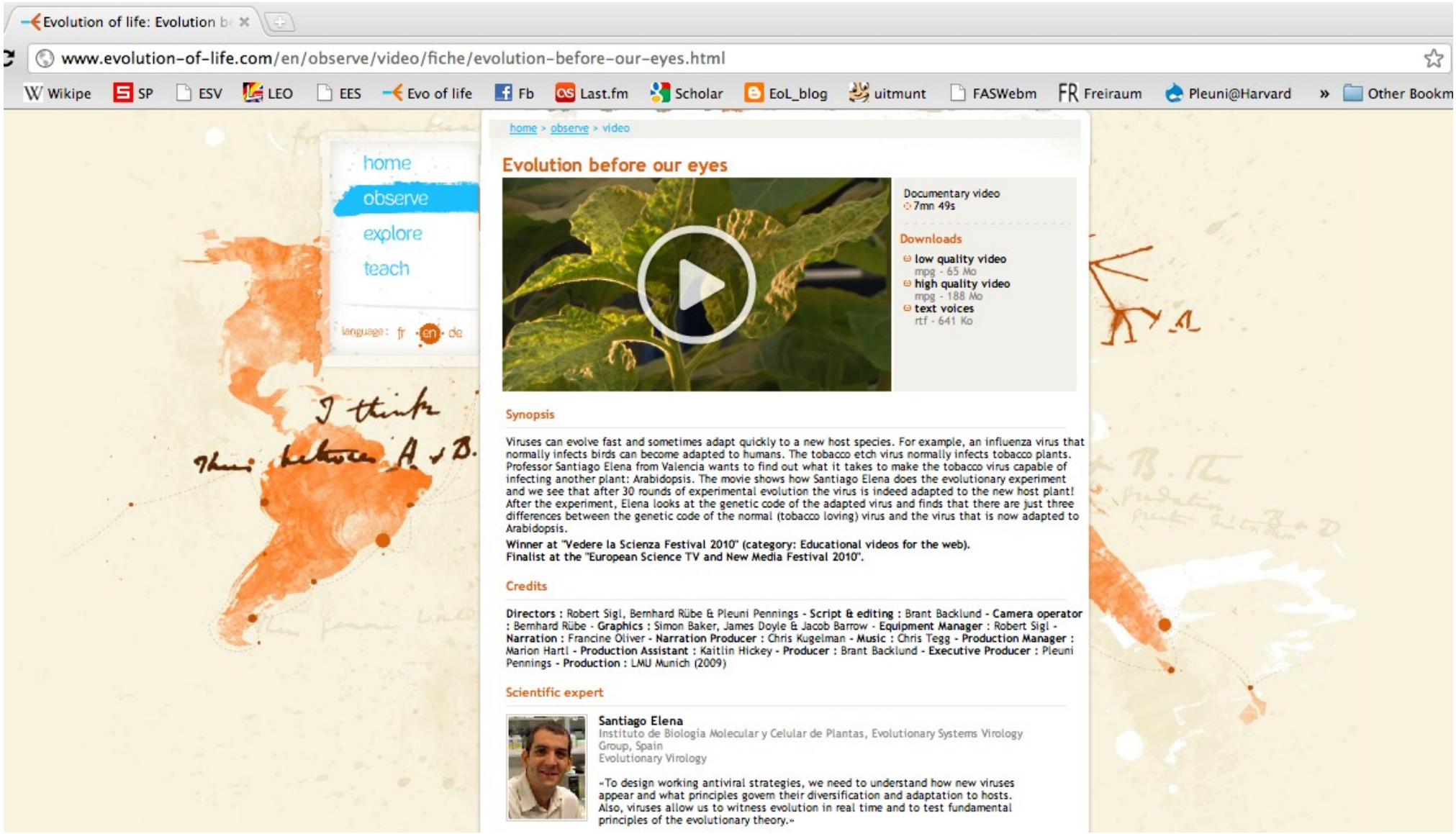
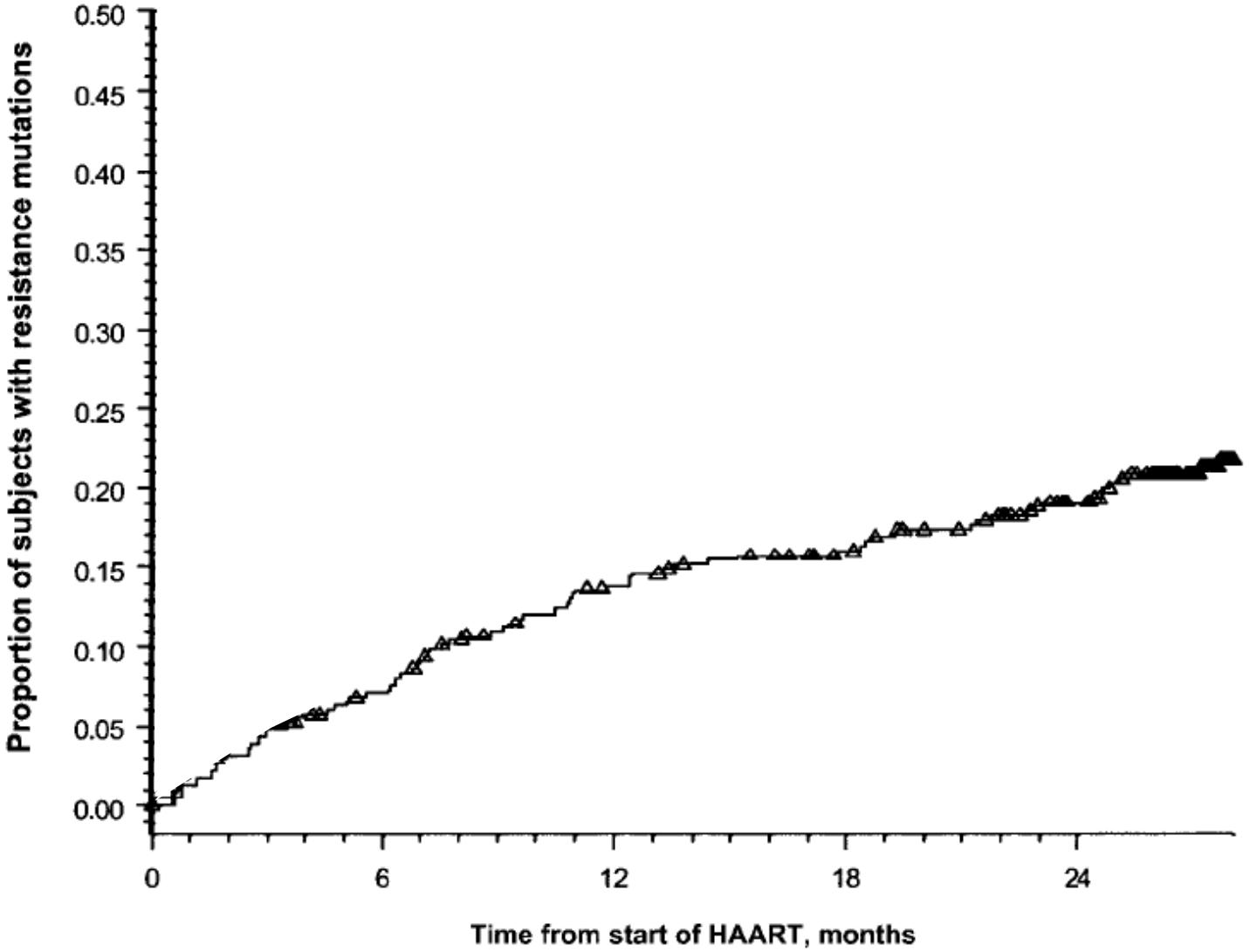
Evolution of life



What determines the rate of evolution of resistance of HIV?

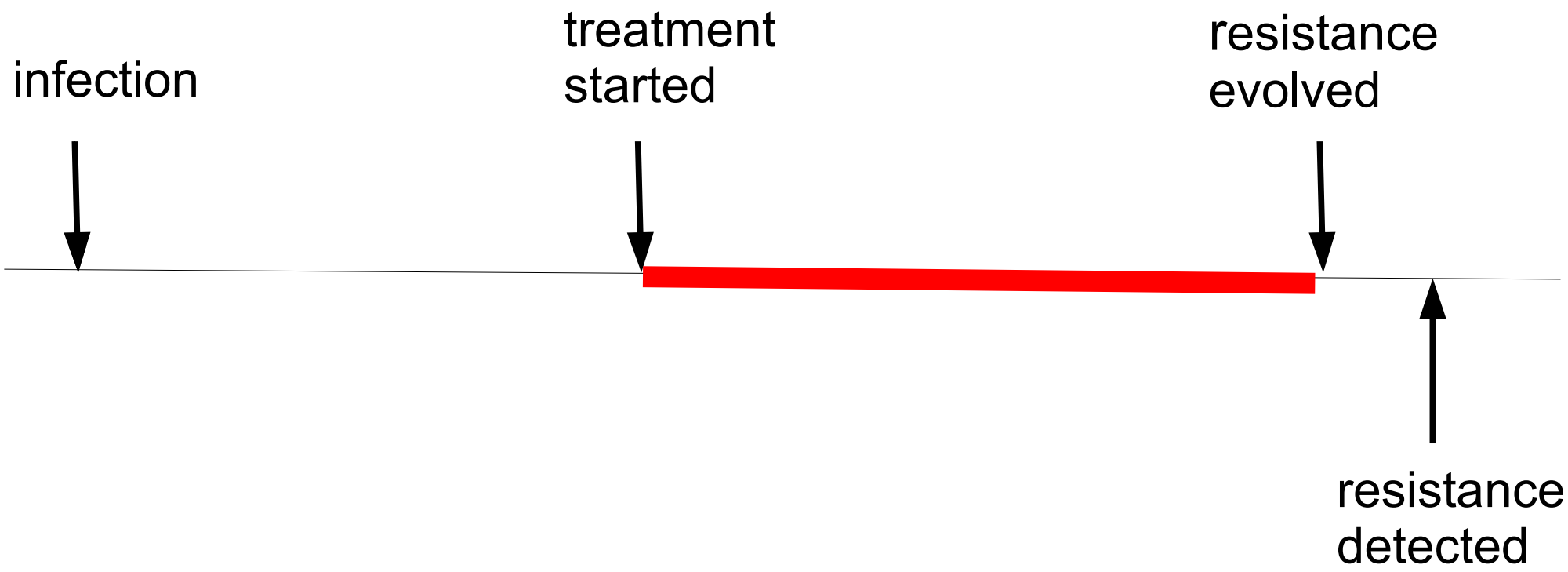
Pleuni Pennings
March 2011
KITP, Santa Barbara

