

# ← evolution of life

← Evolution of life: Evolution b... x


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## Evolution before our eyes



Documentary video  
7mn 49s

**Downloads**

- low quality video  
mpg - 65 Mo
- high quality video  
mpg - 188 Mo
- text voices  
rtf - 641 Ko

**Synopsis**


Viruses can evolve fast and sometimes adapt quickly to a new host species. For example, an influenza virus that normally infects birds can become adapted to humans. The tobacco etch virus normally infects tobacco plants. Professor Santiago Elena from Valencia wants to find out what it takes to make the tobacco virus capable of infecting another plant: Arabidopsis. The movie shows how Santiago Elena does the evolutionary experiment and we see that after 30 rounds of experimental evolution the virus is indeed adapted to the new host plant! After the experiment, Elena looks at the genetic code of the adapted virus and finds that there are just three differences between the genetic code of the normal (tobacco loving) virus and the virus that is now adapted to Arabidopsis.

Winner at "Vedere la Scienza Festival 2010" (category: Educational videos for the web).  
Finalist at the "European Science TV and New Media Festival 2010".

**Credits**

Directors : Robert Sigl, Bernhard Rube & Pleuni Pennings - Script & editing : Brant Backlund - Camera operator : Bernhard Rube - Graphics : Simon Baker, James Doyle & Jacob Barrow - Equipment Manager : Robert Sigl - Narration : Francine Oliver - Narration Producer : Chris Kugelmann - Music : Chris Tegg - Production Manager : Marion Hartl - Production Assistant : Kaitlin Hickey - Producer : Brant Backlund - Executive Producer : Pleuni Pennings - Production : LMU Munich (2009)

**Scientific expert**



**Santiago Elena**  
Instituto de Biología Molecular y Celular de Plantas, Evolutionary Systems Virology Group, Spain  
Evolutionary Virology

-To design working antiviral strategies, we need to understand how new viruses appear and what principles govern their diversification and adaptation to hosts. Also, viruses allow us to witness evolution in real time and to test fundamental principles of the evolutionary theory.-

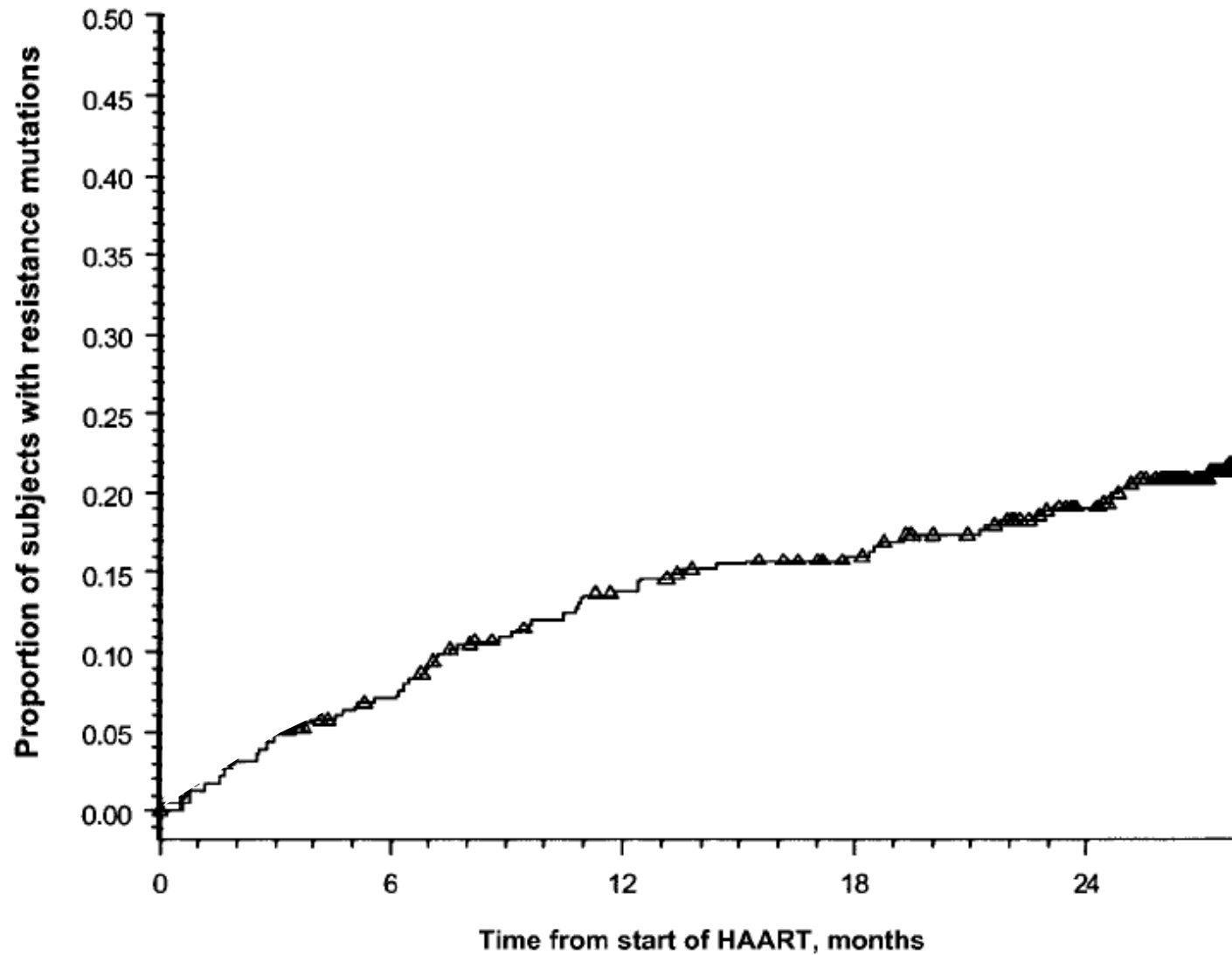
I think there's between A & B.

