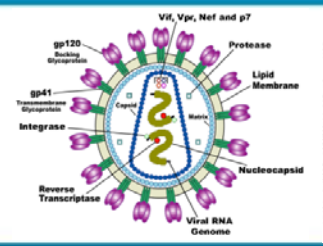
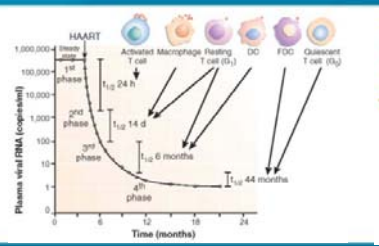
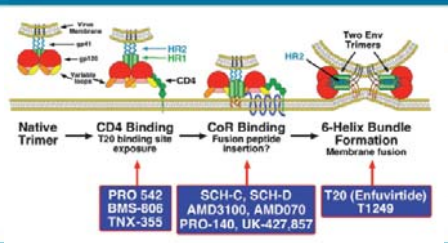
Max von Kleist, PhD student
Research Group Computational Physiology
Hamilton Institute, NUI Maynooth

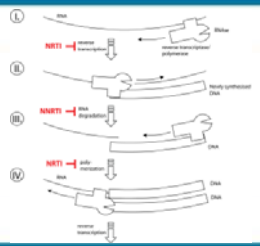
Dr. Wilhelm Huisinga

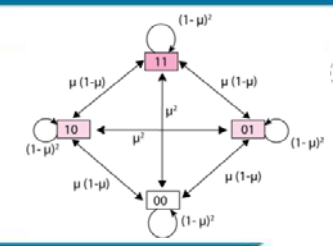
Pharmacokinetics and Pharmacodynamics of antivirals and its connection to viral escape

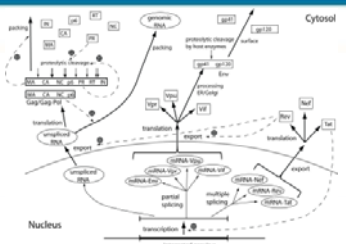












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Outline

- Motivation/Big Picture
  - What do we want?
- Detailed Example
  - What do we do?
  - How do we do it?
- Summary
- Outlook

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HIV, therapy & challenges

- **Motivation/Big Picture**
  - What do we want?
- Detailed Example
  - What do we do?
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- Since 1996 AIDS is treated with
  Highly Active Anti-Retroviral Therapy (HAART)
  - Combination of 2-4 drugs for therapy.
- Combination therapy can suppress, but not eliminate the virus
- Emergence of drug-resistance

- **Motivation/Big Picture**
  - What do we want?
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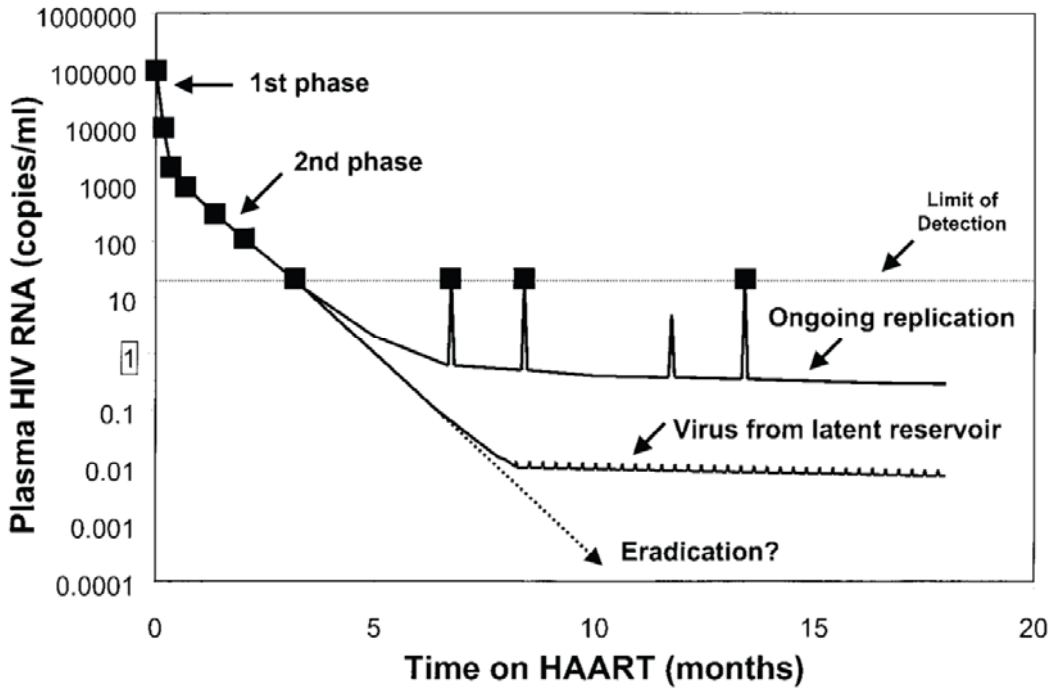
Pierson et al., Ann. Rev. Immunol. (2000)



Theories

I. Latency under suppressive HAART
II. Compartimentalization, sub-optimal HAART

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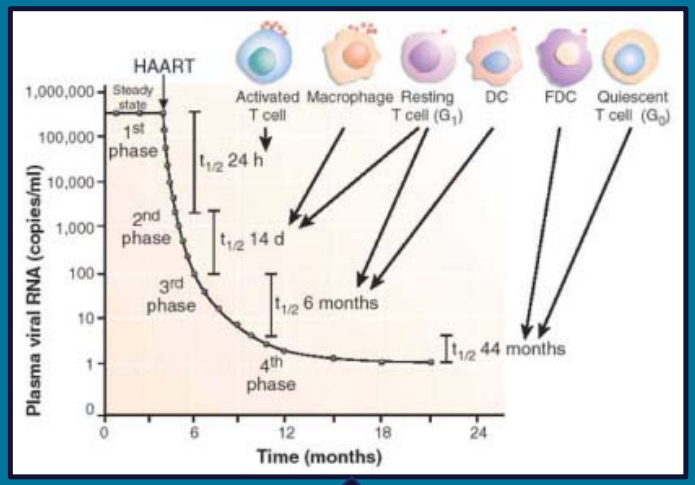
Theories

I. **Latency under suppressive HAART**

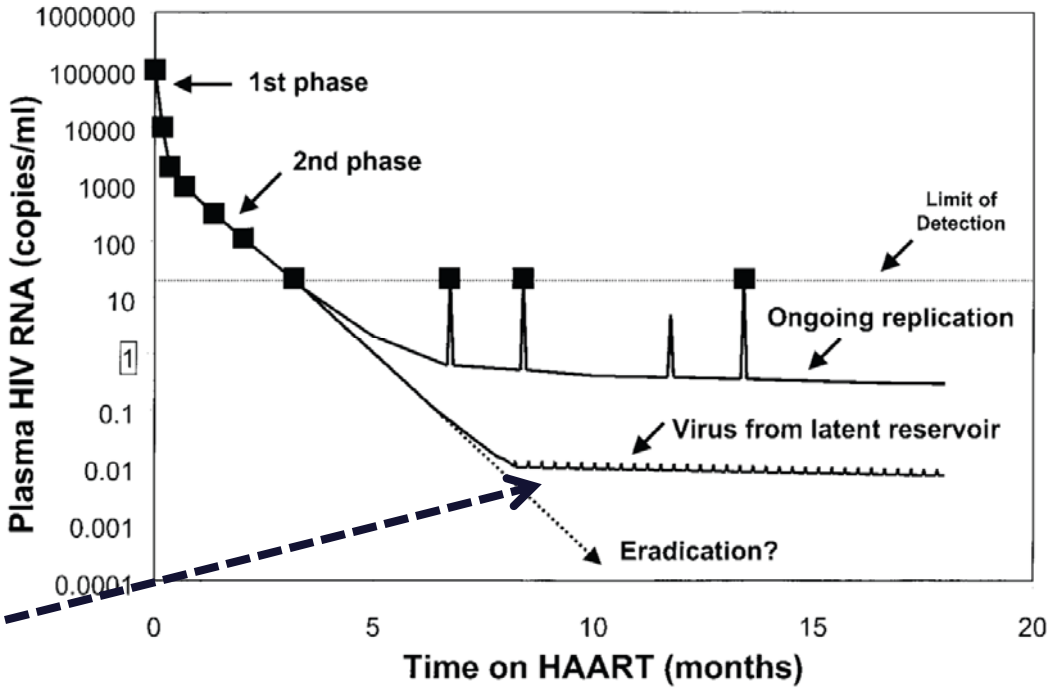
II. Compartimentalization, sub-optimal HAART

Stevenson , Nat. Med. (2003)



Long-lived infected cells

No replication: no mutations



Pierson et al., Ann. Rev. Immunol. (2000)