Distribution of waiting times

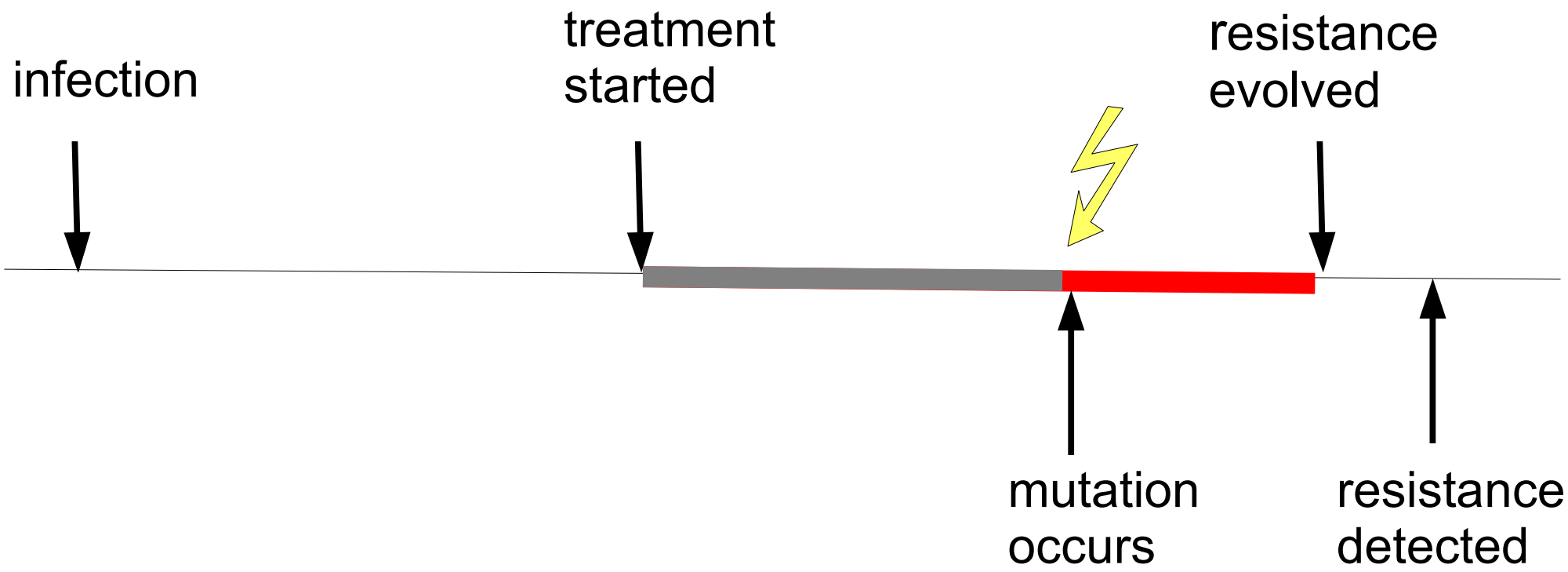


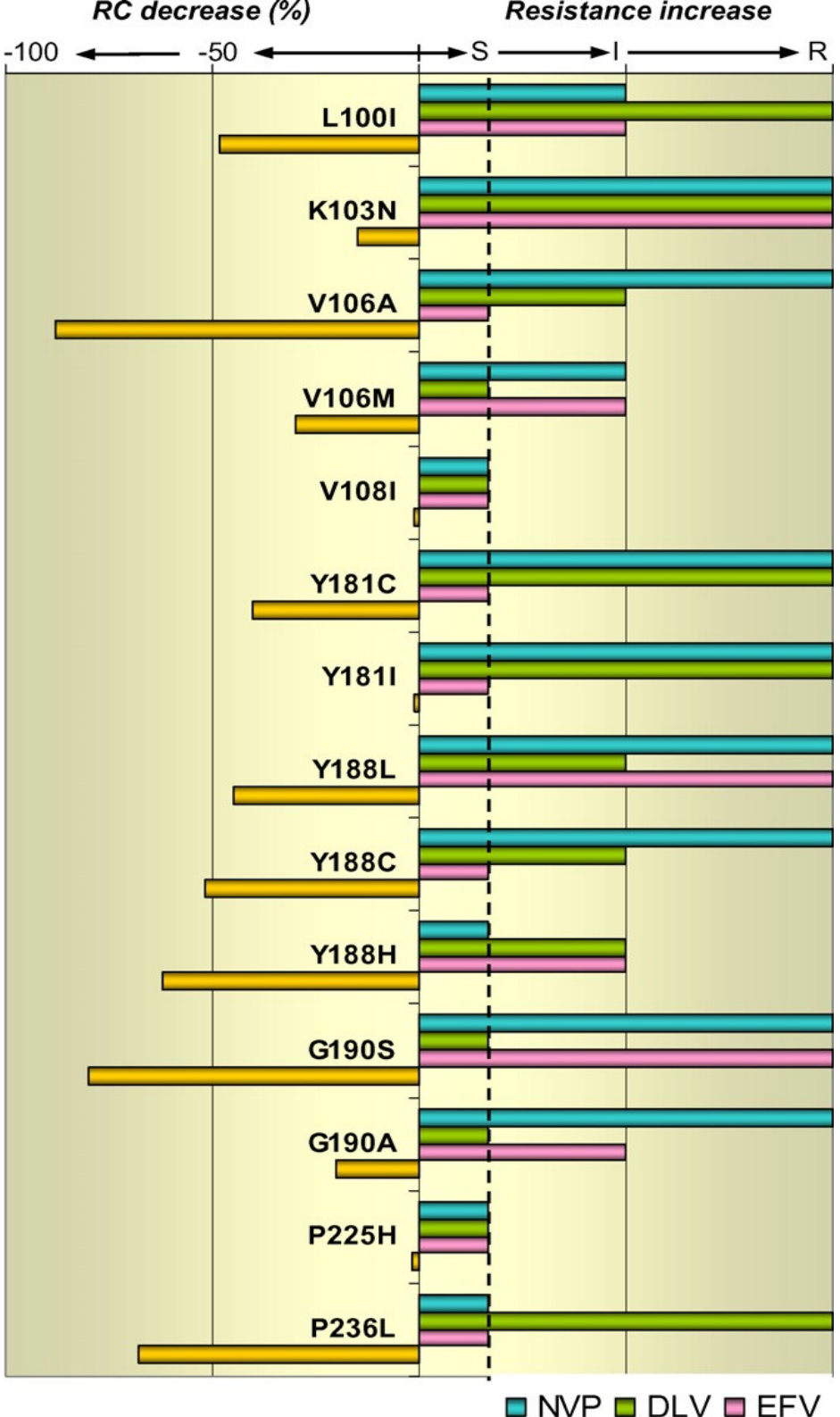
Harrigan 2005 JID

Timeline


infection
treatment started
resistance evolved
resistance detected

Timeline

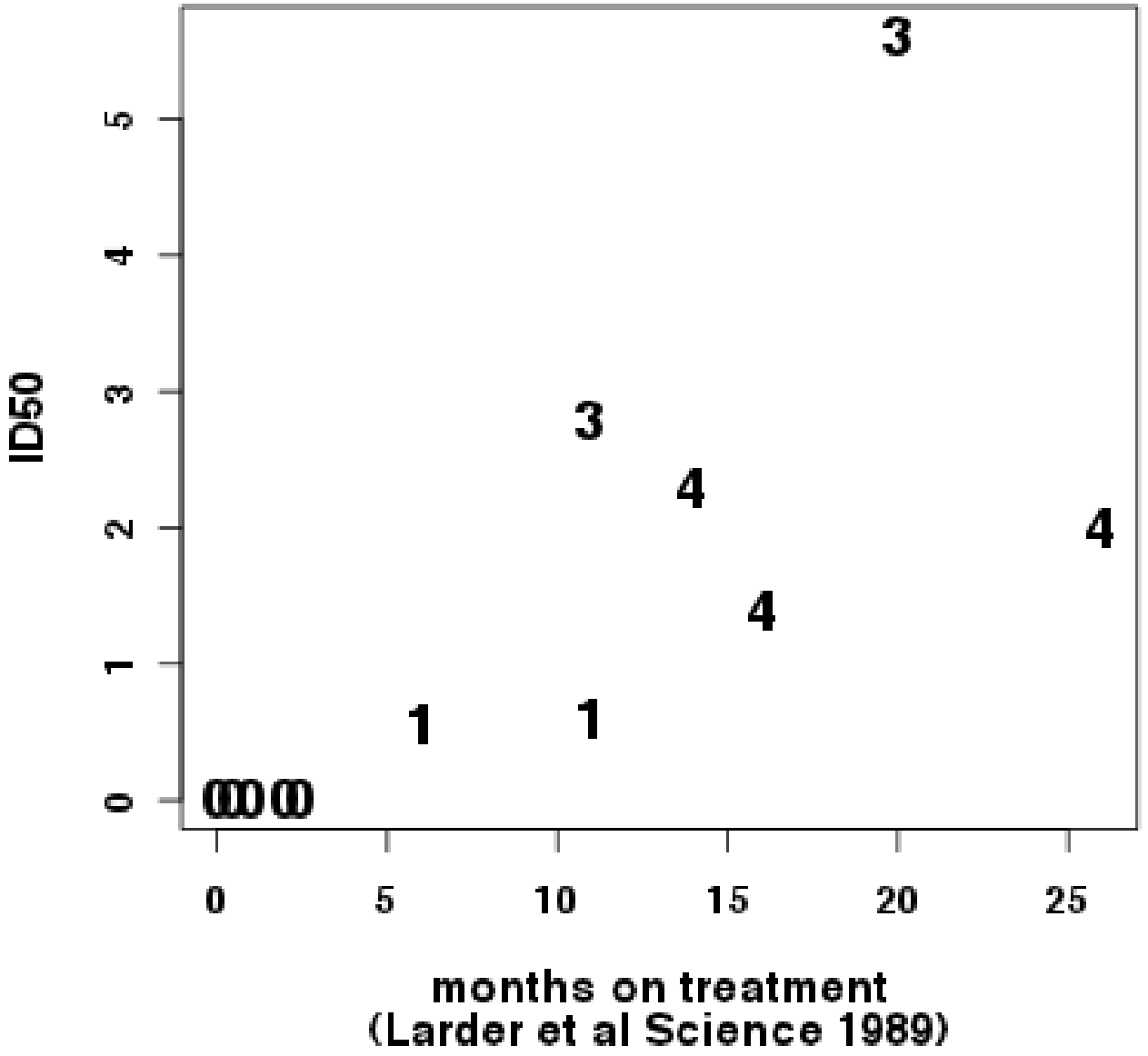

infection
treatment started
resistance evolved
mutation occurs
resistance detected