B. The production of the virus is...

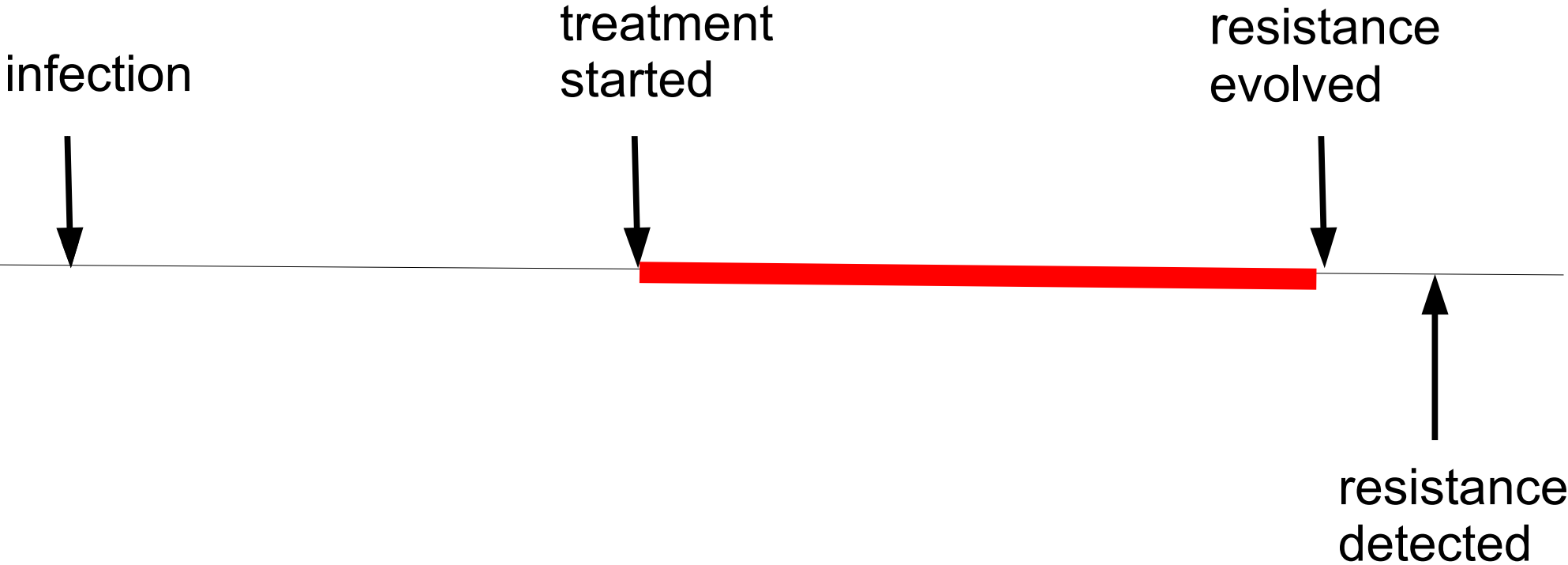
What determines the rate of evolution  
of resistance of HIV?