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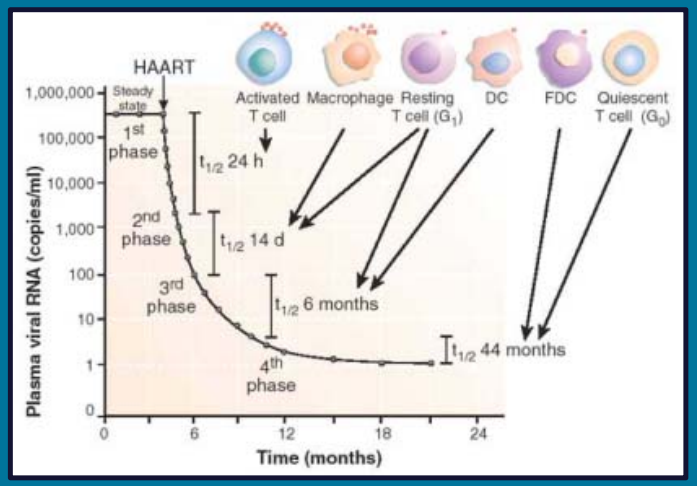
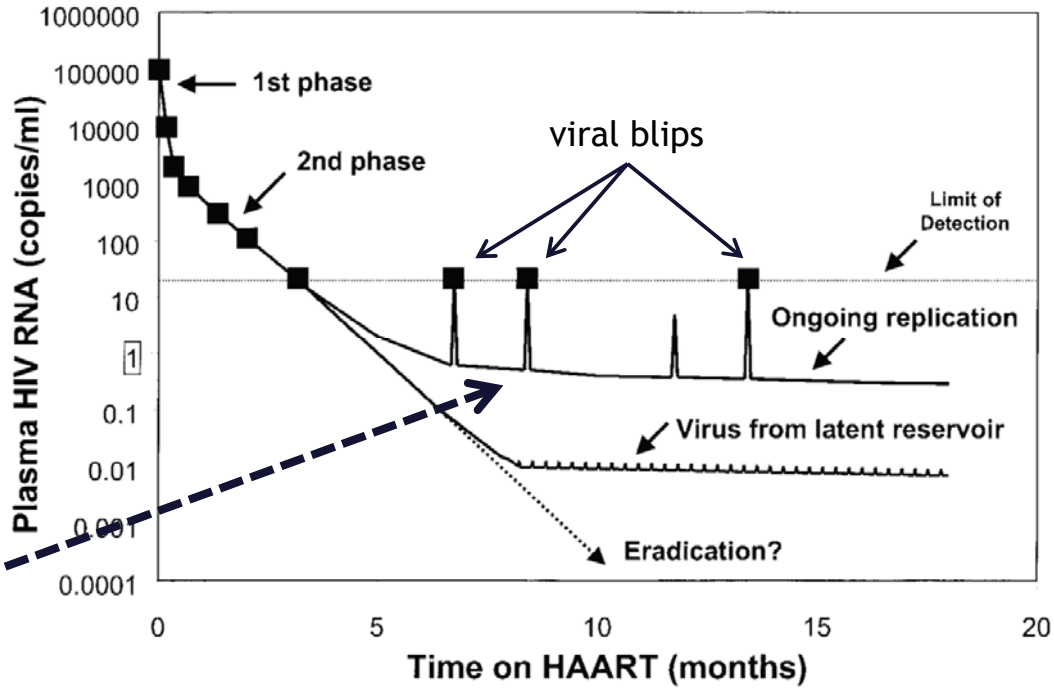
Theories

Target cell diversity



I. Latency under suppressive HAART

II. Compartimentalization, sub-optimal HAART

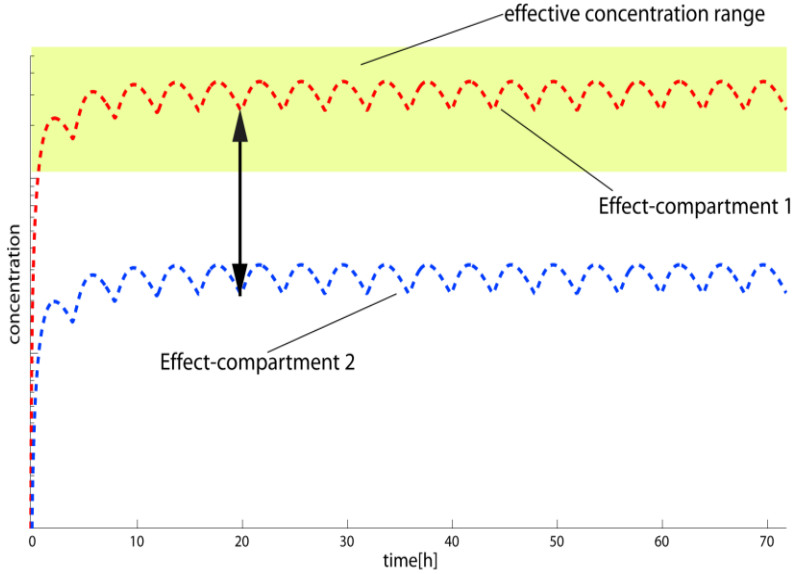


Sub-optimal HAART/ongoing replication: Mutation

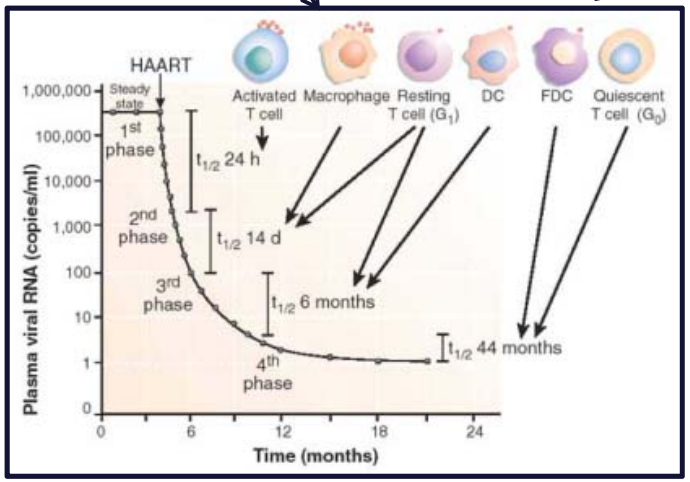
Hypothesis of emergence of drug resistance

Kepler and Perelson, *Drug concentration heterogeneity facilitates the evolution of drug resistance*, PNAS (1998)

Anatomical reservoirs



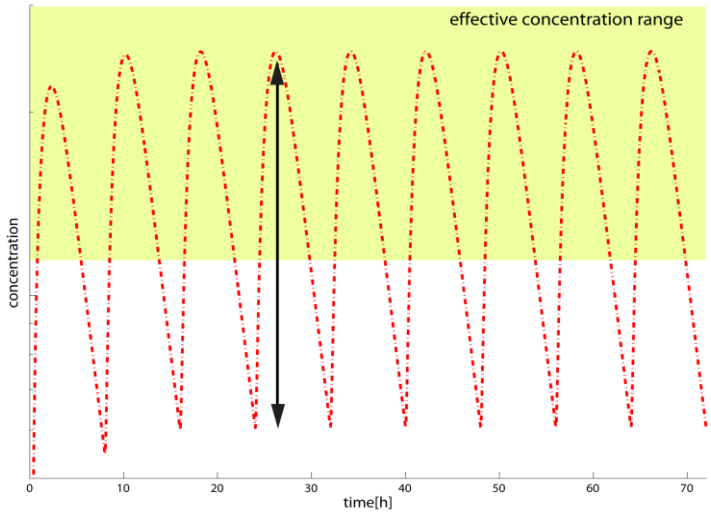
penetration



Hypothesis of emergence of drug resistance

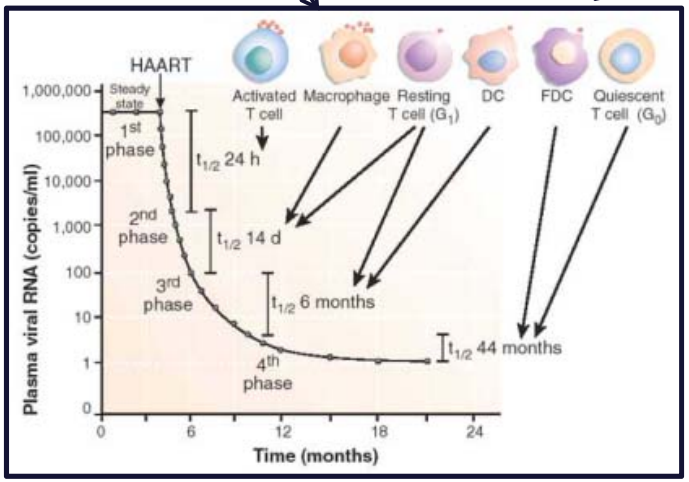
Kepler and Perelson, *Drug concentration heterogeneity facilitates the evolution of drug resistance*, PNAS (1998)

Temporal drug heterogeneities



Kinetics

also:
Compliance
Adherence



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Approach

- **Motivation/Big Picture**
  - What do we want?
- Detailed Example
  - What do we do?
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Question:

- What is the impact of drug pharmacokinetics (concentration heterogeneities) on mutation dynamics and drug resistance?