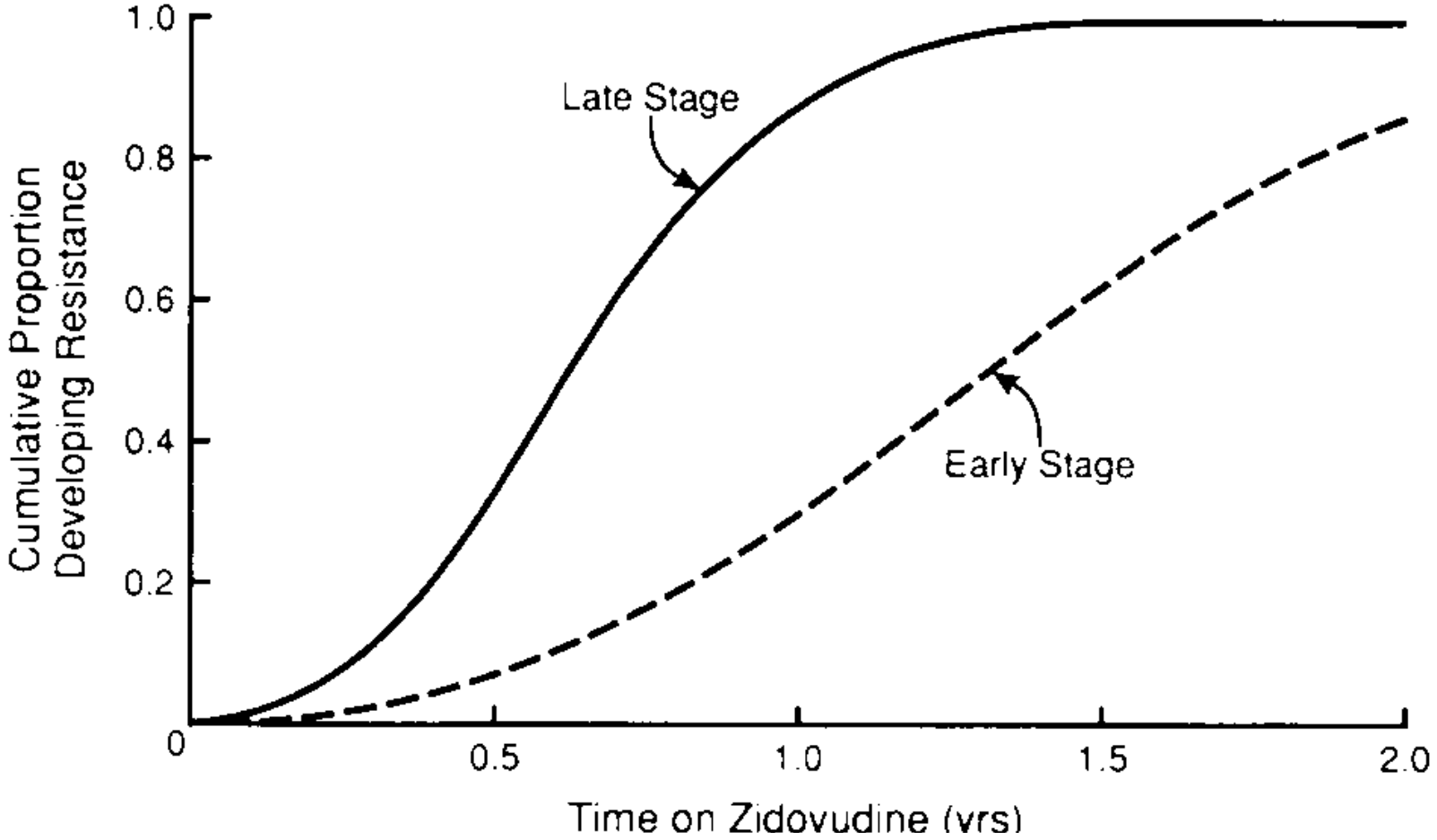
Mutations are well characterized

Martinez-Picado 2008
Virus Research

Resistance against AZT in 12 patients

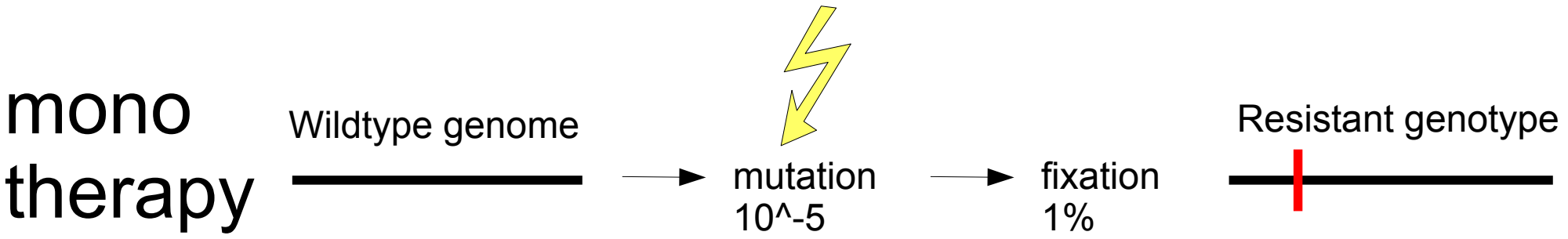


Evolution is mutation limited



Richman et al 1990 JAIDS

Why combination therapy works



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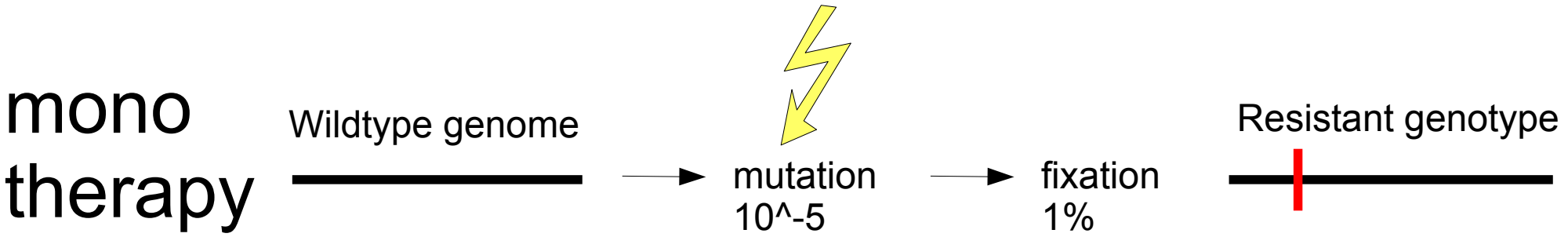
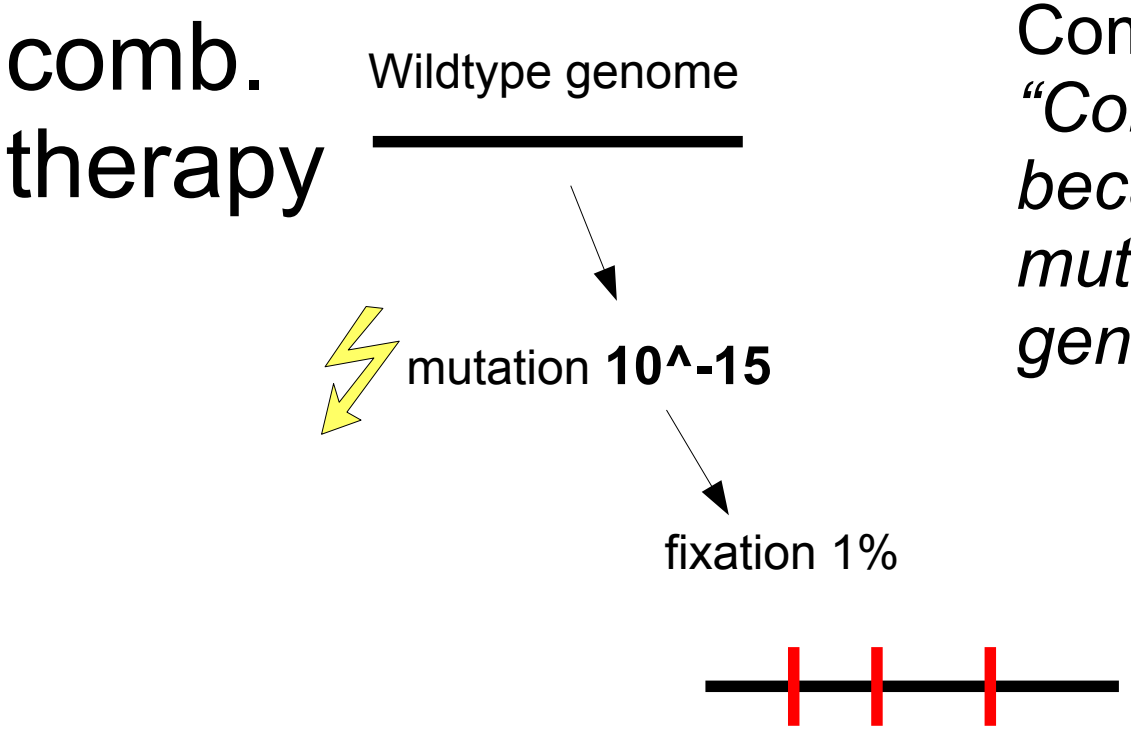
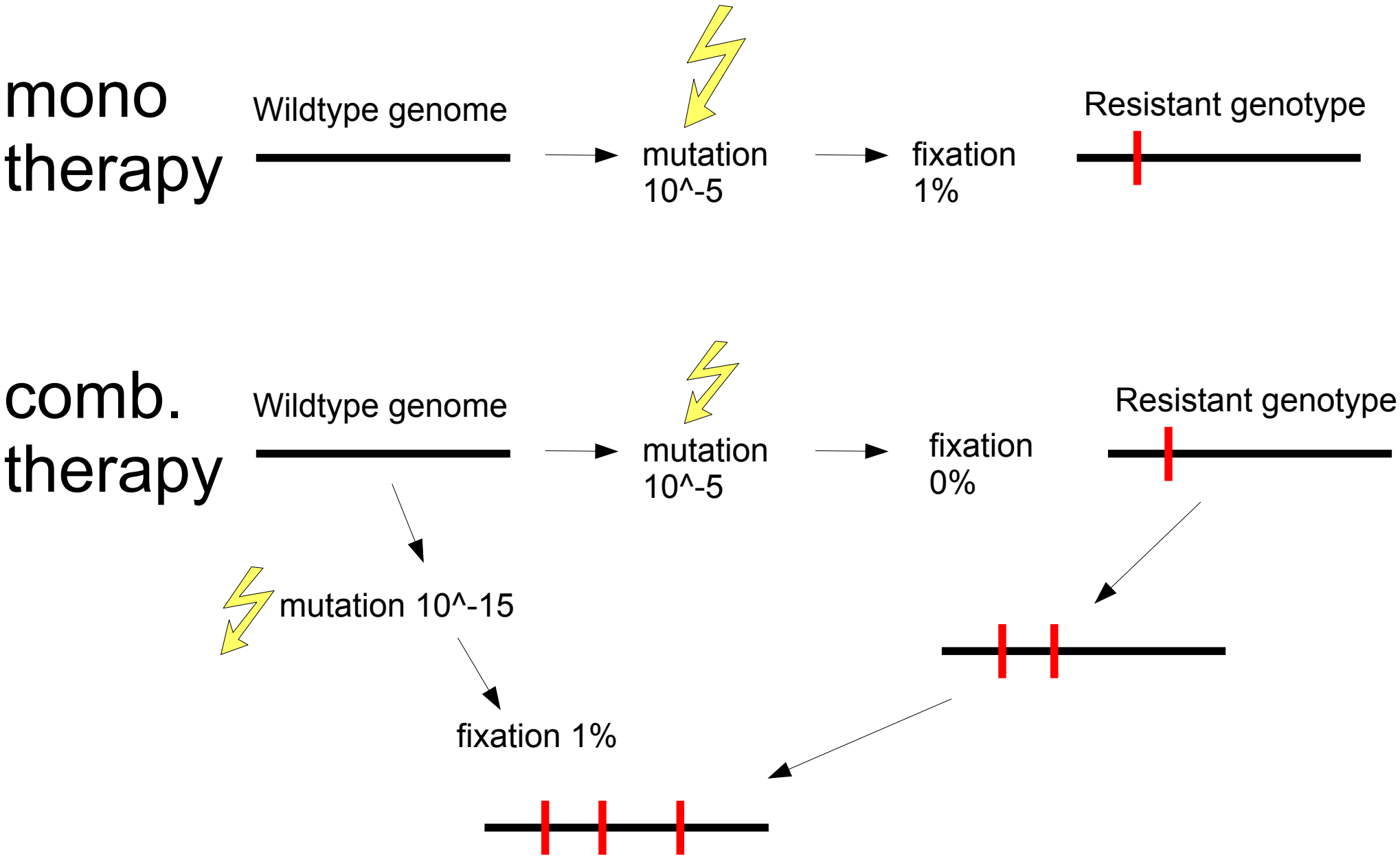




Common belief:
"Combination therapy works because it is unlikely that three mutations happen in one viral genome"

Why combination therapy works



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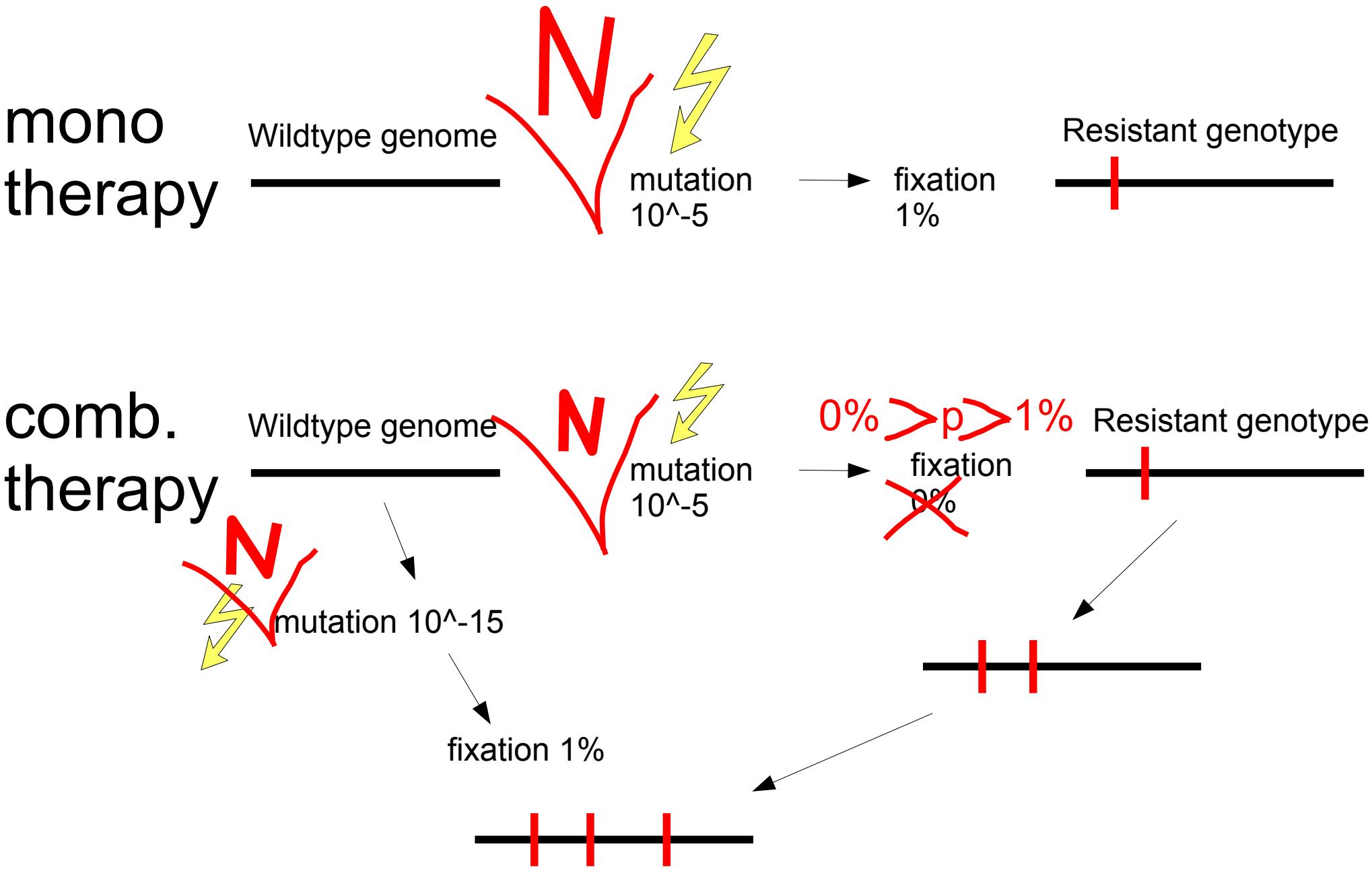

