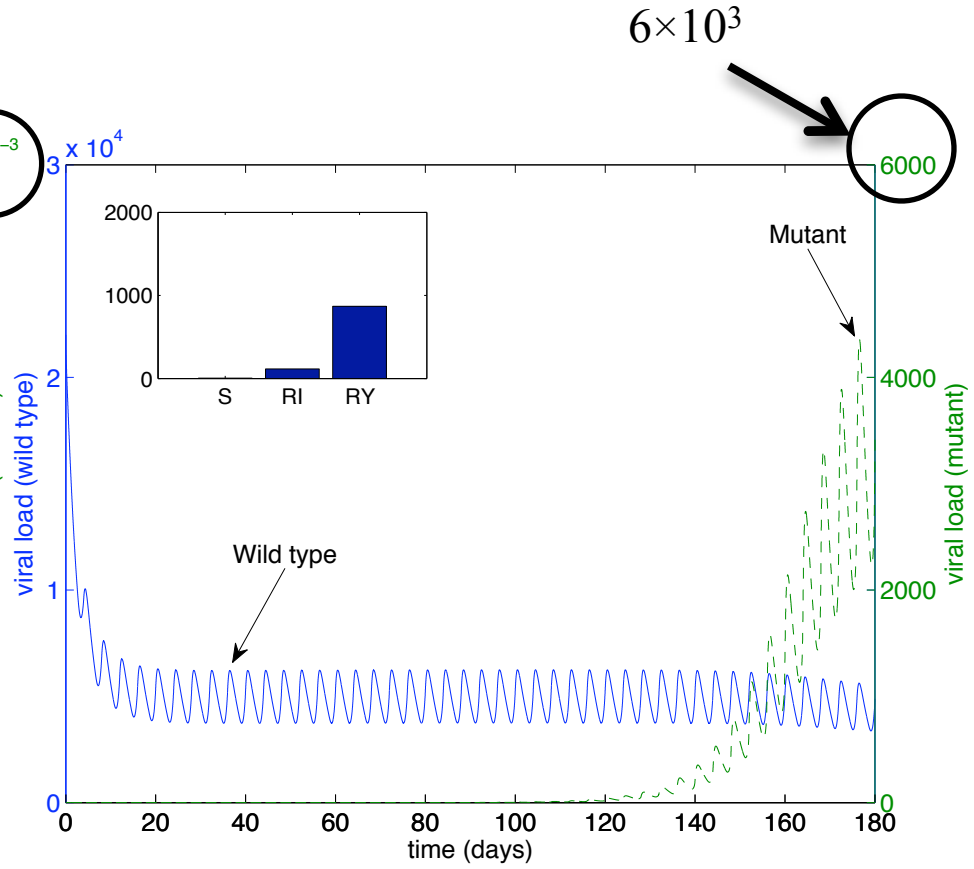


Missing one extra dose during each holiday

Zidovudine (ZDV)