Methodology:

- Mathematical/analytical approach

1. Detailed, mechanistic Models
2. Model reduction
   - Clinical applicability

Utilization of few detailed studies, to interpret the majority of less detailed studies

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Detailed Example

- What do we do?
- How do we do it?

Max von Kleist and Wilhelm Huisinga, *Pharmacokinetic-Pharmacodynamic relationship of NRTIs and its connection to viral escape: An example based on Zidovudine*, Eur J Pharm Sci. 36 (2009), pp. 532-543

HIV -treatment

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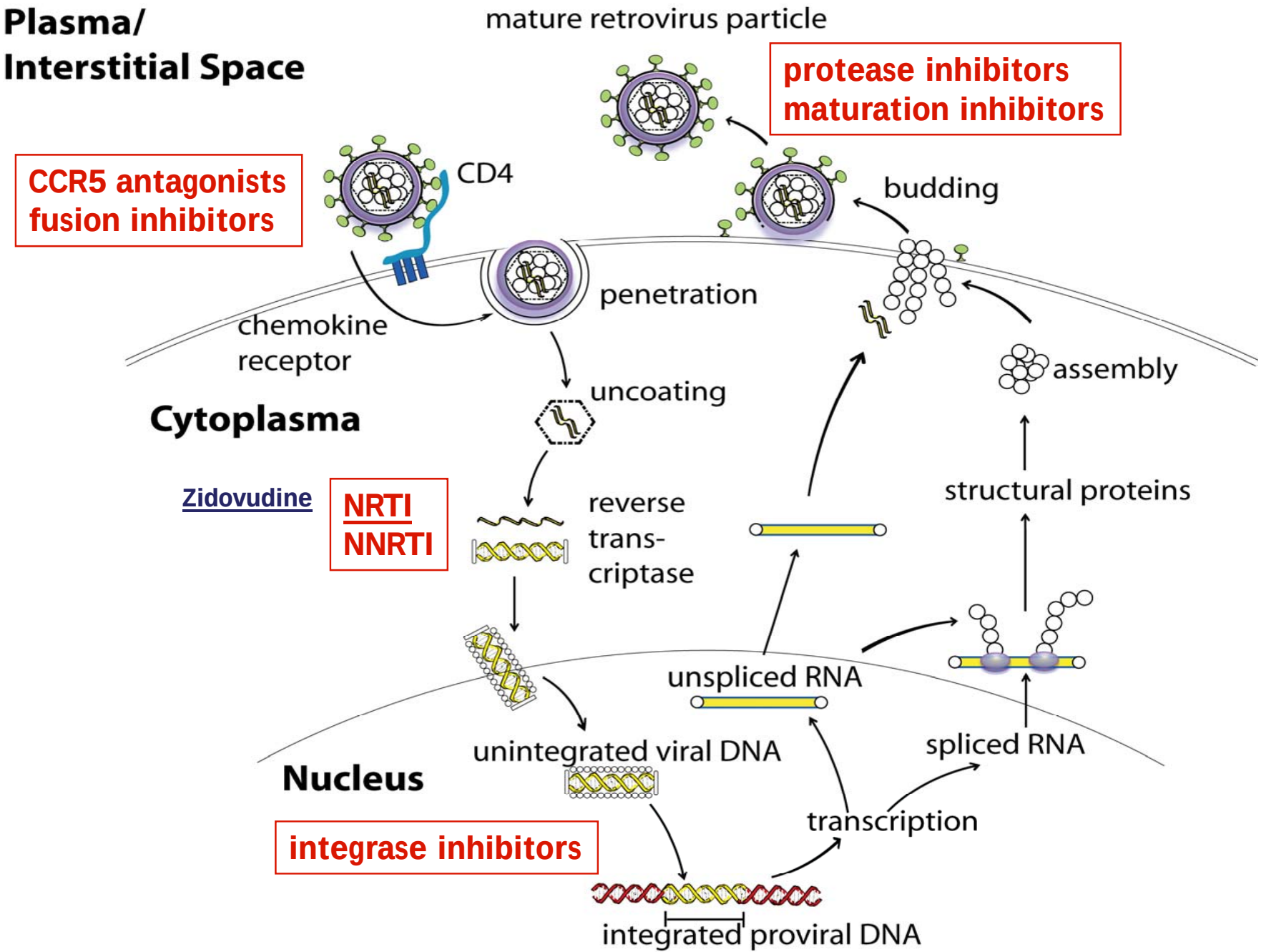

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PK-PD relationship NRTIs: Example AZT

- Motivation/Big Picture
  - What do we want?
- **Detailed Example**
  - What do we do?
  - How do we do it?
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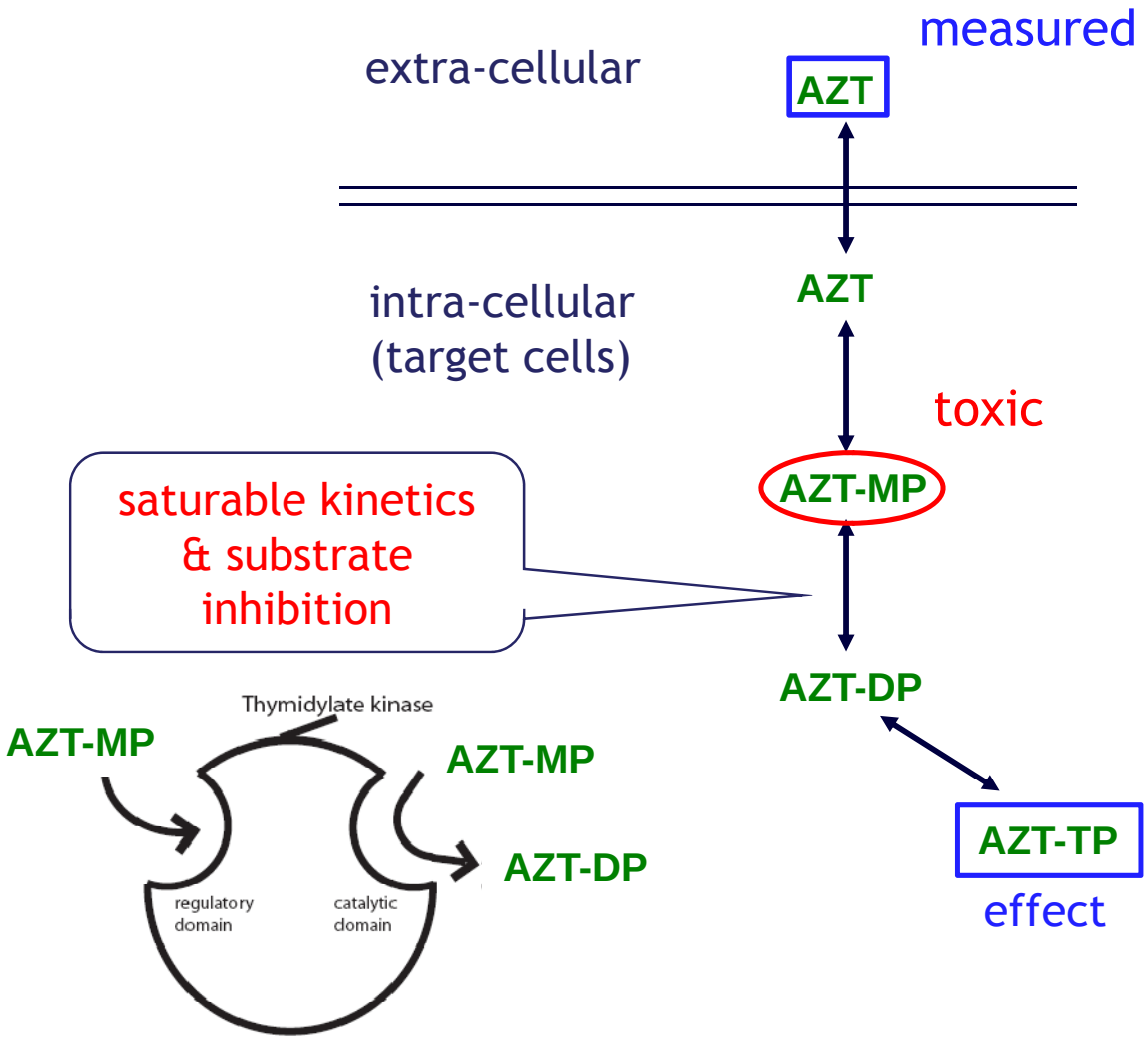
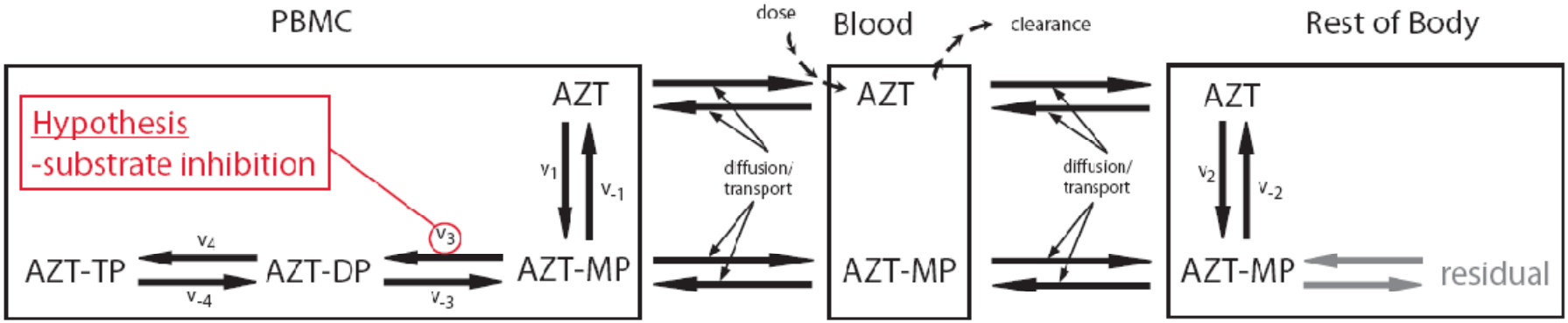
- Outlook