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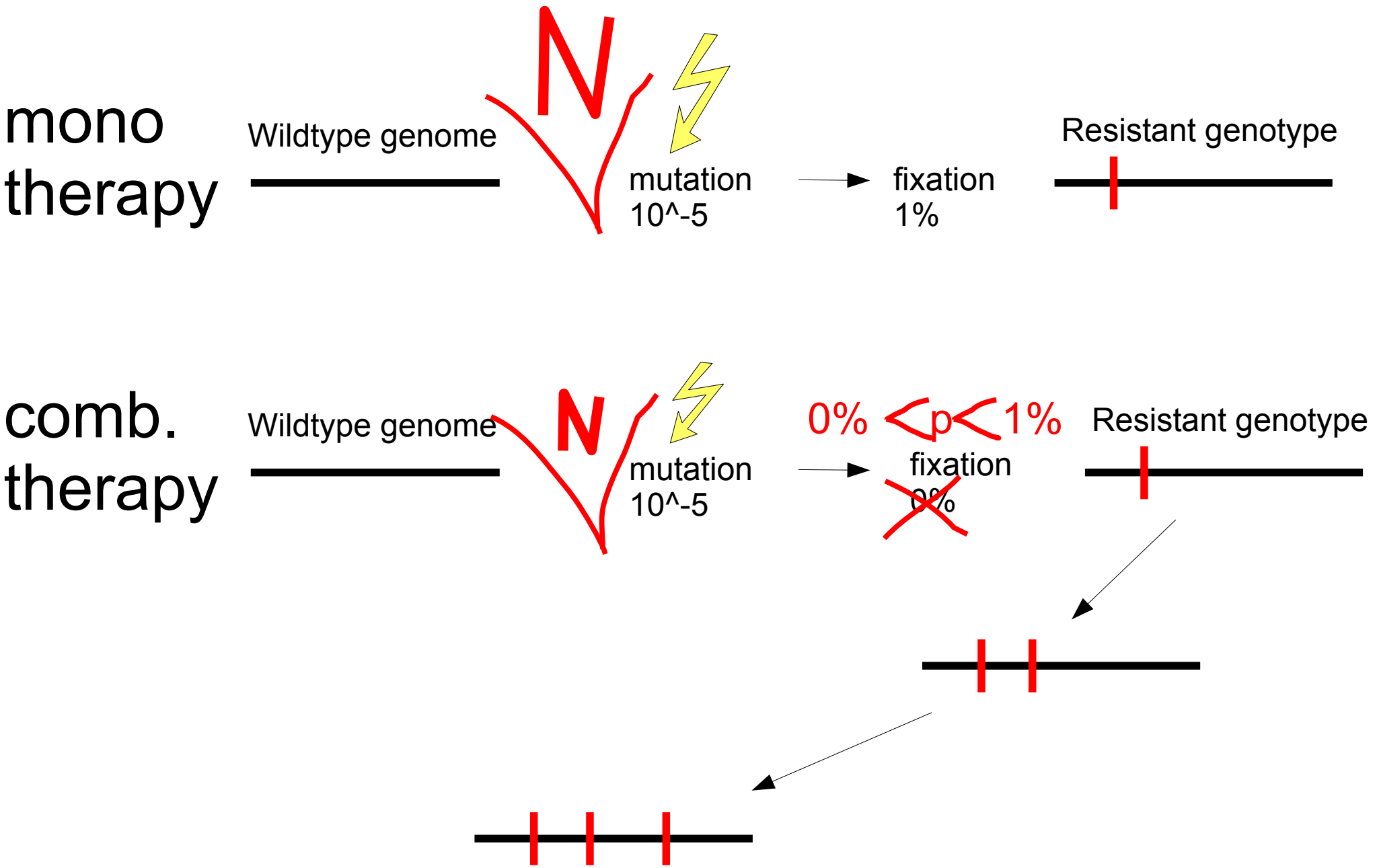
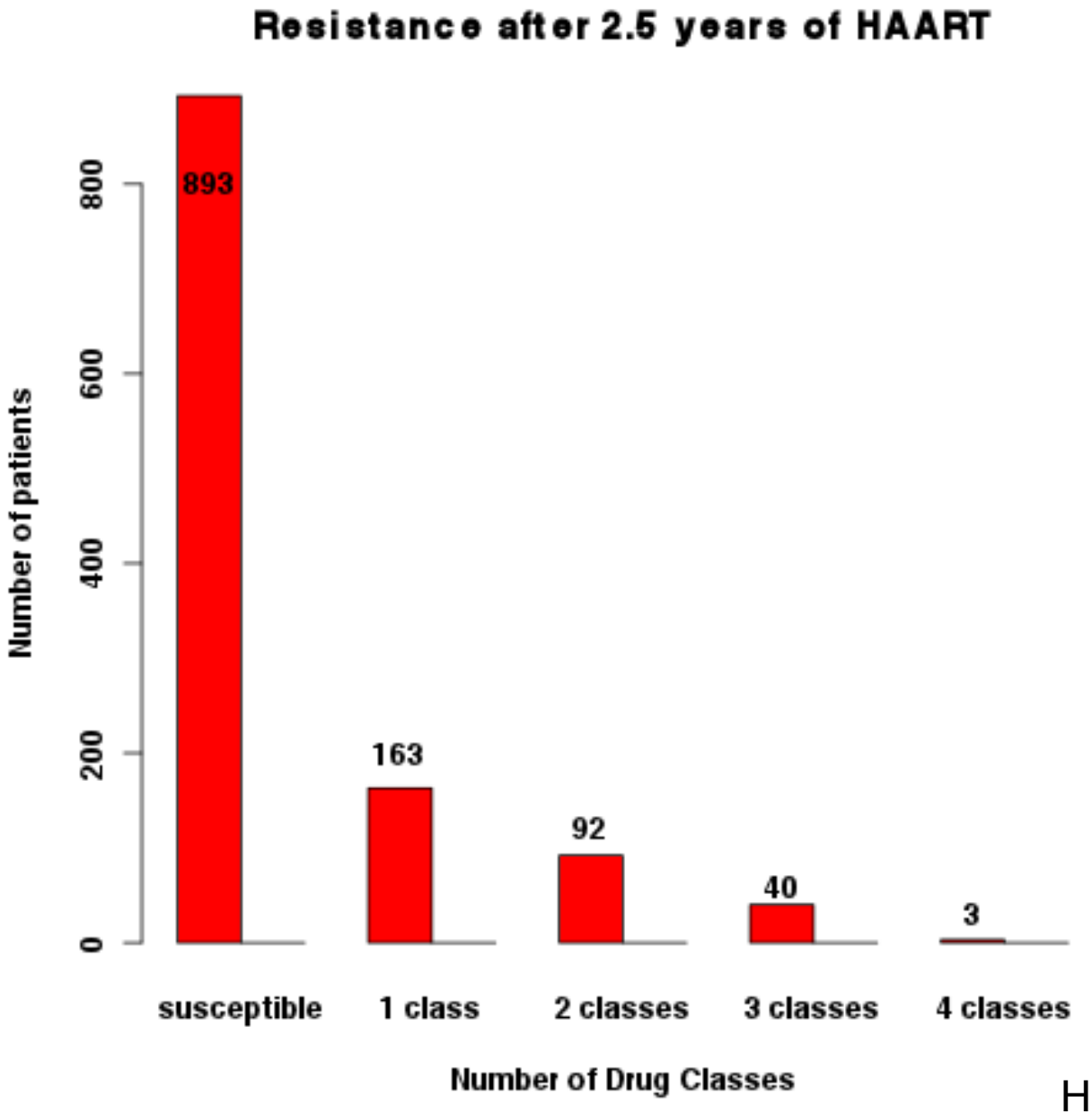


Resistance evolves one drug class at a time



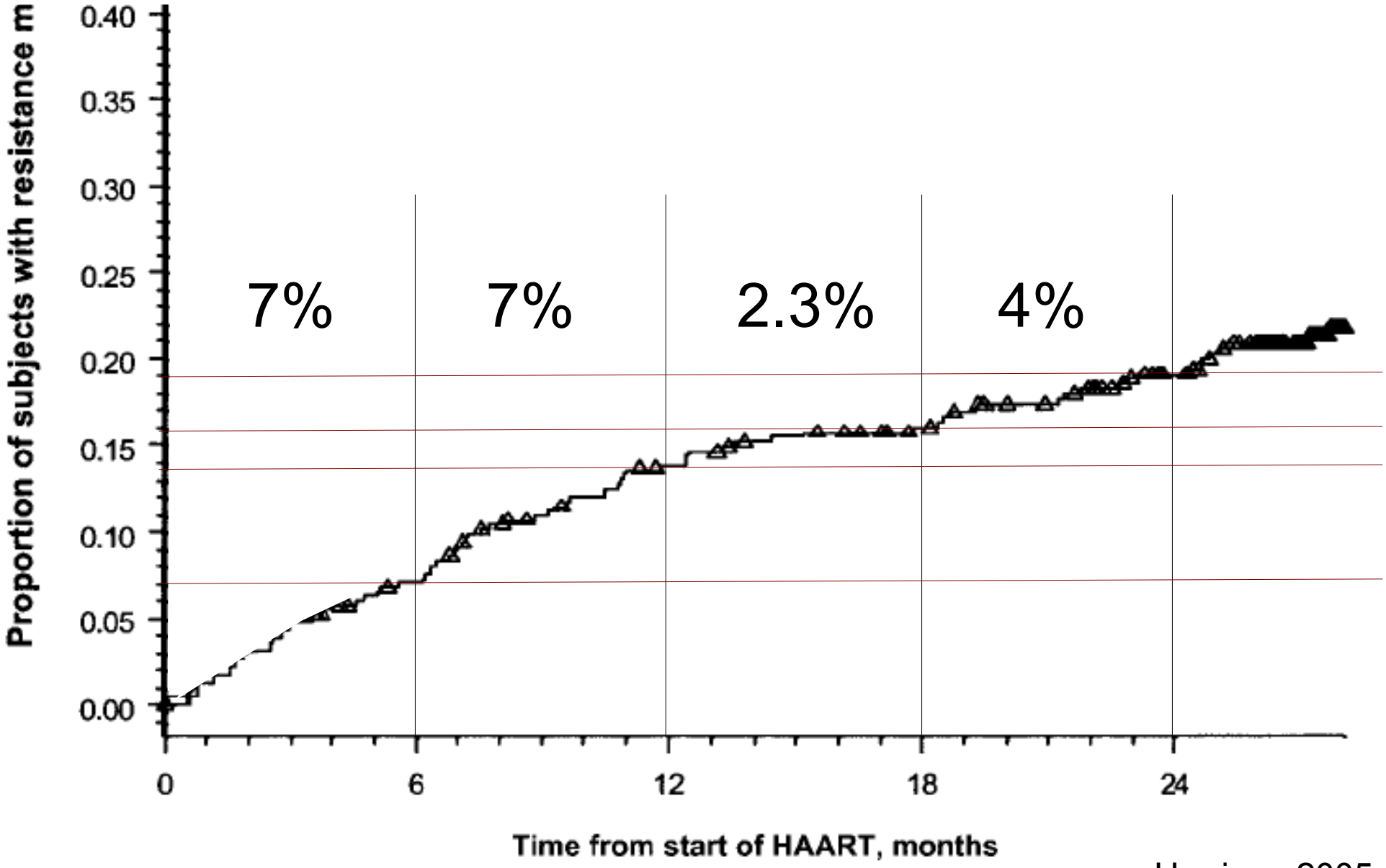
Harrigan et al 2005 JID

Summary of introduction

1. Waiting time distribution can be observed
2. Evolution is limited by mutations
3. First mutation most important
4. HIV evolves resistance one drug-class at a time

It is truly a simple problem!