Pleuni Pennings  
March 2011  
KITP, Santa Barbara

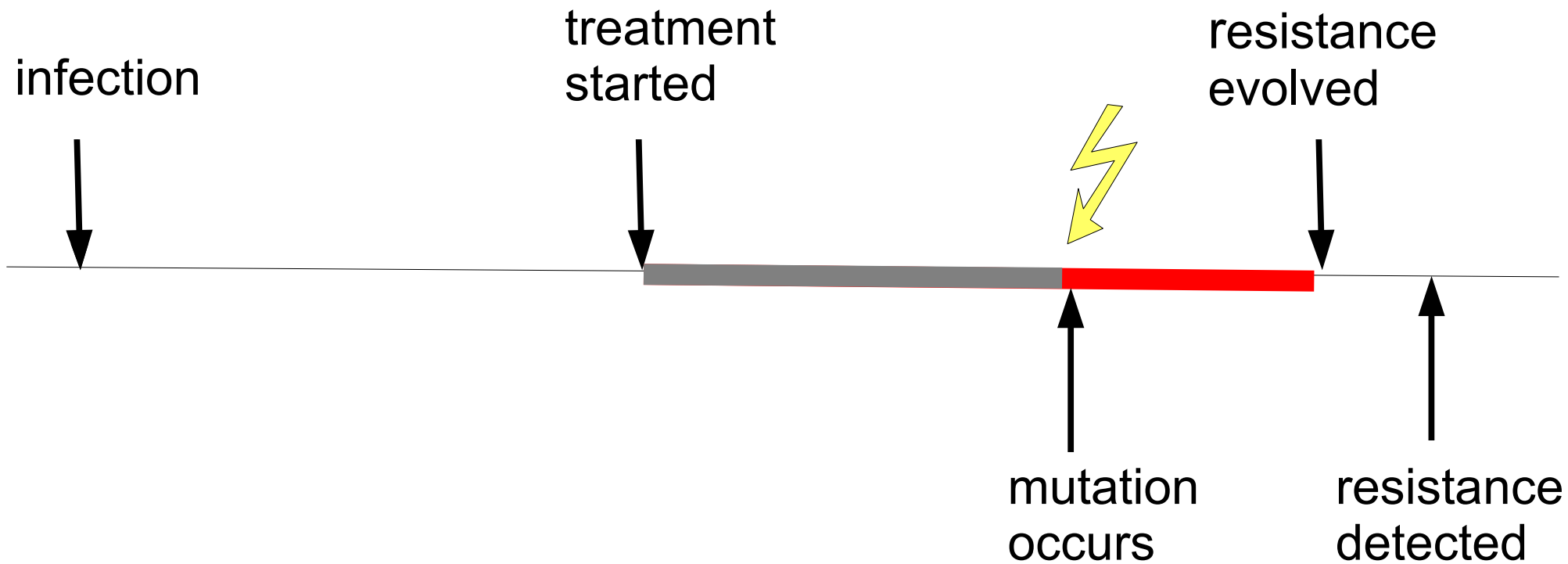
# Distribution of waiting times

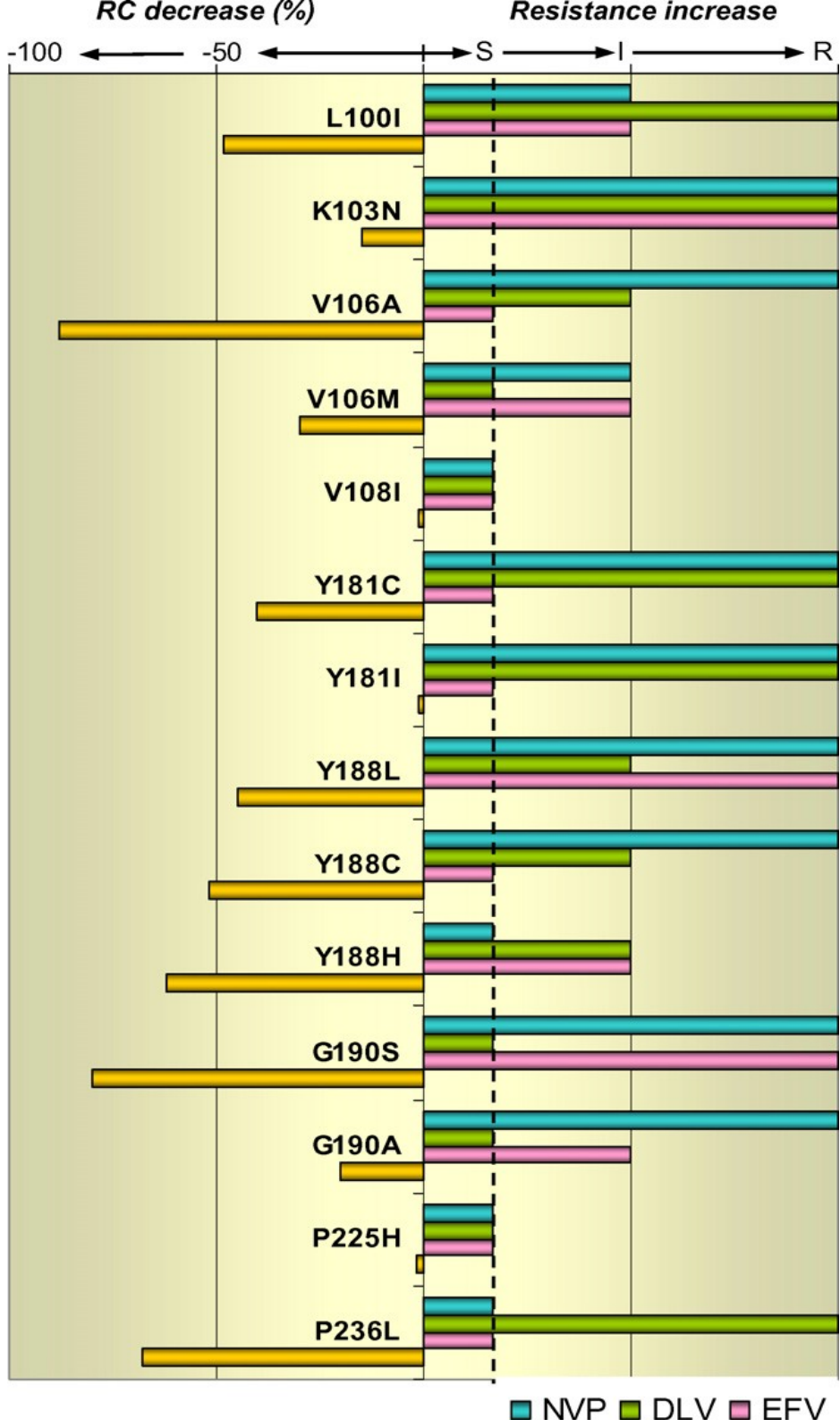