NRTIs – important drug class in HAART

- Intracellular pharmacokinetics of zidovudine (AZT)

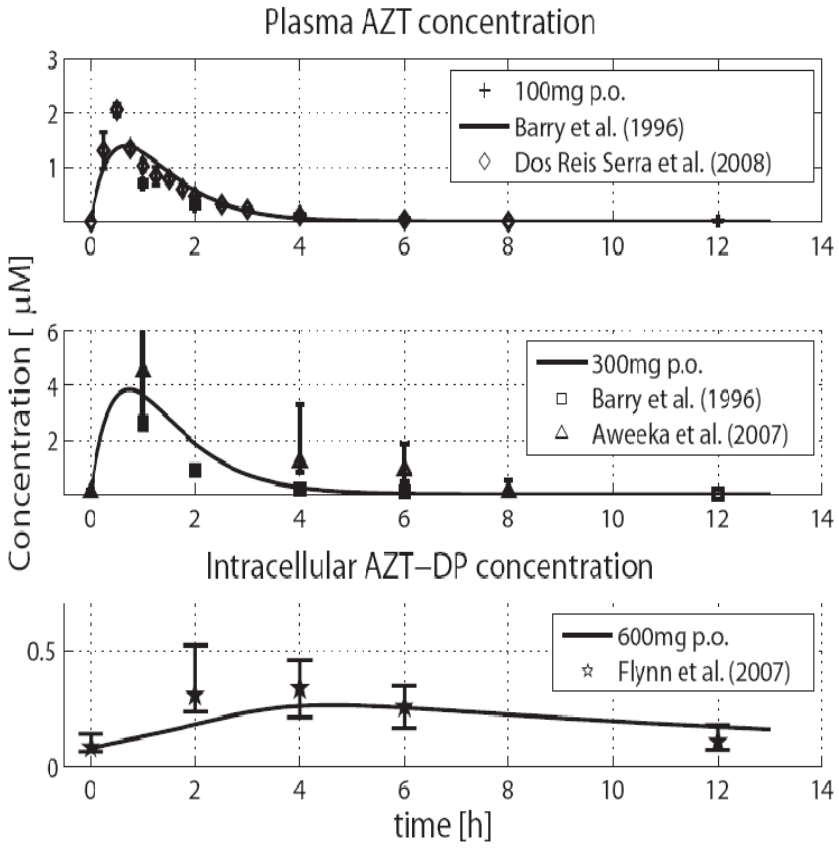


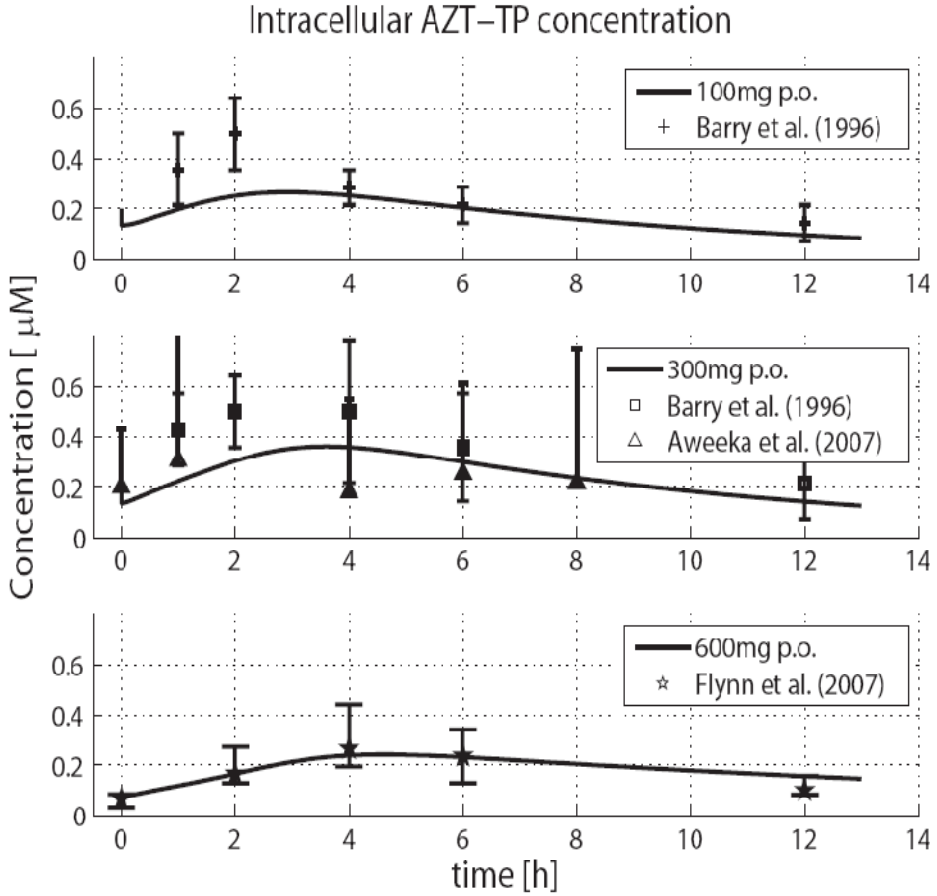
PBPK model for AZT

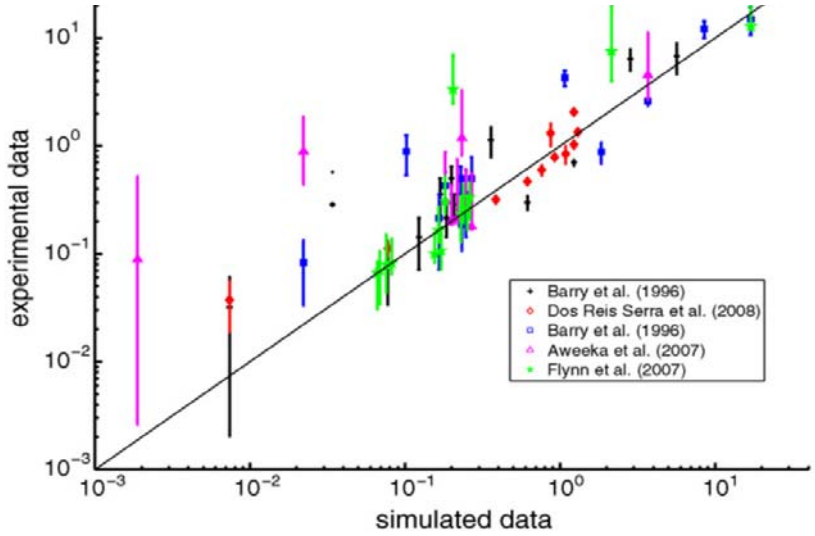


- Parametrization of the PBPK model
  - 25 physiological, pharmacokinetic and physico-chemical parameters (22 in vivo/in vitro parameters, 3 estimated from in vivo data)