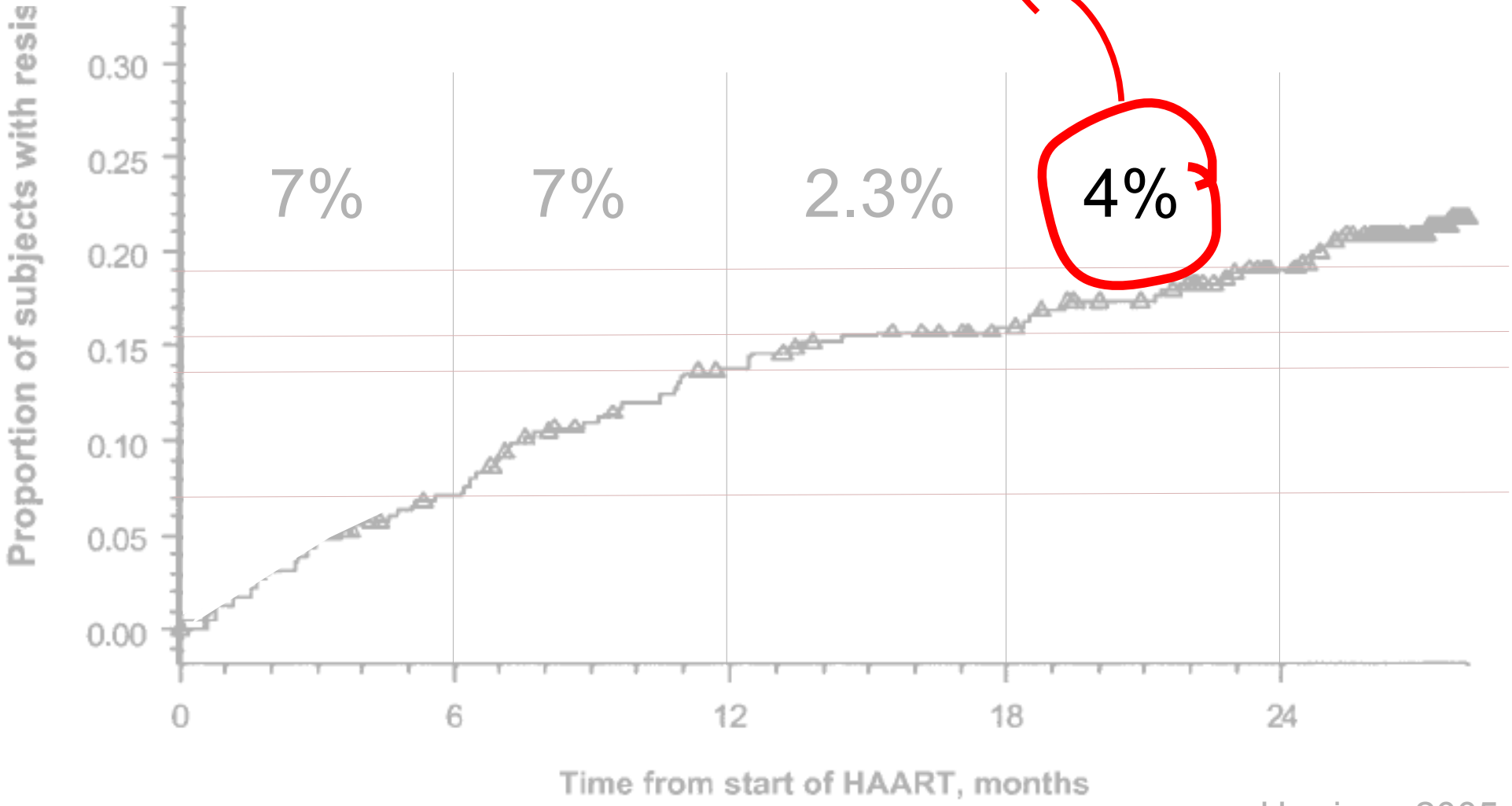
Example calculation



Harrigan 2005 JID

Example calculation

100 generations x 10^-5mut/gen x 40 possible mutations x *100* pop size x *1%* fixation probability



Harrigan 2005 JID

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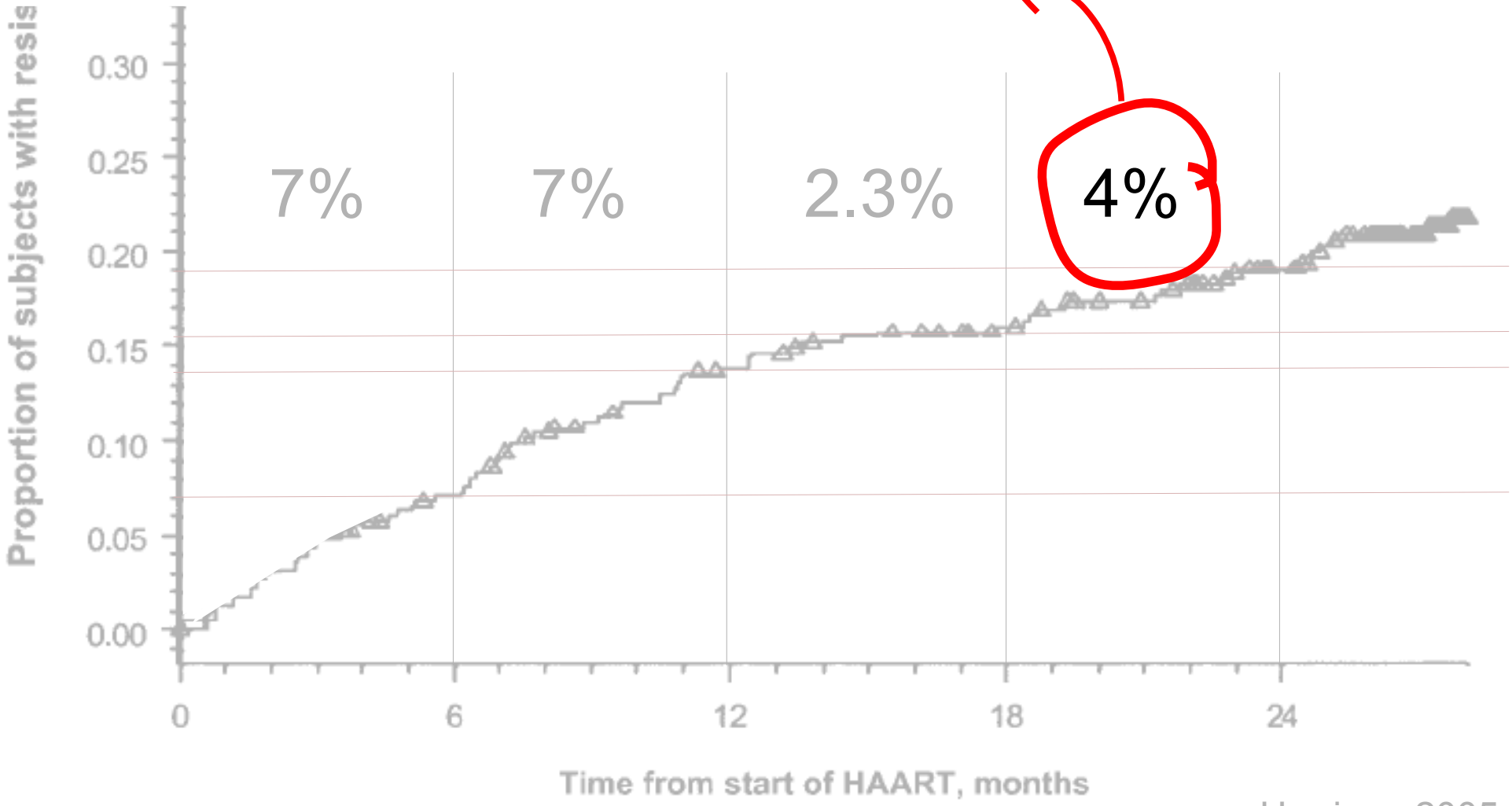
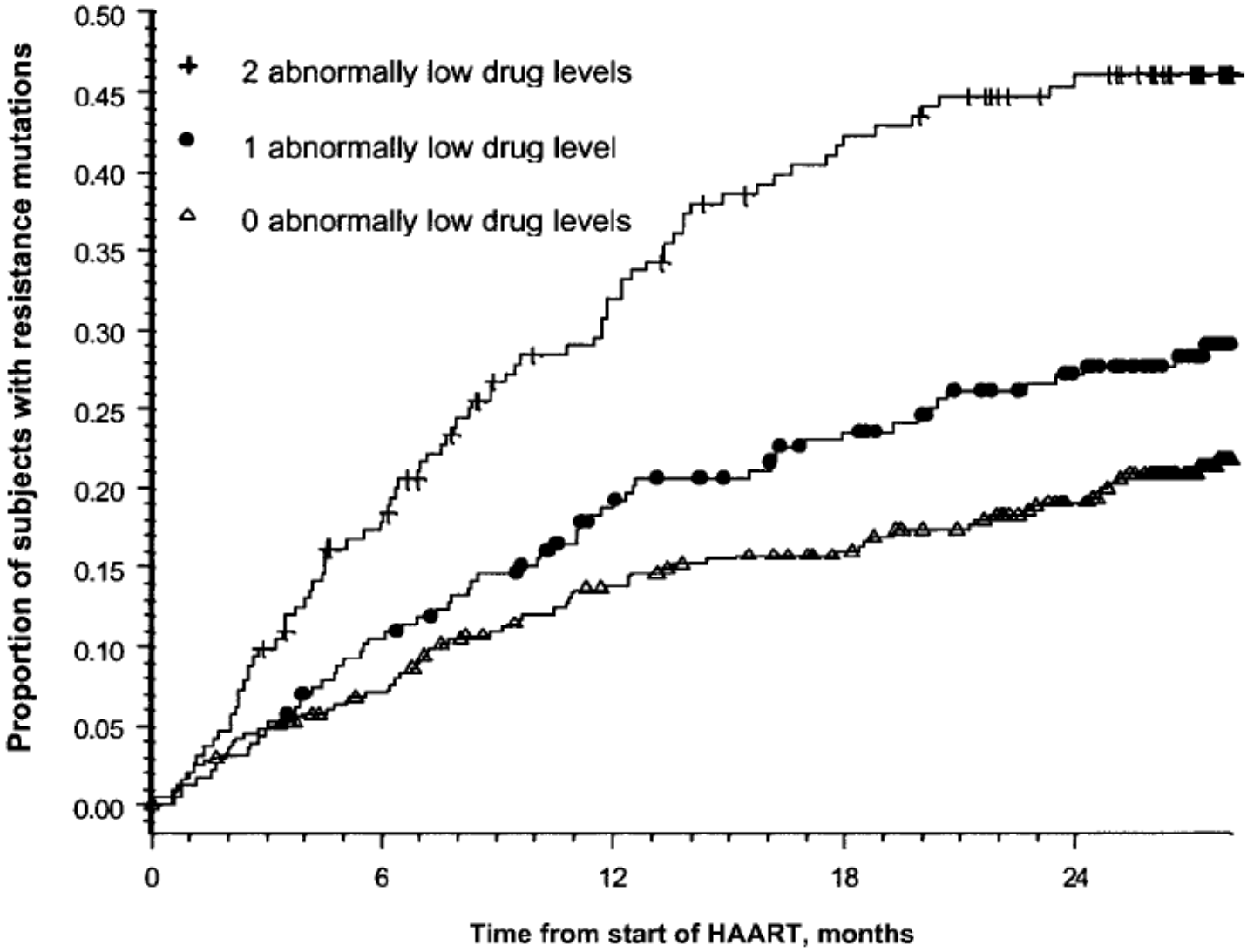


Harrigan 2005 JID

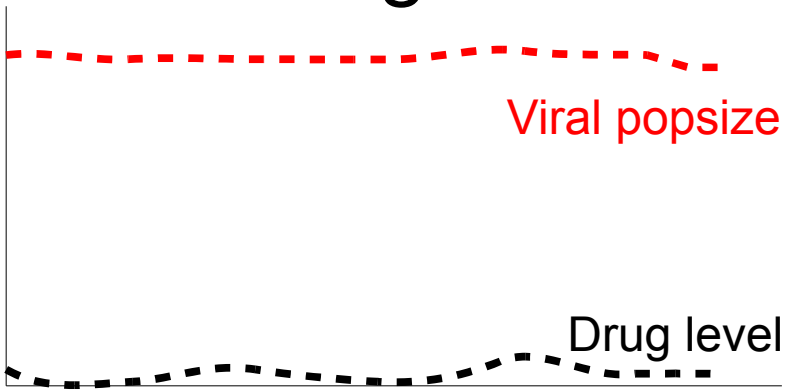
Non-adherence increases rate of evolution



Harrigan 2005 JID

Why non-adherence leads to faster evolution?