# Timeline



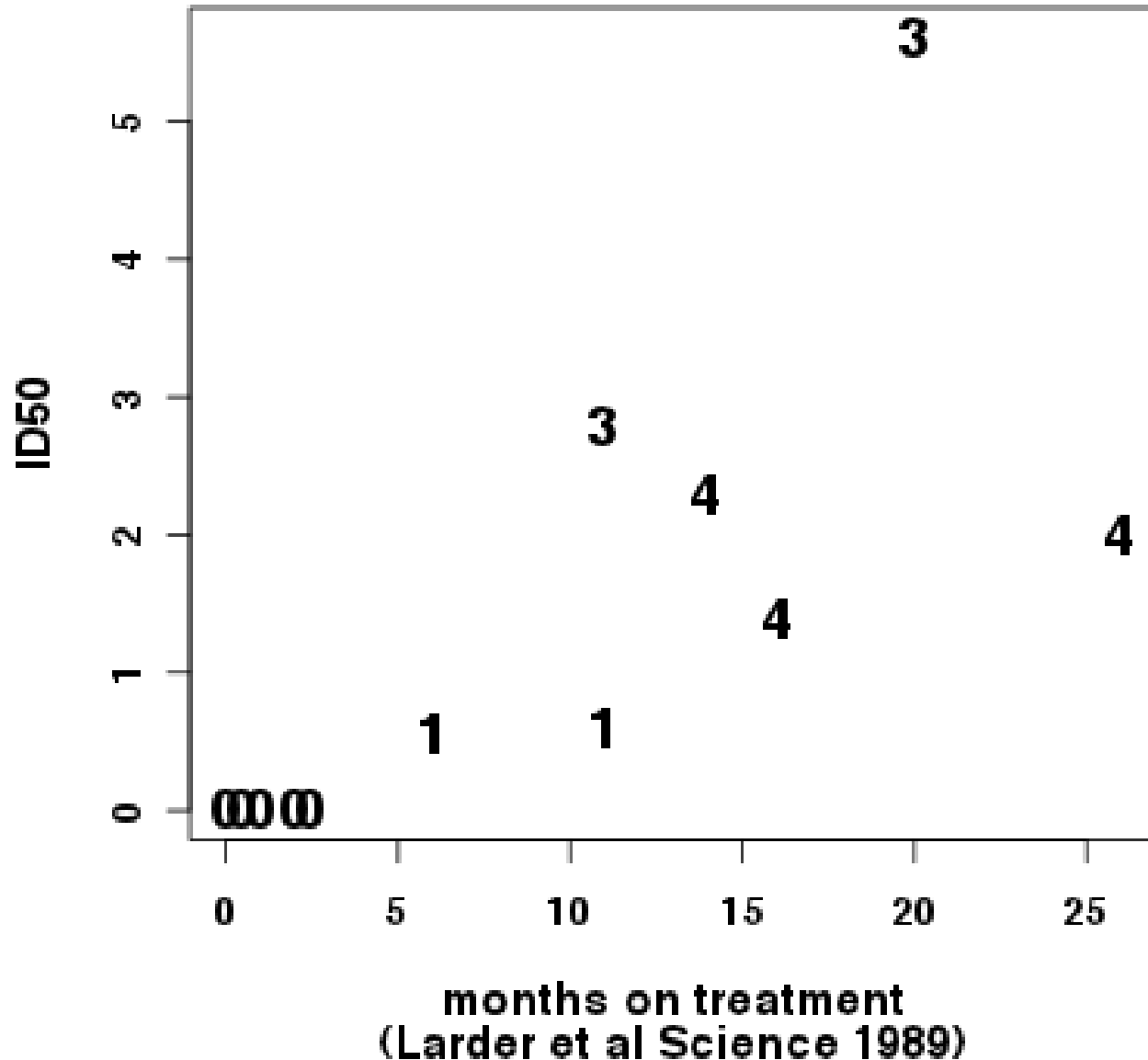
# Timeline



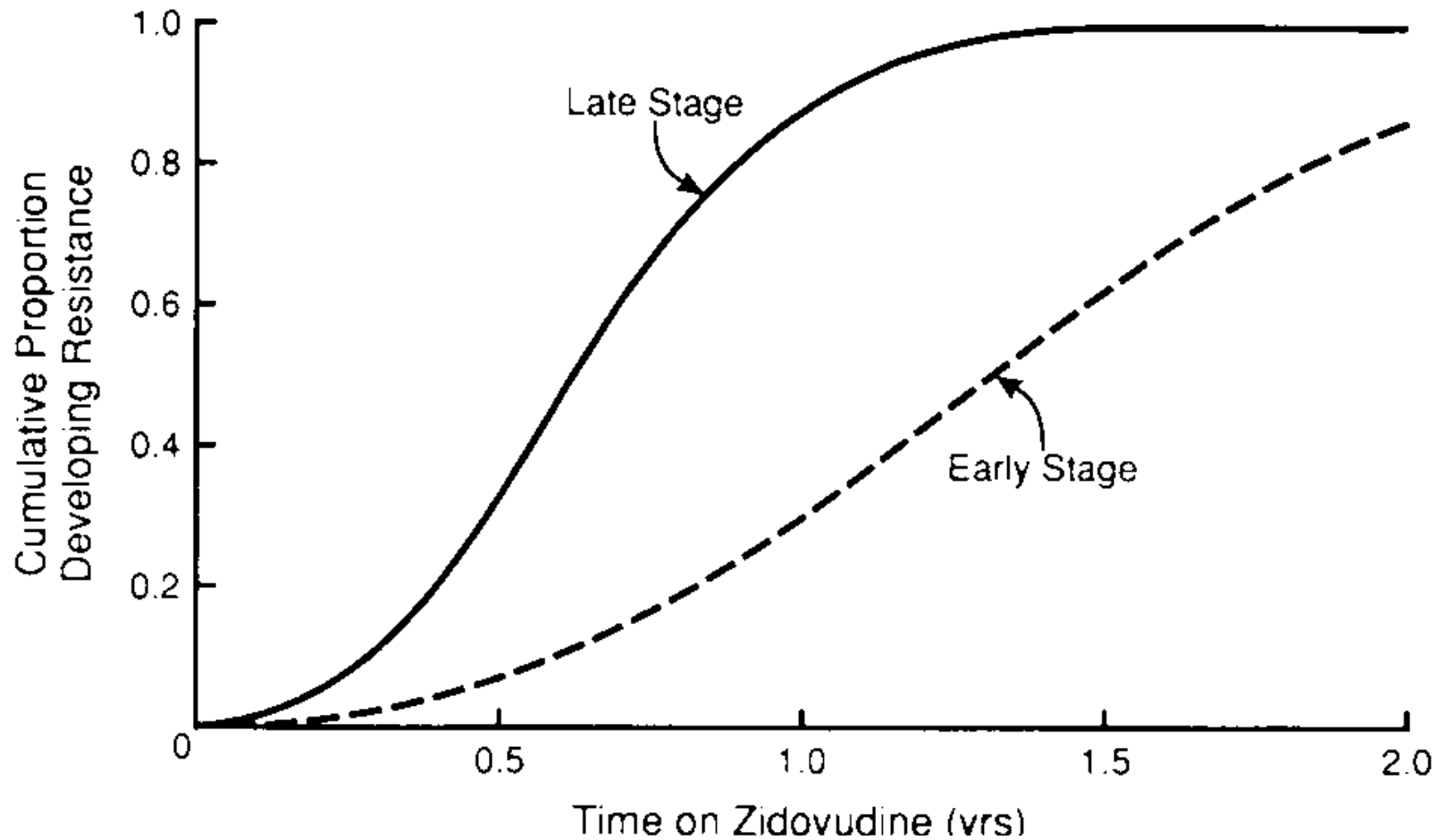


Mutations are well characterized