Model Validation







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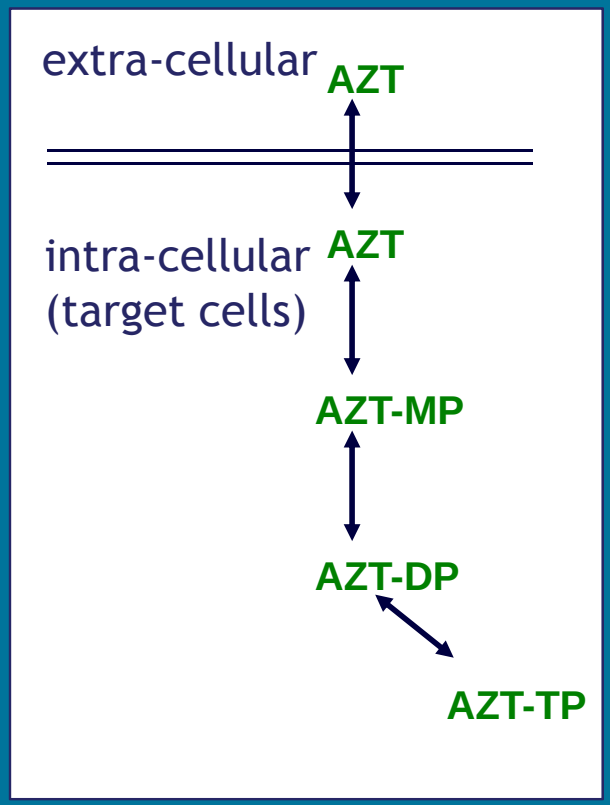
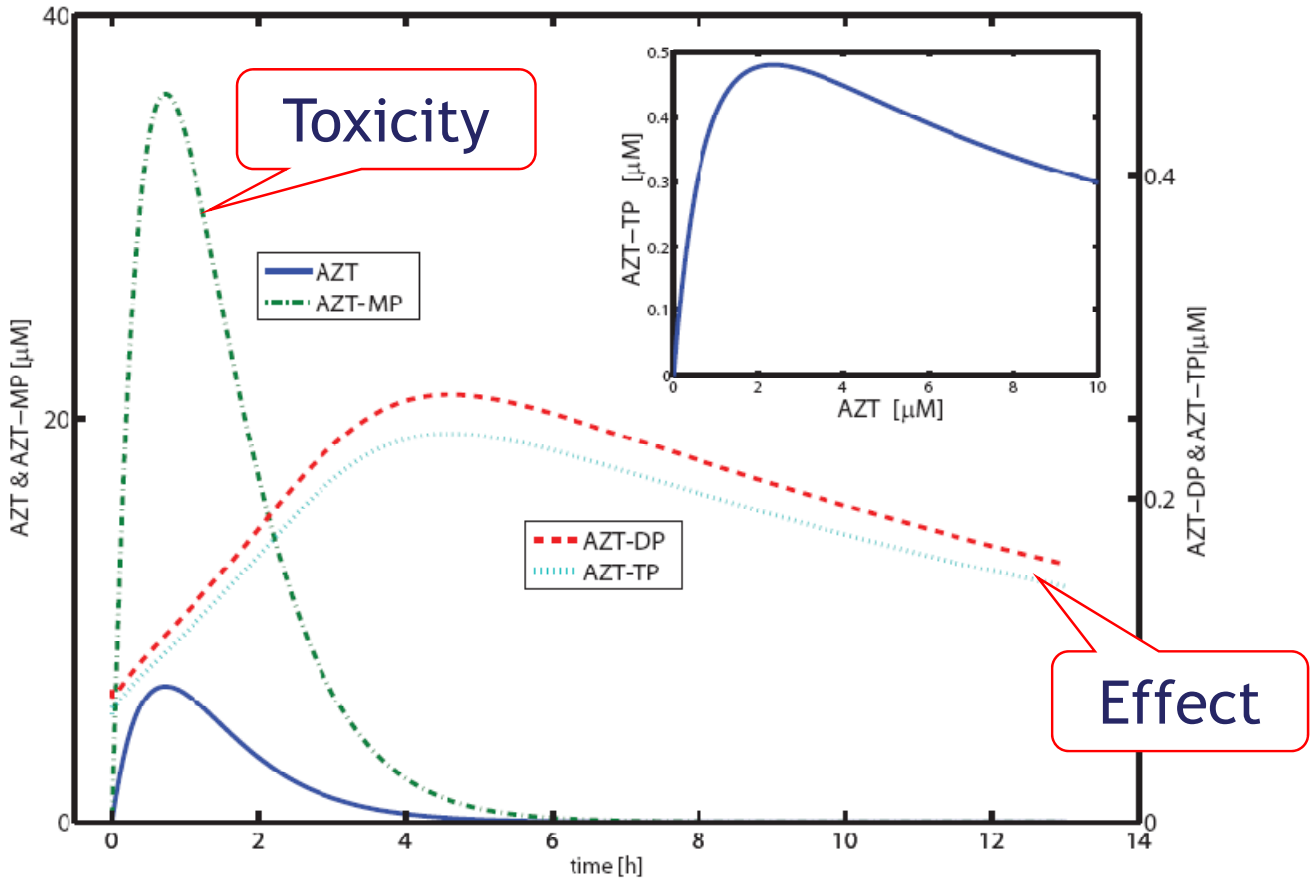
Pharmacokinetics of AZT: Evaluation





- More Dose - More Toxicity
- More Dose - Less Effect

- Motivation/Big Picture
  - What do we want?
- **Detailed Example**
  - What do we do?
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What is the best dose?

➢ understand Pharmacodynamics (Effect)