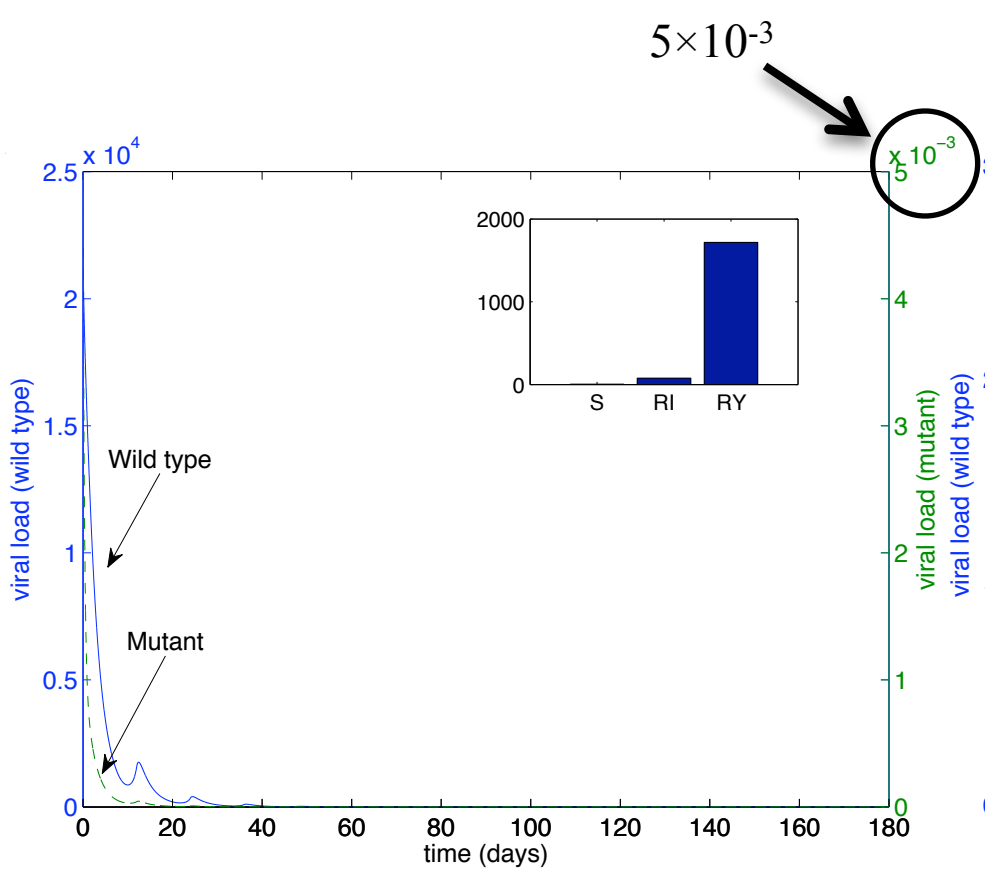


Taking the prescribed drug holidays

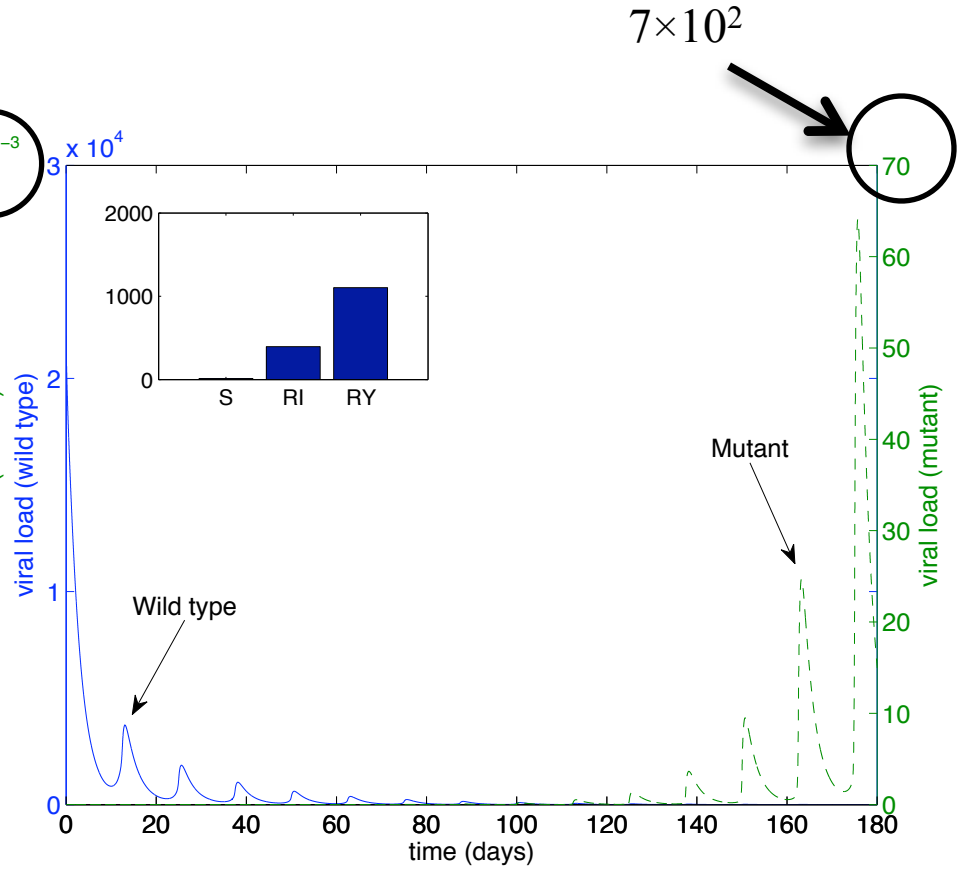


Missing one extra dose during each holiday

Didanosine (ddI)