1. No drugs



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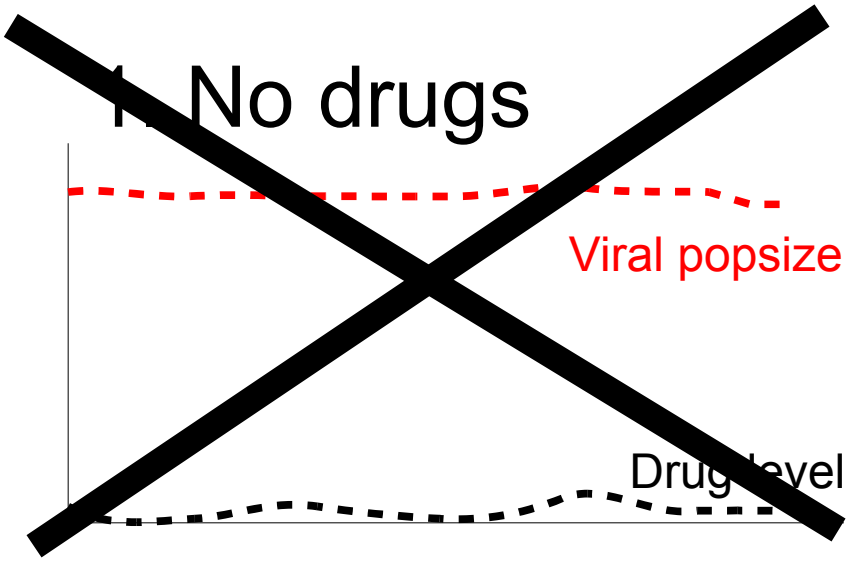
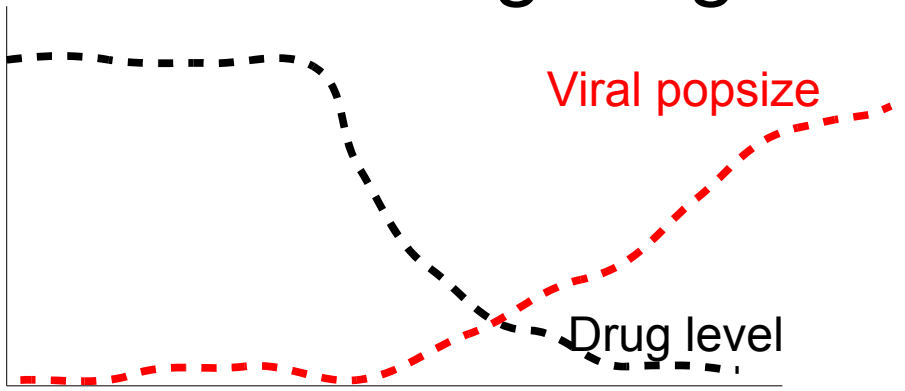


2. Decreasing drug level



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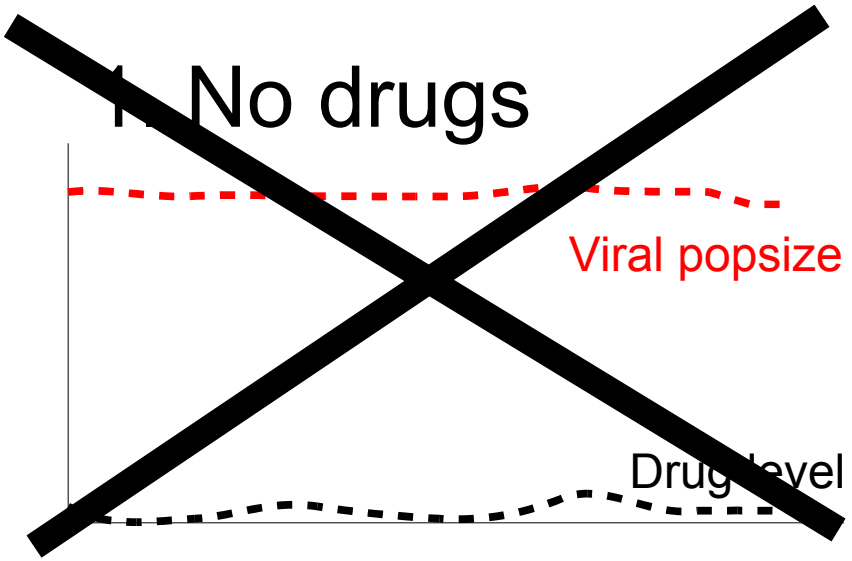

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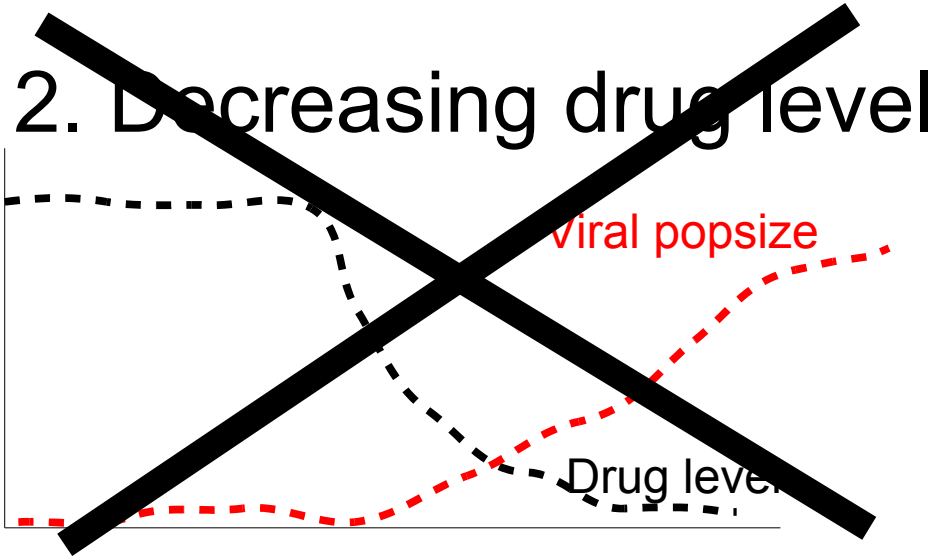
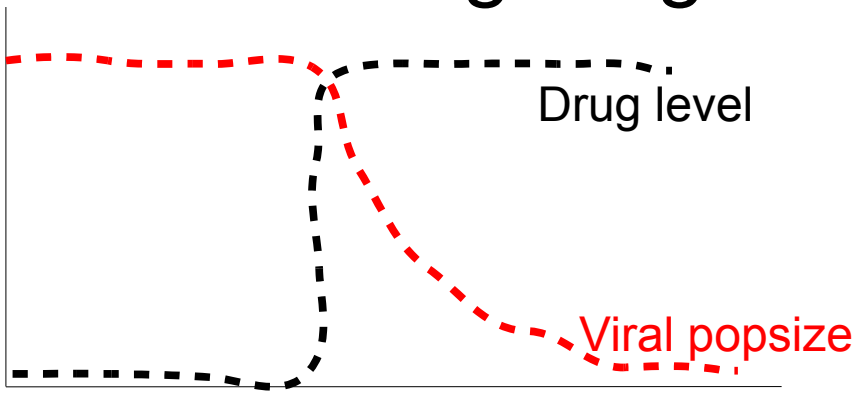


3. Increasing drug level



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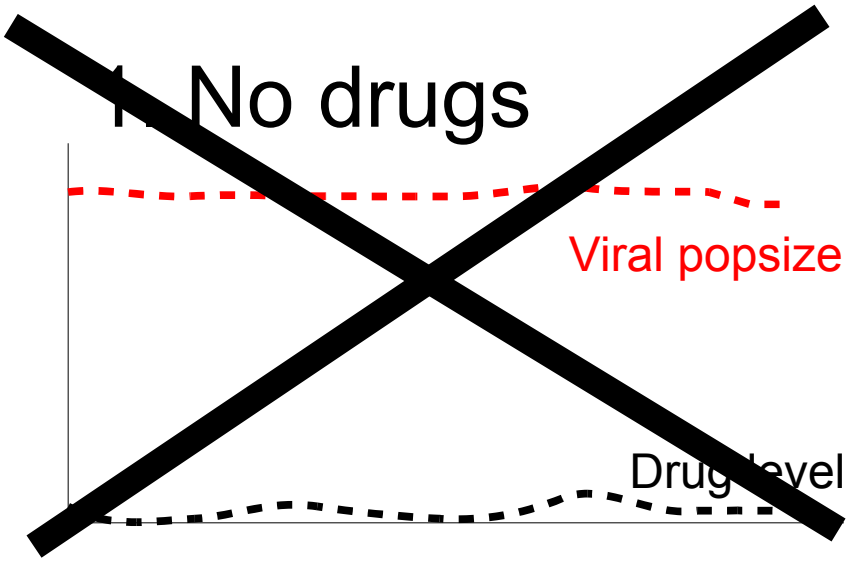

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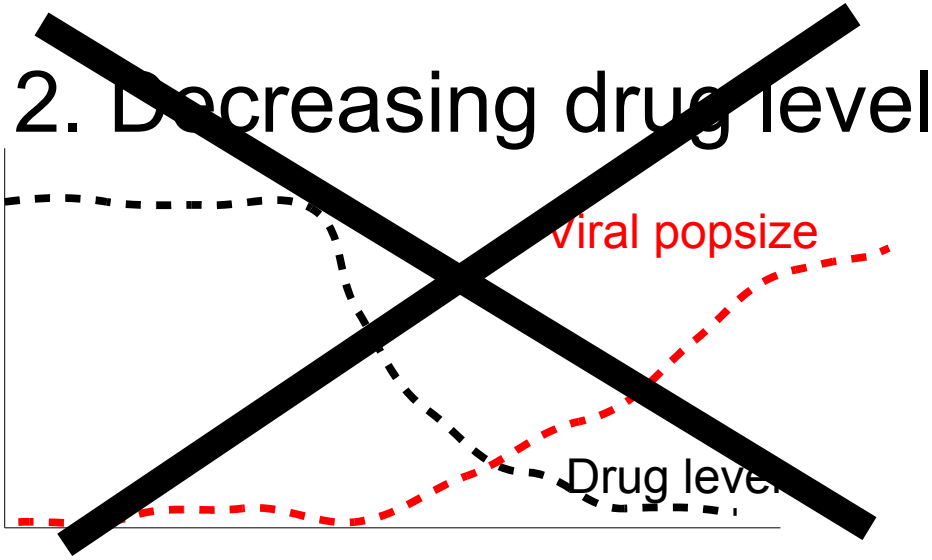

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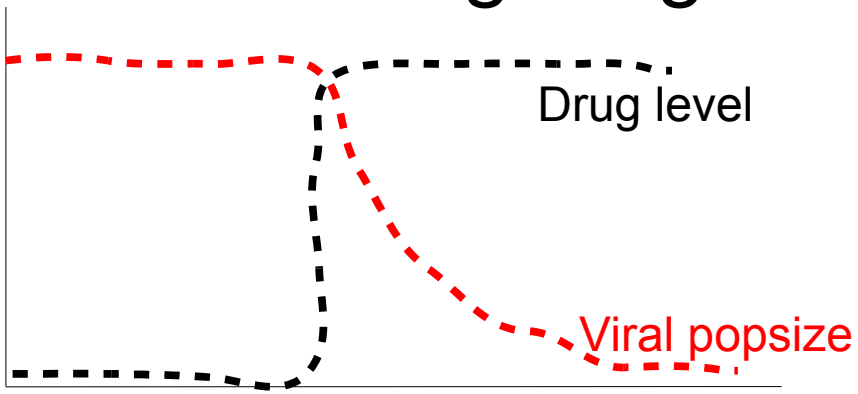
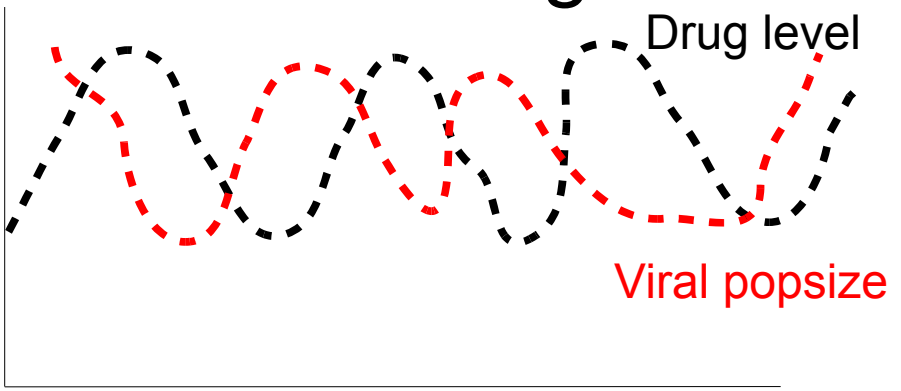