…. Optimize dosing schedule

Effect of NRTIs

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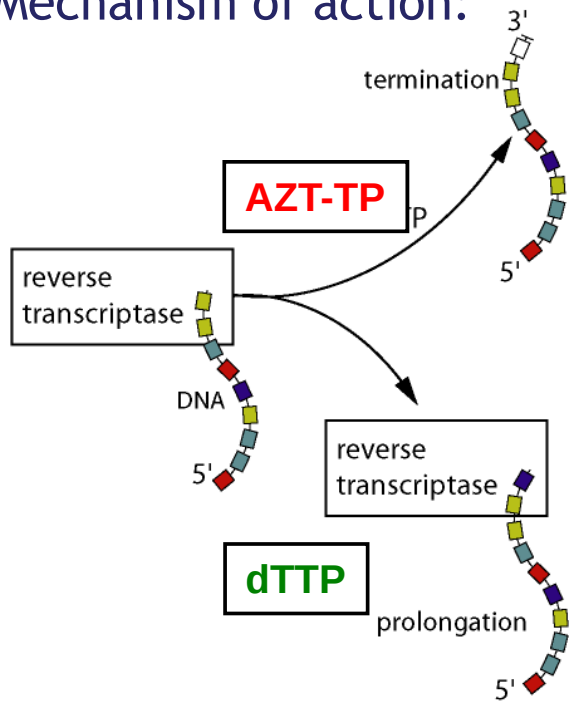
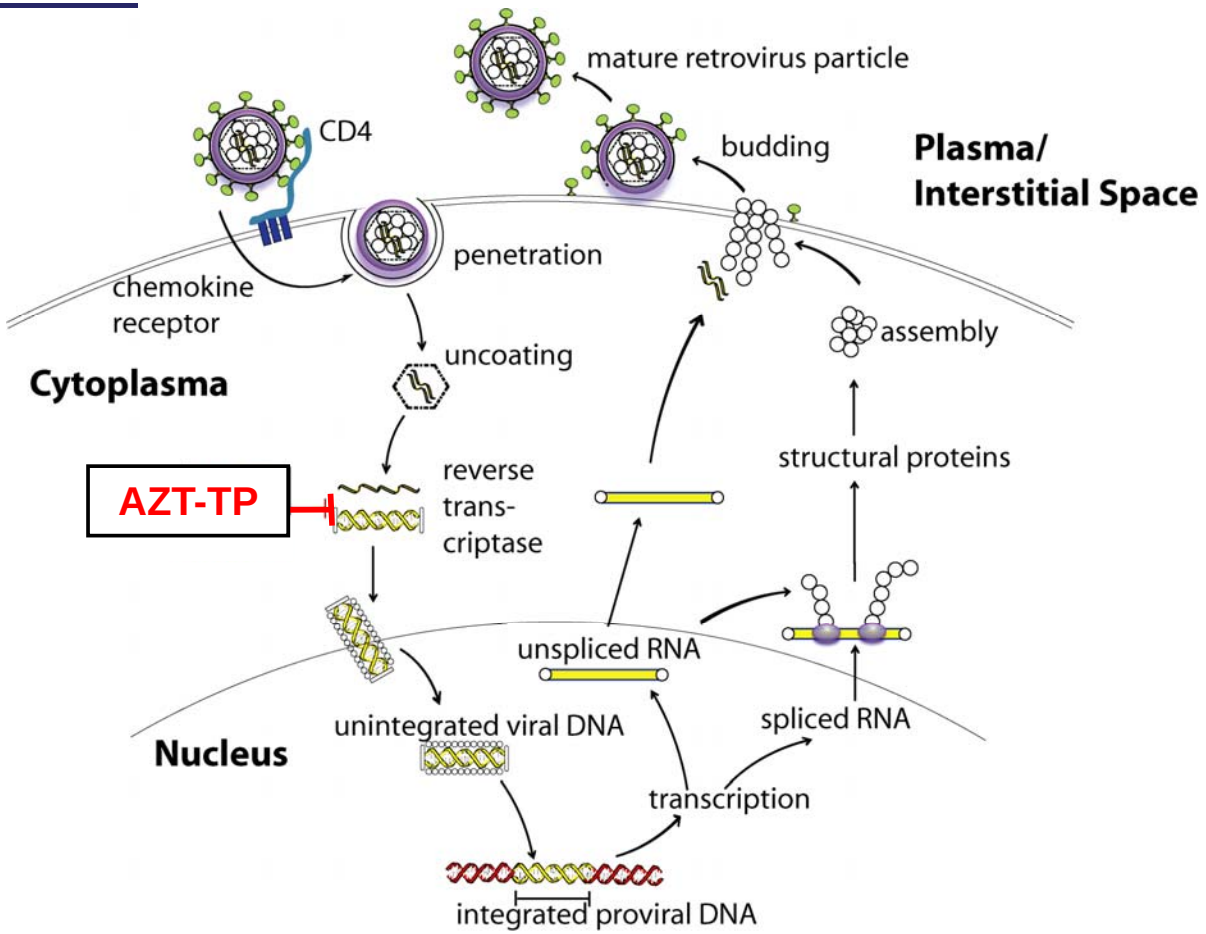
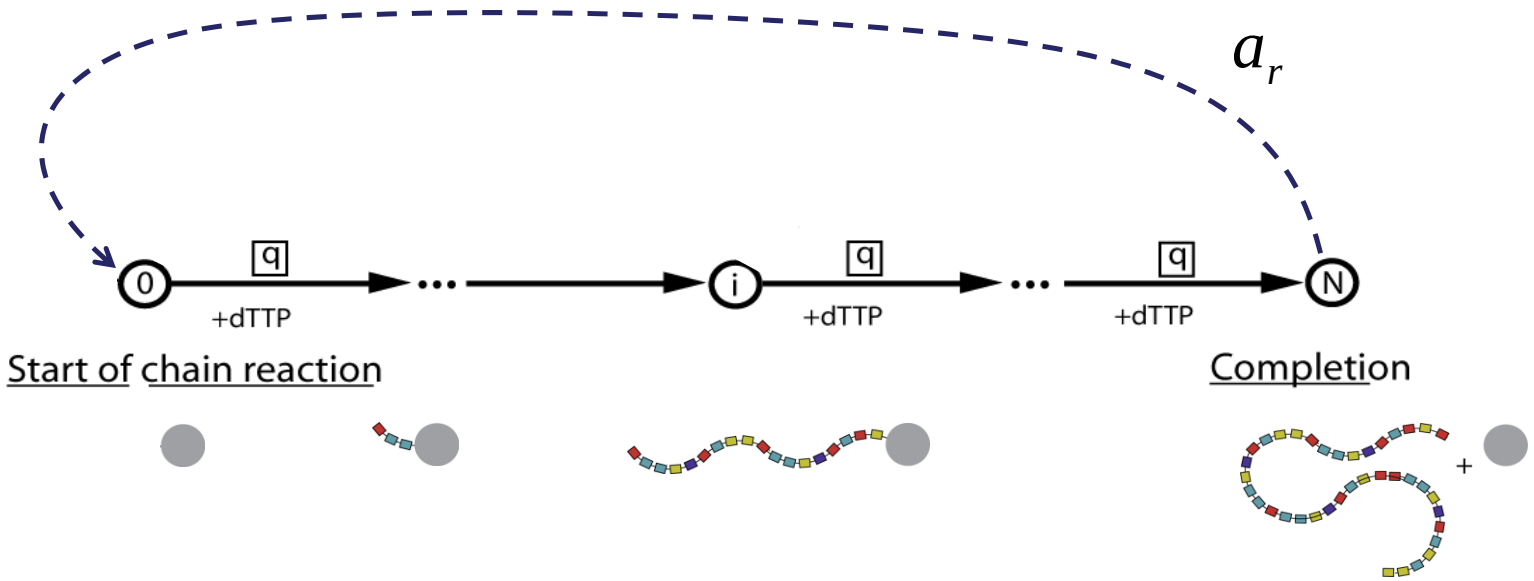
Reverse transcription = **chain reaction**

Mechanism of action:



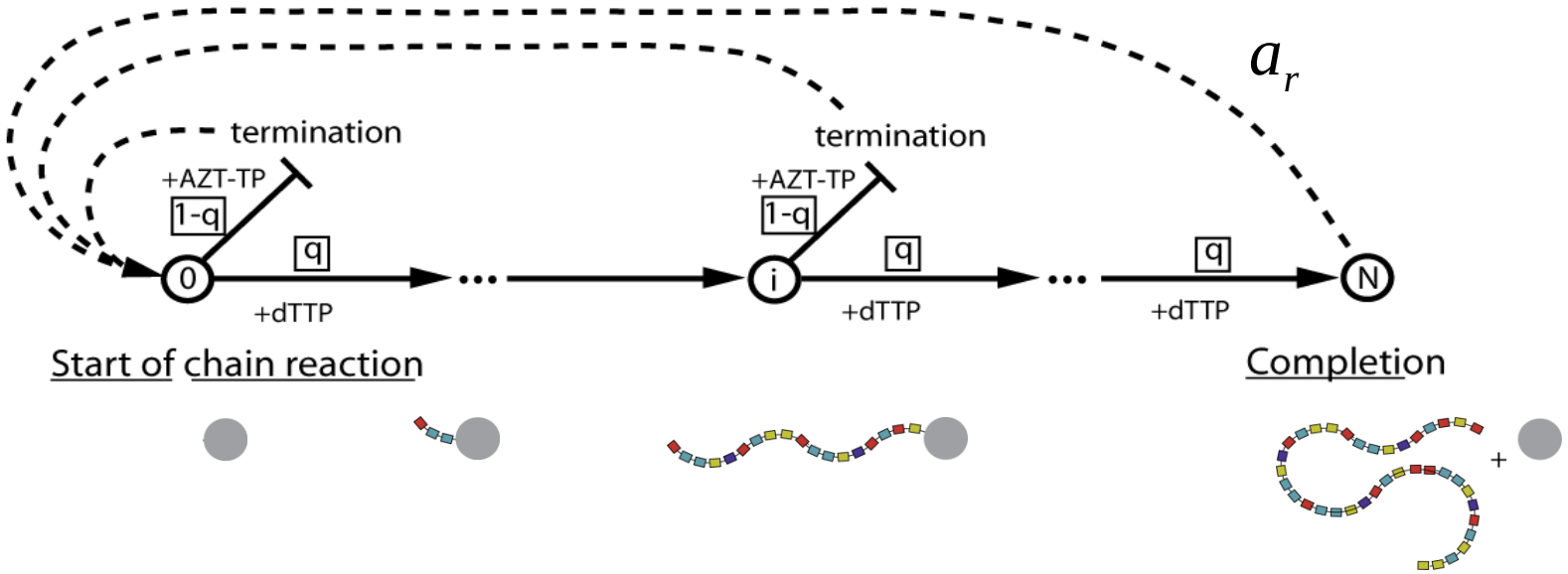


Reverse transcriptase chain reaction



- #thymidine bases: N = 3272 (RNA→DNA) + 2042 (DNA→DNA) ≈ 5300

Effect-Model for NRTIs



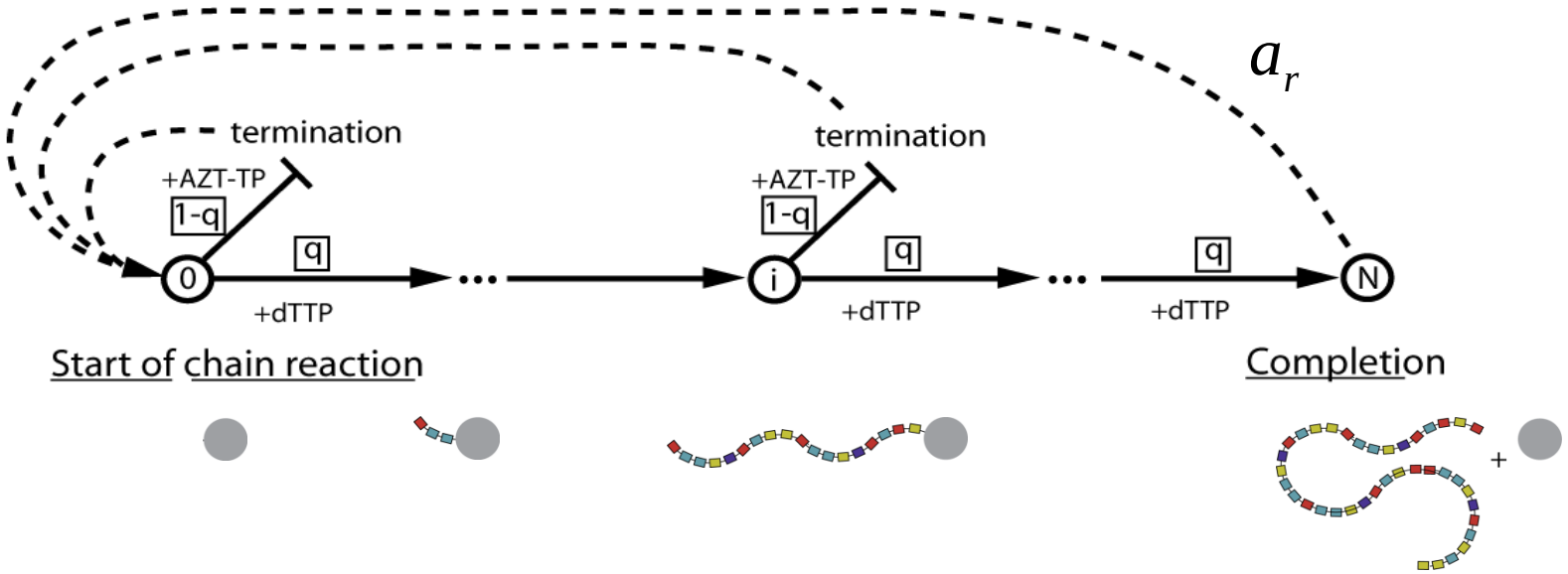
Drug effect = Deceleration of the chain reaction
math:Prolongation of the transit time 0→N

- Likelihood of prolongation:

$$q = \frac{1}{1 + \frac{\mathrm{TP}}{\mathrm{dTTP}} \cdot \frac{K^{\mathrm{RT}}_{\mathrm{m,dTTP}}}{K^{\mathrm{RT}}_{\mathrm{m,TP}}}}$$

- Parameters can be derived from single nucleotide extension assays

Effect-Model for NRTIs



- Percentage reduction in reverse transcription process:

$$p = C \cdot q^{N}$$

with

$$q = \frac{1}{1 + \frac{\mathrm{TP}}{\mathrm{dTTP}} \cdot \frac{K^{\mathrm{RT}}_{\mathrm{m,dTTP}}}{K^{\mathrm{RT}}_{\mathrm{m,TP}}}}$$

Likelihood termination (1-q)	Residual reverse transcription (p)
0.01 %	≈ 60 %
0.1 %	≈ 0.7 %
1 %	≈ 10^{-20} %

Sensitivity of the effect-Model

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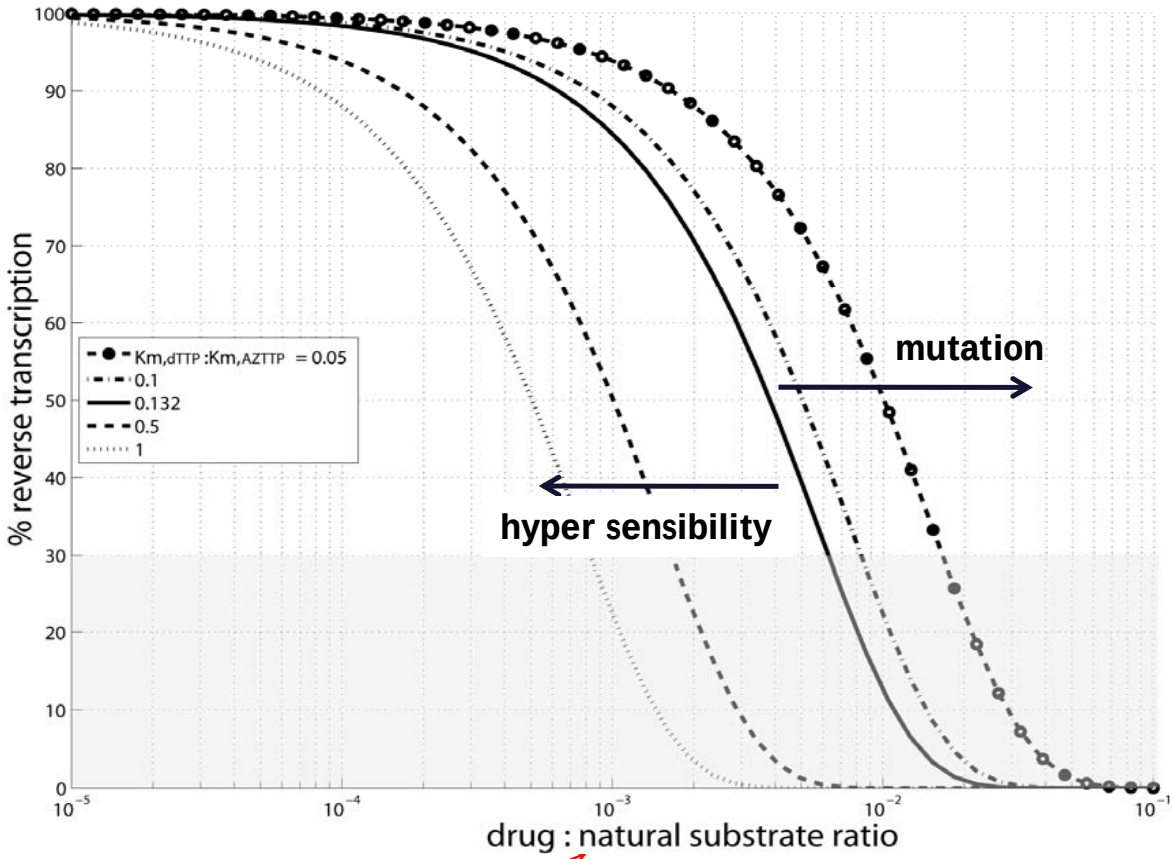

$$q = \frac{1}{1 + \frac{\mathrm{TP}}{\mathrm{dTTP}} \cdot \frac{K^{\mathrm{RT}}_{\mathrm{m,dTTP}}}{K^{\mathrm{RT}}_{\mathrm{m,TP}}}}$$

$$p = C \cdot q^{N}$$

Combining pharmacokinetics and pharmacodynamics

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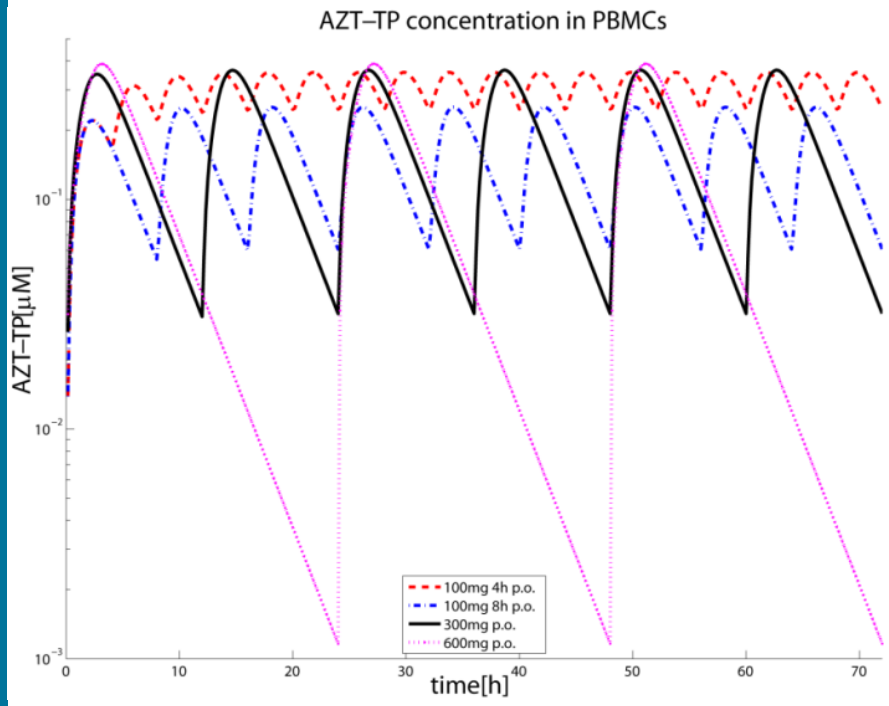
What is the best dose?