# Resistance against AZT in 12 patients

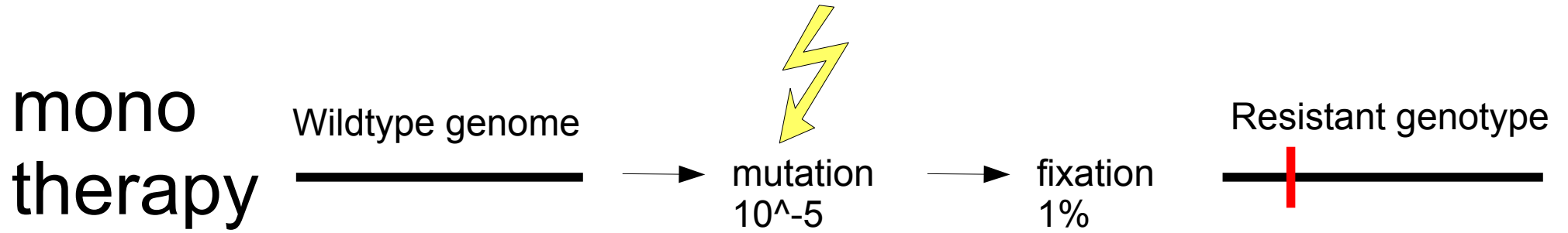


# Evolution is mutation limited



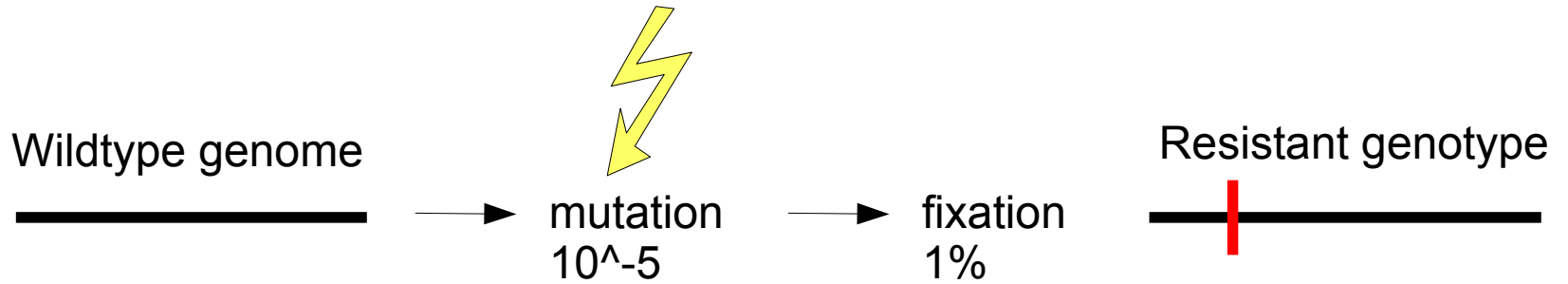