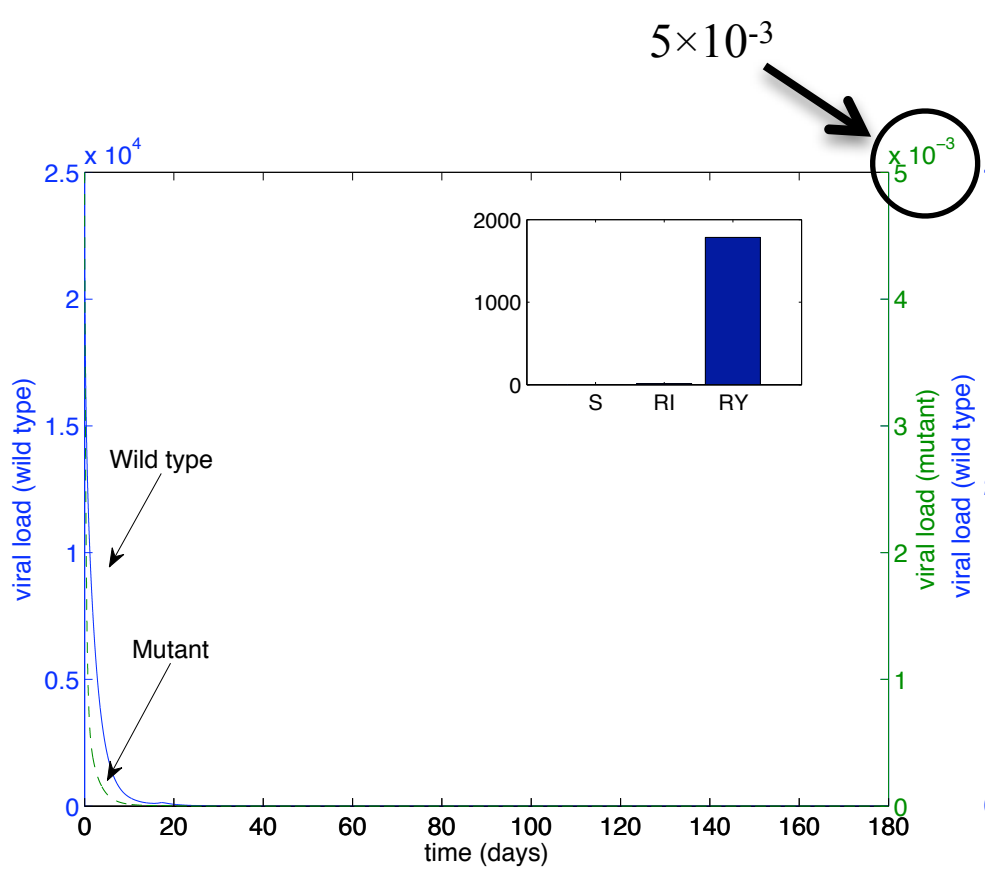


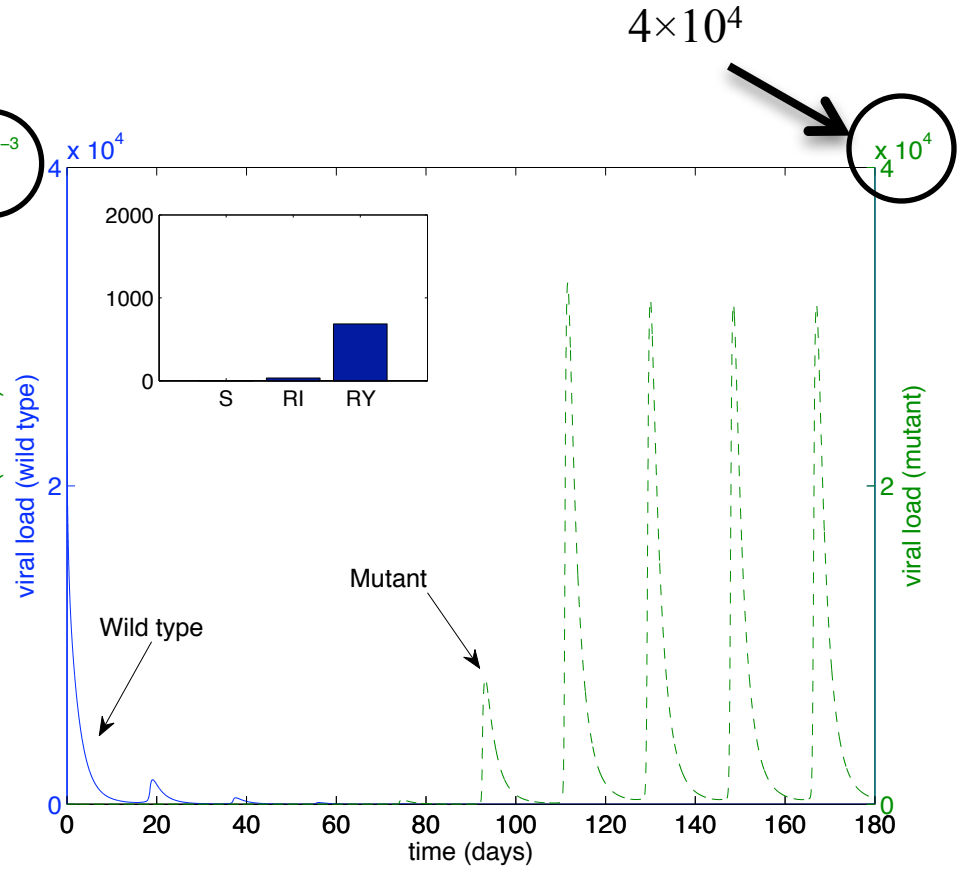
Taking the prescribed drug holidays



Missing one extra dose during each holiday

Nevirapine (NVP)





Taking the prescribed drug holidays

Missing three extra doses during each holiday

Drug Holidays

For a 180 day induction phase, you can have:

FDA-approved combination			Number of drug holidays	Length of each holiday (days)	Minimum subsquent therapy (days)
ABC*	3TC	NVP	16	3	7
ABC*	3TC	EFV	16	3	7
TDF	3TC*	EFV	14	3.5	8.5
ddI	3TC*	EFV	14	3.5	8.5
d4T*	3TC	EFV	50	1	2.5
d4T*	3TC	NVP	50	1	2.5
ddI*	FTC	EFV	13	5	7.5
TDF	FTC*	EFV	7	6	17
TDF	FTC	NVP*	9	5	12.5
ZDV*	3TC	ABC	44	1.33	2.66
ZDV*	3TC	EFV	44	1.33	2.66
ZDV*	3TC	NVP	44	1.33	2.66
ZDV*	3TC	TDF	44	1.33	2.66
ZDV*	DLV	3TC	44	1.33	2.66
ZDV*	DLV	ddI	44	1.33	2.66

* denotes the drug which reaches R_2 first.

Comparison with clinical results

- Long interruptions:
  - SMART trial (2006) - 16 month interruptions
  - DART trial (2008) - 12 week interruptions
- No benefit observed
- SMART trial was halted prematurely due to significant mortality and moribity
- Observed a 2-fold risk of AIDS or death for treatment interruptions greater than 3 months
- Thus, long treatment interruptions do not appear viable.

Short interruptions

- 2-6 week breaks observed no benefit...

  ...but no increase in viral resistance either
- <7 day interruptions resulted in only 5% of participants increasing HIV counts
- Thus, short breaks appear to be tolerable.

FOTO: Five On, Two Off

- A 2007 pilot study
- Guided in part by our earlier modelling
- Virologic suppression in 89.6% of patients
- Excellent adherence and strong preference for this adherence regimen
- FOTO only failed for ZDV, d4T and DLV, which is predicted by our results (max 1.33, 1 and 1.67 days, respectively)
- All others maintained 100% virologic suppression
- Results strongly correlate with our predictions.

Summary

- Inductive therapy is a regimen with an endpoint
- This presents special challenges to adherence
- Treatment interruptions need to be considered on a drug-specific basis
- For all PI-sparing FDA-approved combinations, we can determine the length and number of drug holidays that can be taken, as well as the number of doses that must be taken subsequently
- FOTO therapy is extremely promising and in line with our predictions.

Conclusions

- Induction therapy with partial adherence is tolerable
- However, the outcome depends on the specific drug cocktail
- If treatment interruptions occur, they must be short and followed by a strict period of dose taking
- FOTO is acceptable for all PI-sparing cocktails, except those containing ZDV, d4T or DLV, which can only tolerate extremely short drug holidays.