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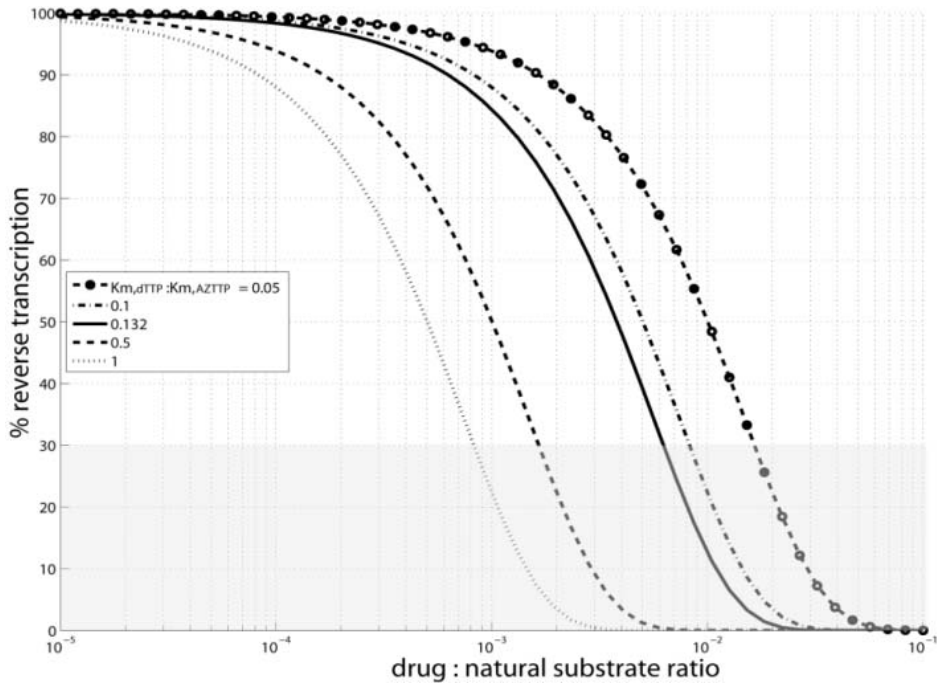
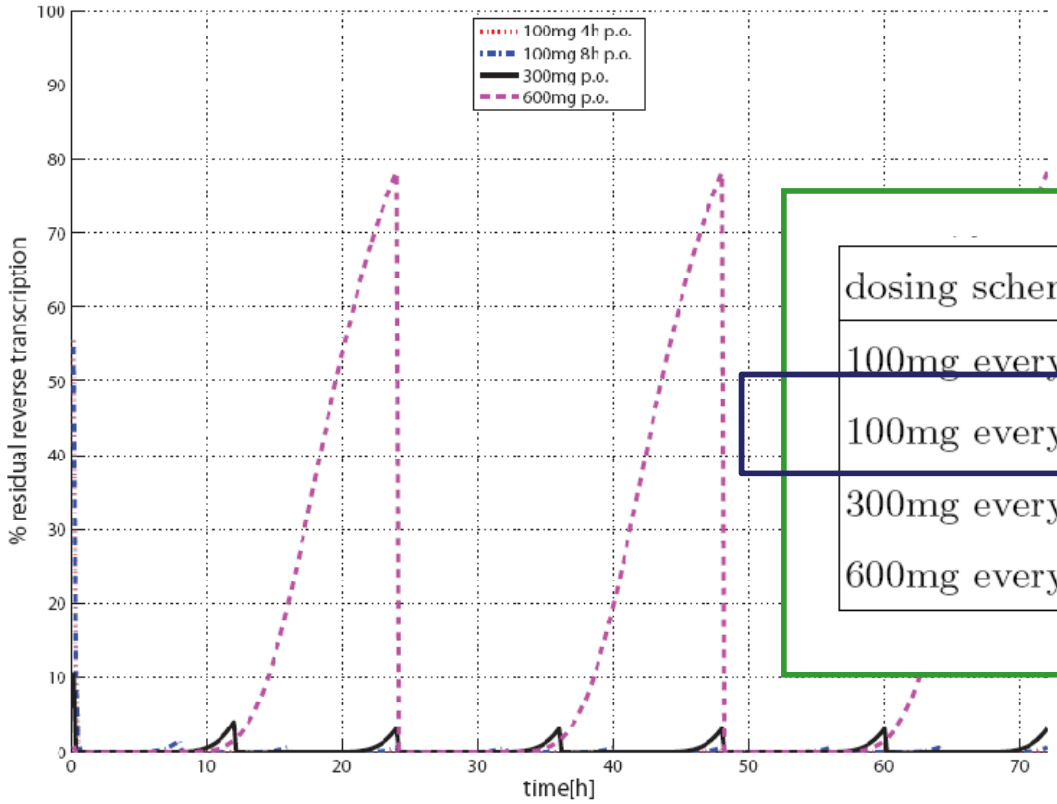


Tested dosing schemes

- 100mg every 4h
- 100mg every 8h
- 300mg every 12h
- 600mg every 24h

Residual reverse transcription with different dosage regimes



Toxicity

Effect

dosing scheme	AUC_{0-24} (AZT-MP)	% res. RT activity
100mg every 4h	70.4 [h·μM]	$3.6 \cdot 10^{-8}$
100mg every 8h	35.4 [h·μM]	$5.9 \cdot 10^{-2}$
300mg every 12h	70.8[h·μM]	0.26
600mg every 24h	70.8 [h·μM]	18.9

- Some dosage regimes provide insufficient antiviral suppression for several hours
- Important implications for drug compliance

- Motivation/Big Picture
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- **Summary**
- Outlook

Question:

- What is the impact of drug pharmacokinetics/concentration heterogeneities on resistance dynamics?

Methodology:

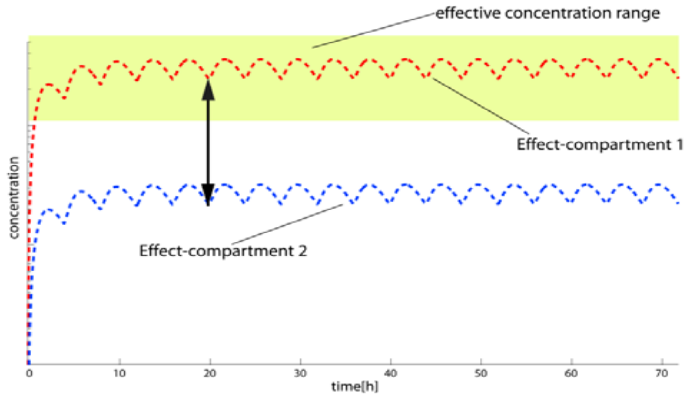
- (mechanistic) Pharmacokinetic modelling
- (mechanistic) Pharmacodynamic modelling
- Utilization of different in vivo/in vitro information

➢ Theoretic insights
➢ Model reduction: What are the essential features?
➢ Translation into practice

What are the dynamics of resistance development?

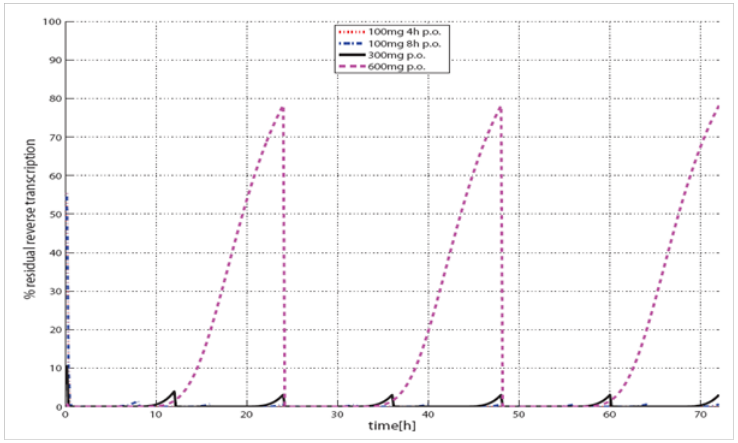
- Where?

pharmacokinetics



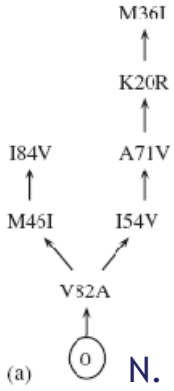
- When?

PK-PD



- How?

Ordered accumulation of mutations



N. Beerenwinkel et al. PNAS (2002)

Outlook

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- How can resistance development be avoided?
- Optimize HAART to avoid drug resistance development

Thank you for your attention!

Acknowledgements

Niko Beerenwinkel, ETH Basel, Switzerland

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Sabine Pilari Sebastian Ueckert