# Why combination therapy works

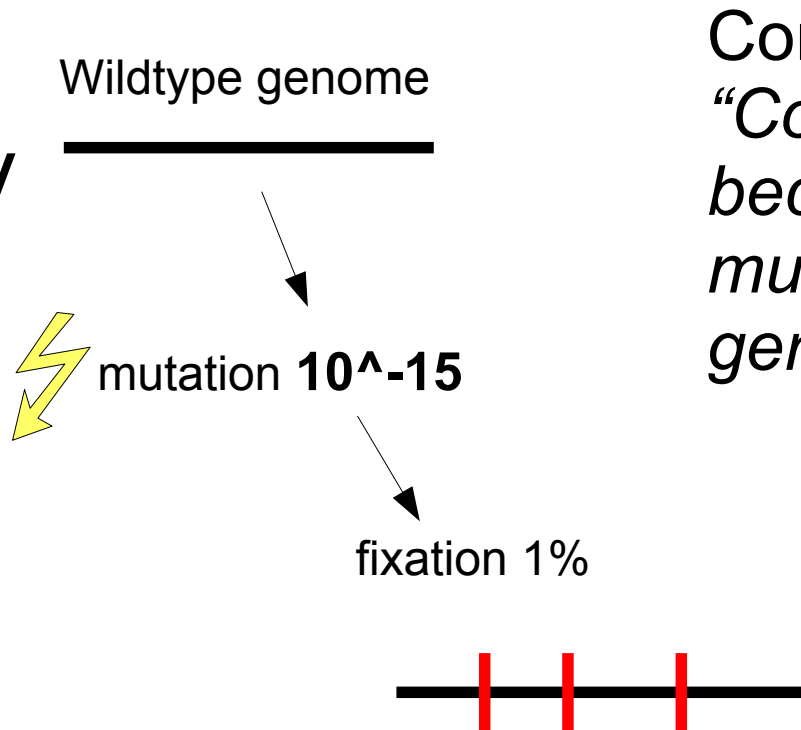


# Why combination therapy works

mono  
therapy



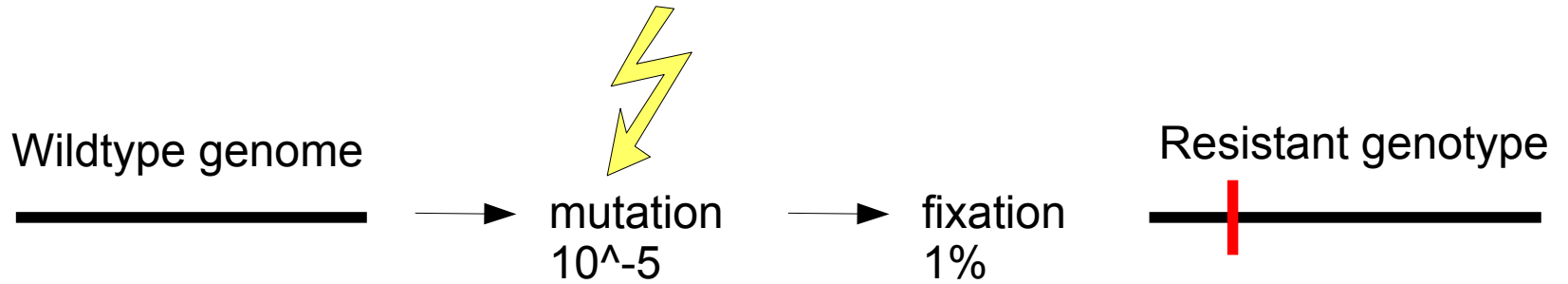
comb.  
therapy