4. Quick changes



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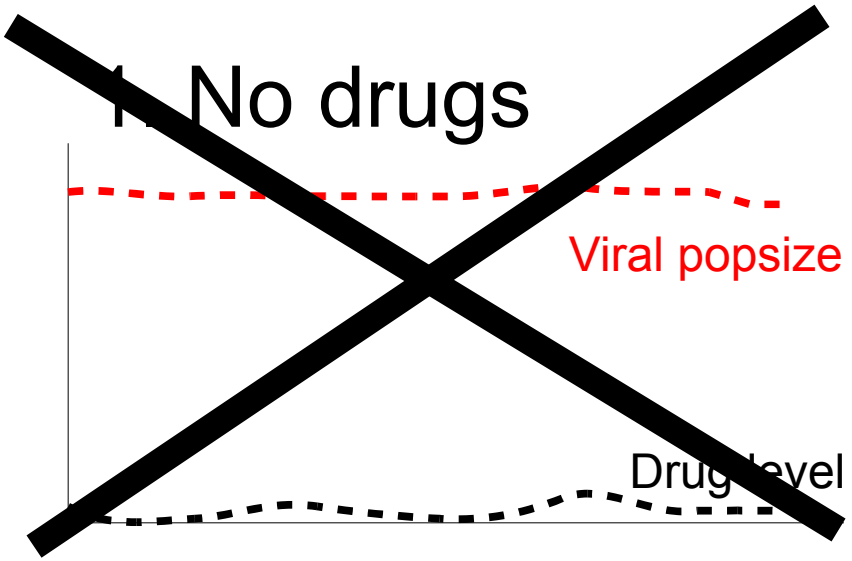

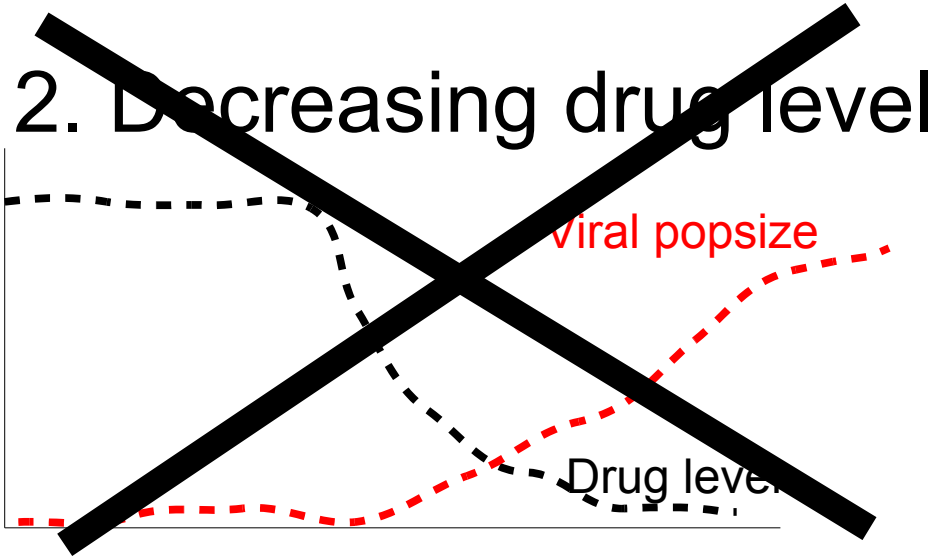

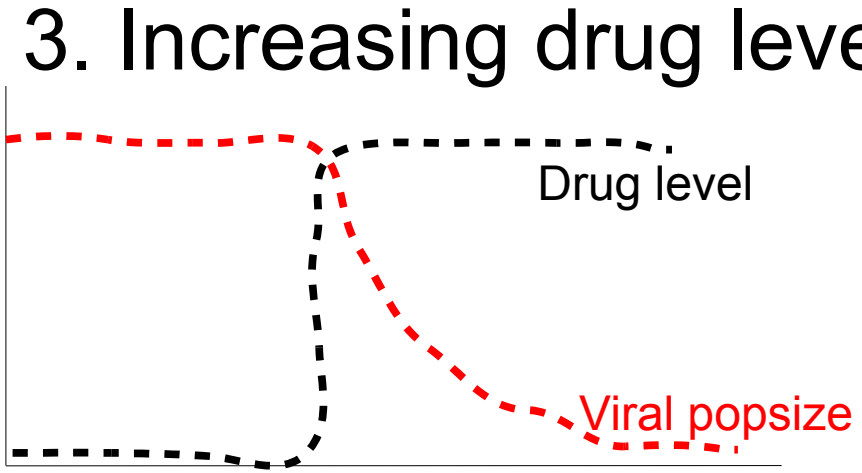

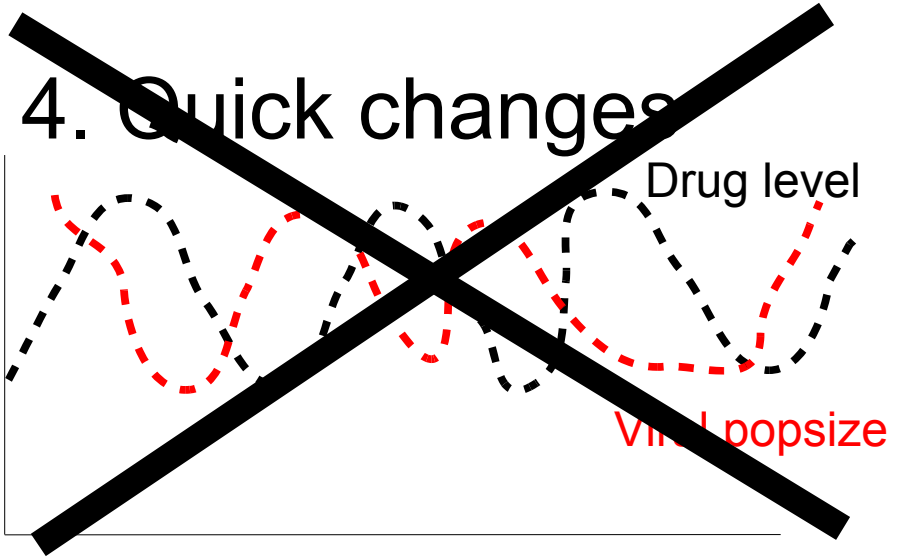

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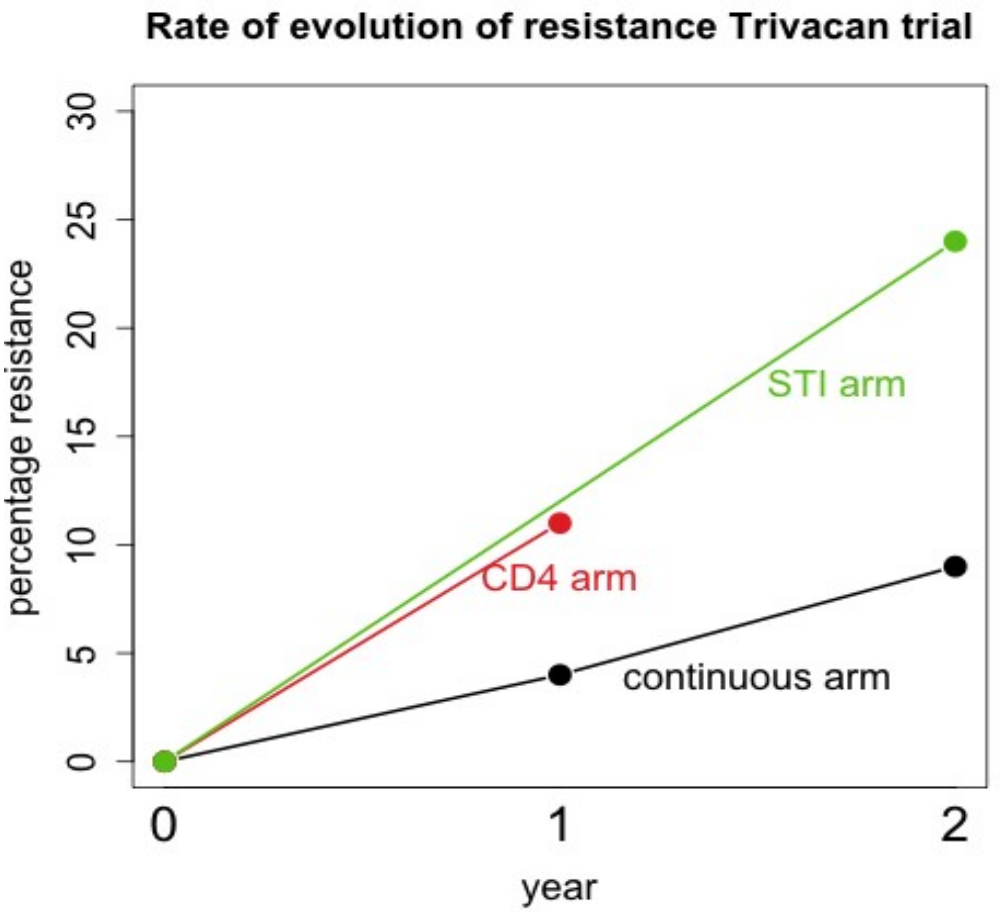
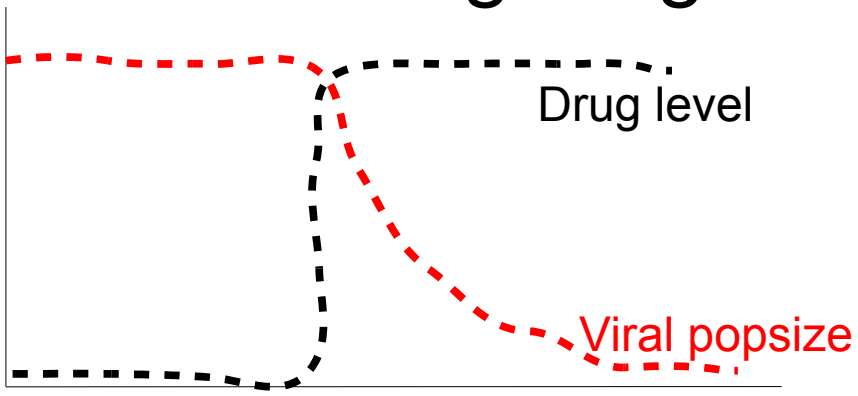
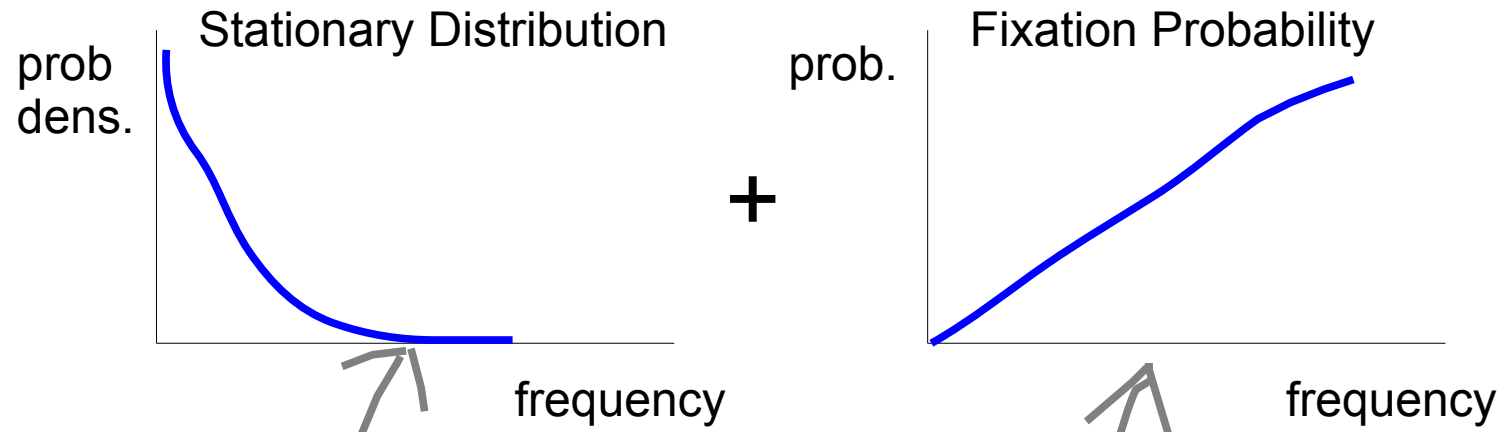