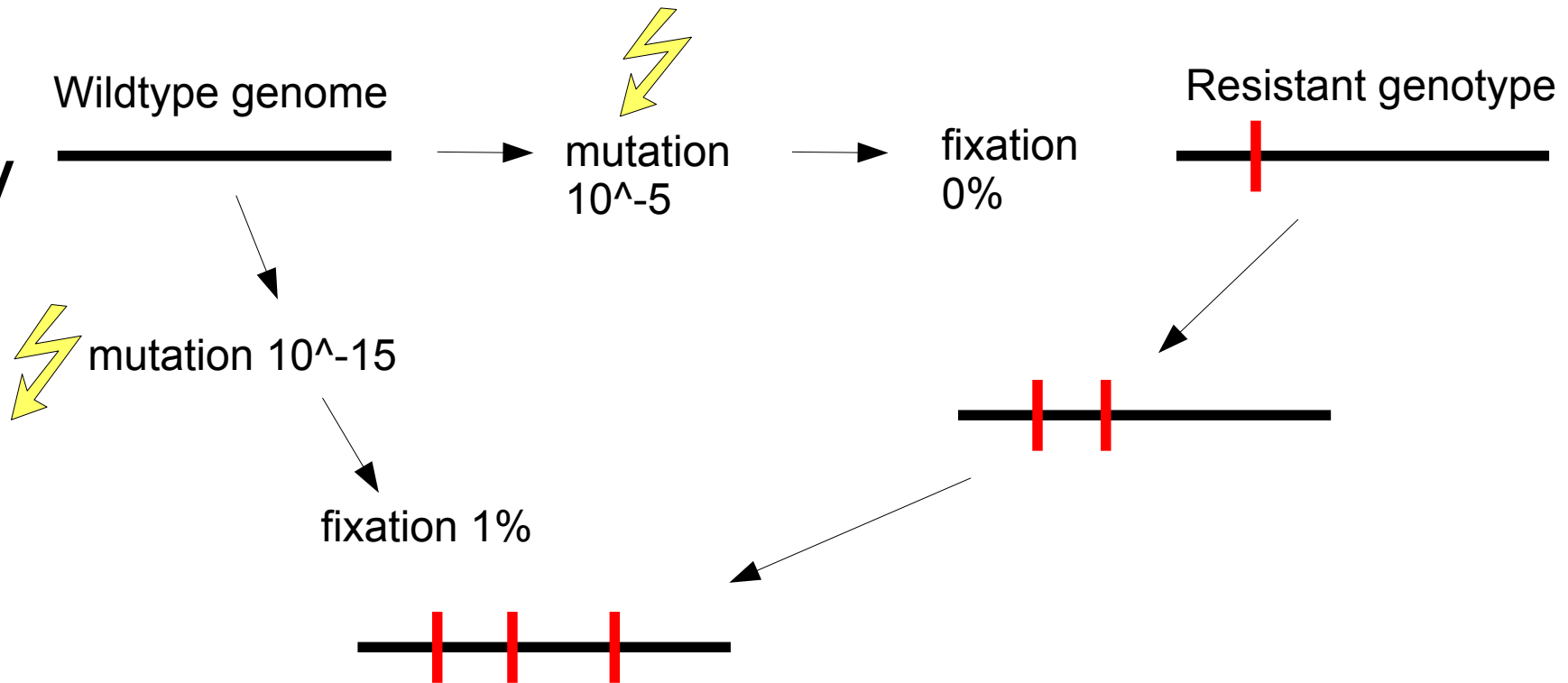
Common belief:  
*“Combination therapy works because it is unlikely that three mutations happen in one viral genome”*