3. Increasing drug level



Danel et al 2006, 2009

Adaptation from standing genetic variation



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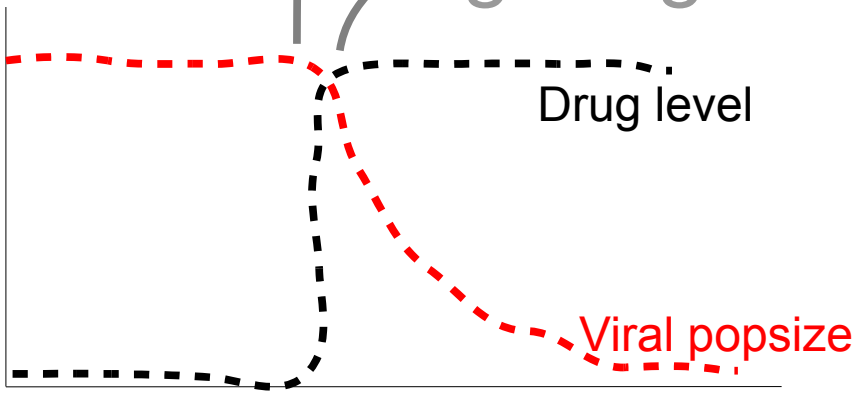
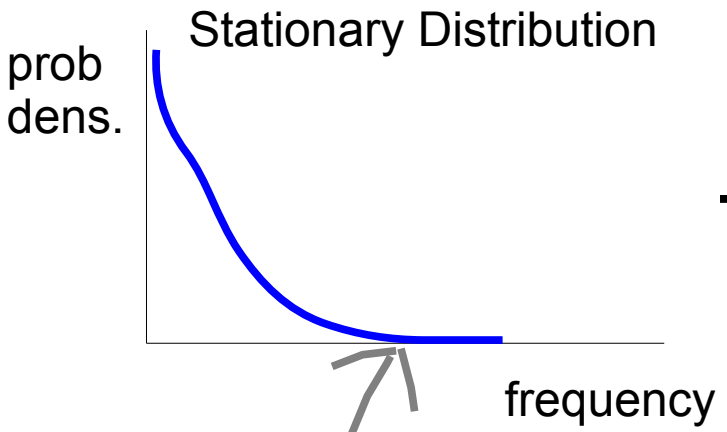
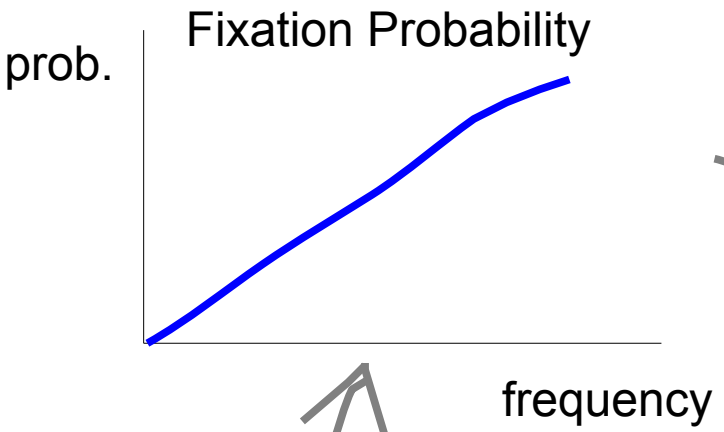


Hermisson & Pennings, Genetics 2005

Adaptation from standing genetic variation



+



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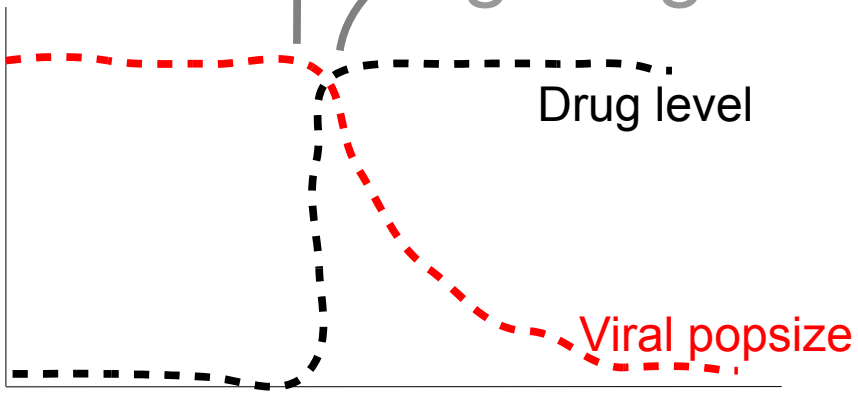

$$P_{sgv} = 1 - \left(1 + \frac{0.5\, p_{fix}}{cost}\right)^{-N\mu}$$

Hermisson & Pennings, Genetics 2005

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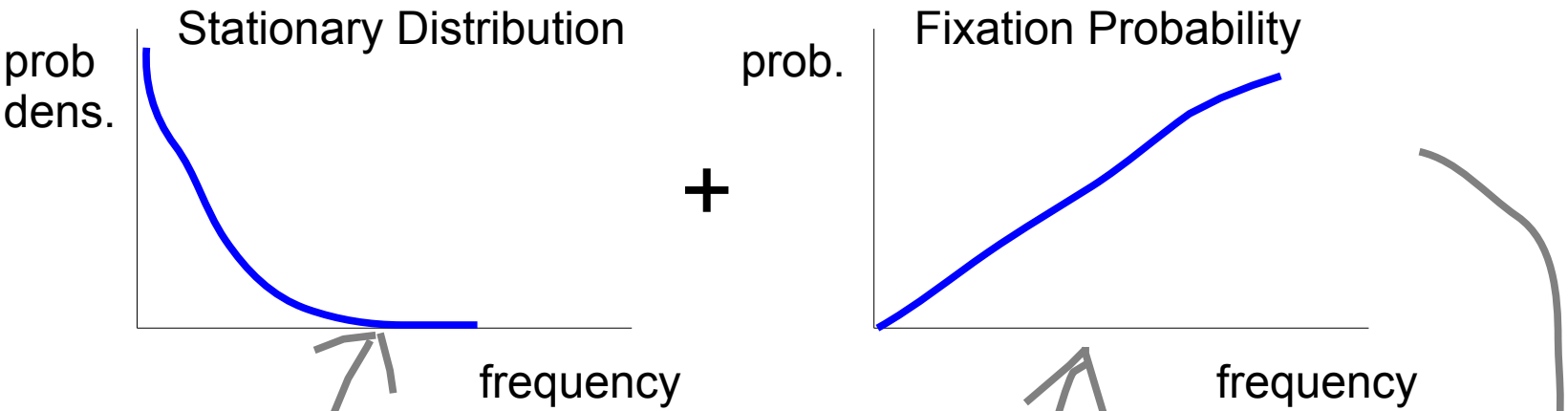

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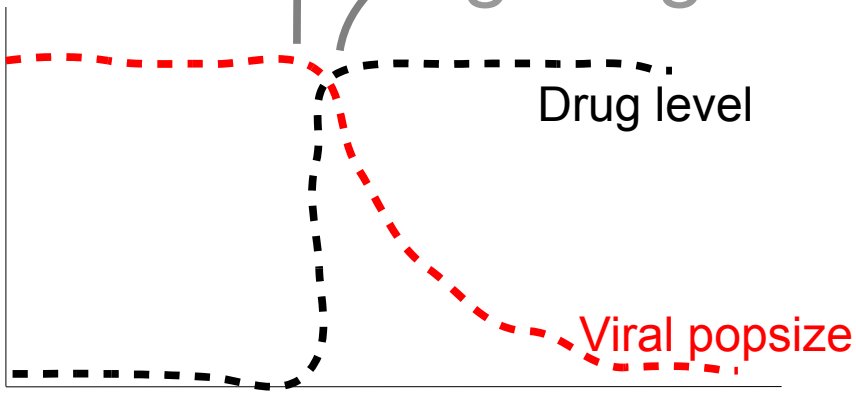


$$P_{sgv} = 1 - \left(1 + \frac{0.5\, p_{fix}}{cost}\right)^{-N\mu}$$

Hermisson & Pennings, Genetics 2005

Data

7 trials of “Structured Treatment Interruptions”

Example: Swiss-Spanish Intermittent Treatment Trial

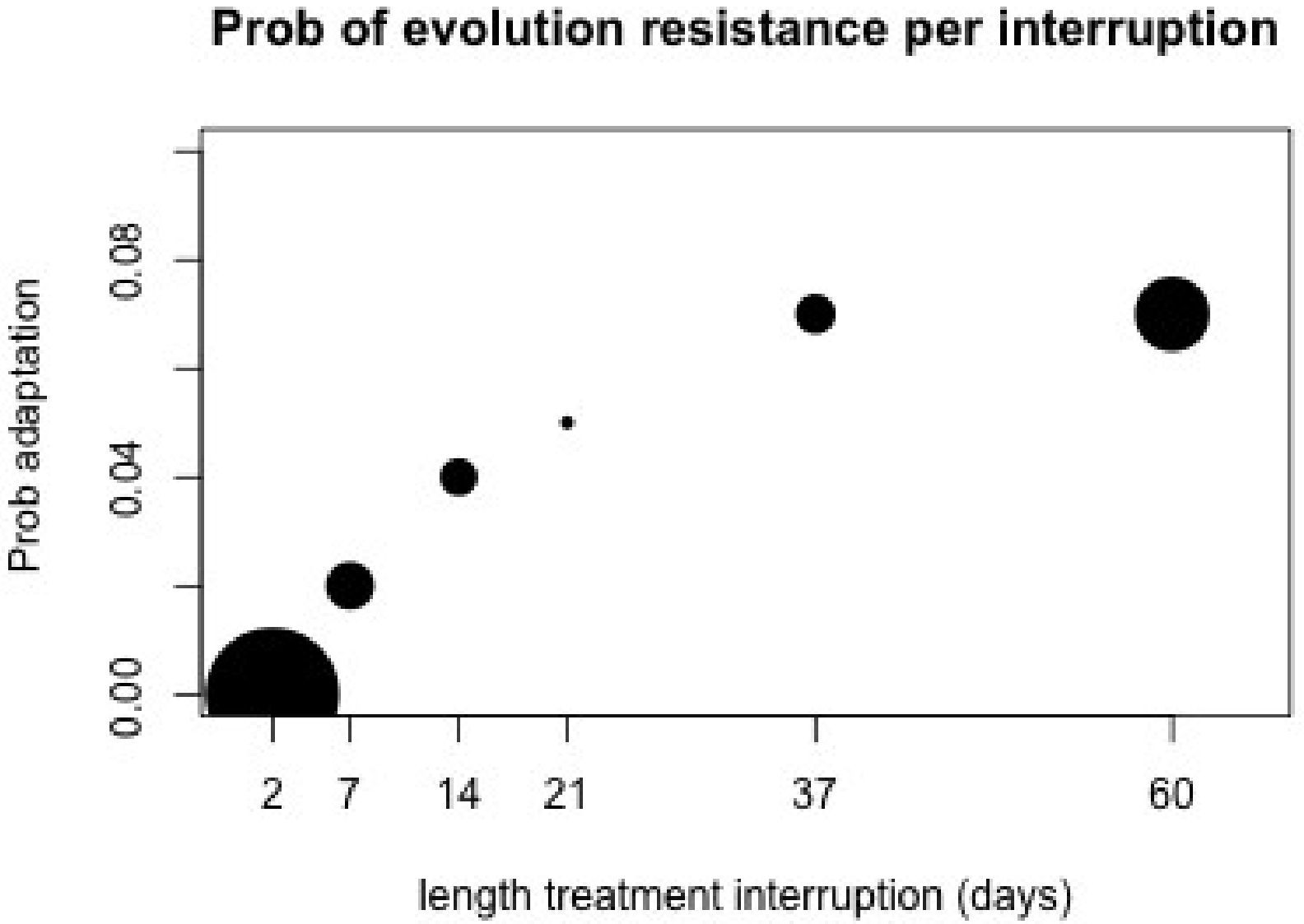
87 patients (-7)

4 interruptions of 14 days

11 patients had resistance

$$\frac{69}{80} = (1-x)^4 \qquad x = 0.04$$

Data


Prob of evolution resistance per interruption
Prob adaptation
0.00
0.04
0.08
2
7
14
21
37
60
length treatment interruption (days)

$$P_{sgv} = 1 - \left(1 + \frac{0.5\, p_{fix}}{cost}\right)^{-N\mu}$$

$$7\% = 1 - \left(1 + \frac{0.5 \;\; 1\%}{5\%}\right)^{\left(-N\, 40\, 10^{-5}\right)}$$

10^-5mut/gen x 40 possible mutations

1% fixation probability

5% cost

N = 1875

First year bonus?

	YEAR 1	YEAR 2	YEAR 3	P_SGV
Margot 2006	10.5	3.4	4.0	6.8
Harrigan 2005	14	6		8

Conclusions

- Very simple models work well - predictions fit with data.

- Population size can explain why treatment interruptions lead to faster evolution.

- HIV uses both standing variation and new mutations to adapt.

- Idea: adaptation from standing variation can be avoided with different treatment protocol.

- Unclear: how come Ne is so low?

- How can single-drug resistance evolve?

Thanks

John Wakeley (Harvard)

Joachim Hermisson (Vienna)

Dan Kuritzkes (Harvard)

Jonathan Li (Harvard)

Many people here and elsewhere for discussions