# Why combination therapy works

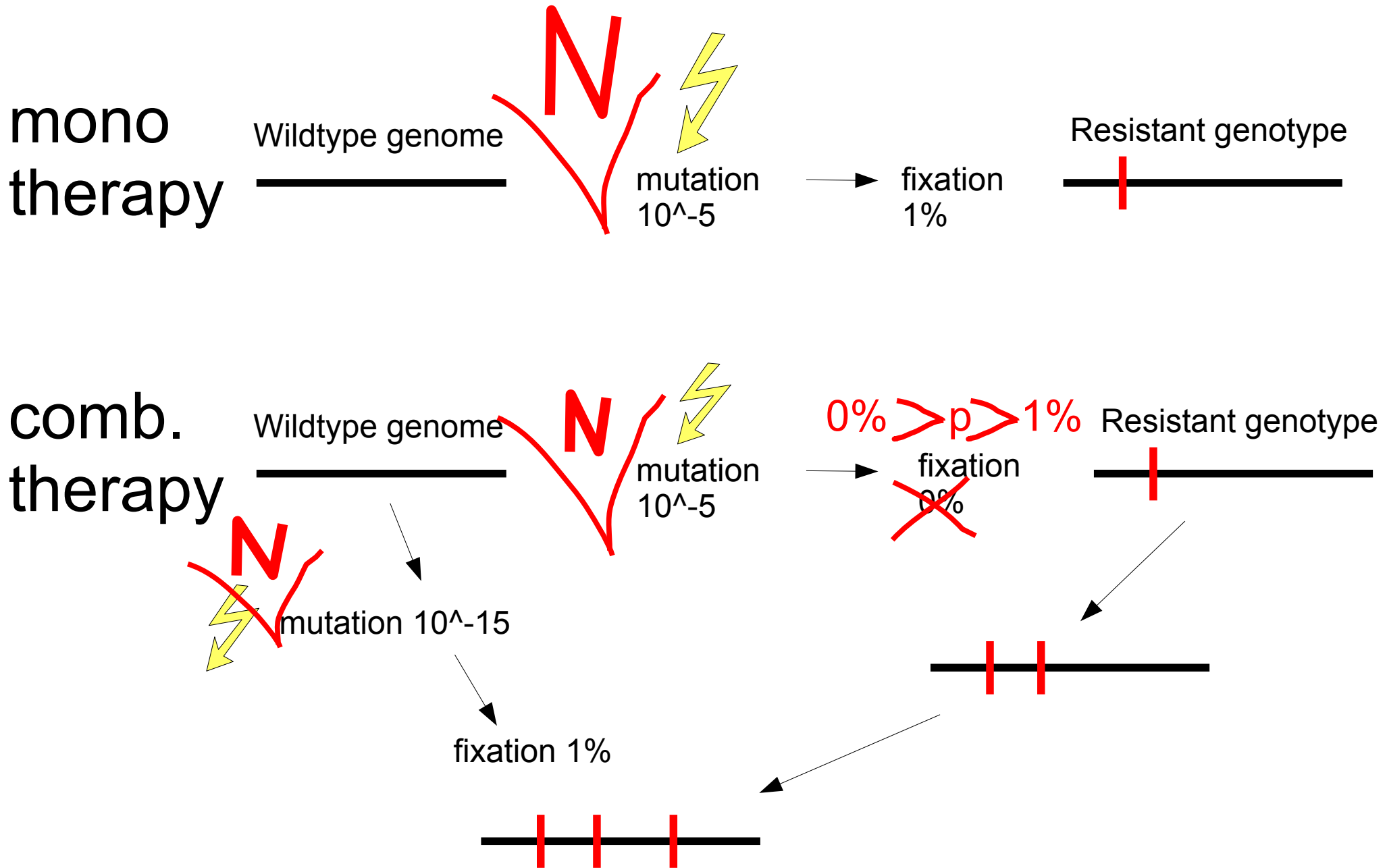
mono  
therapy



comb.  
therapy

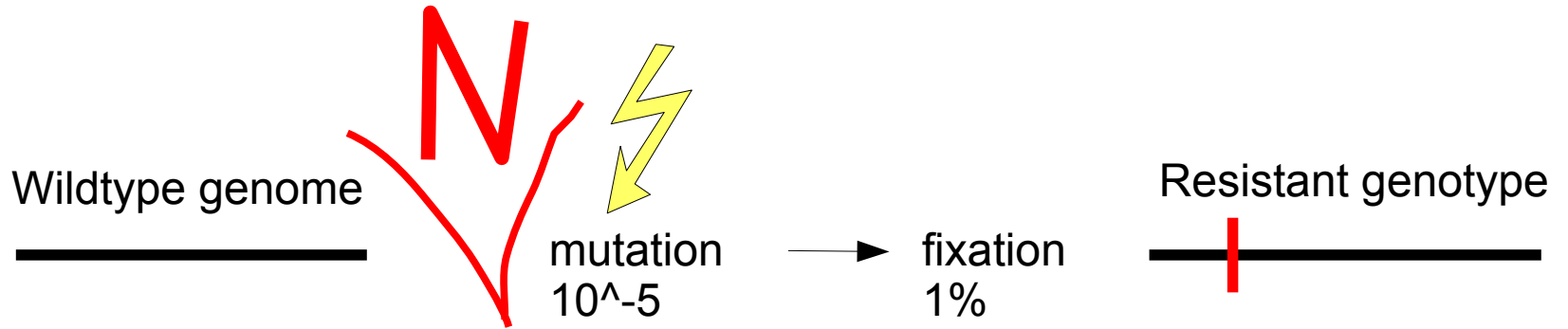


# Why combination therapy works

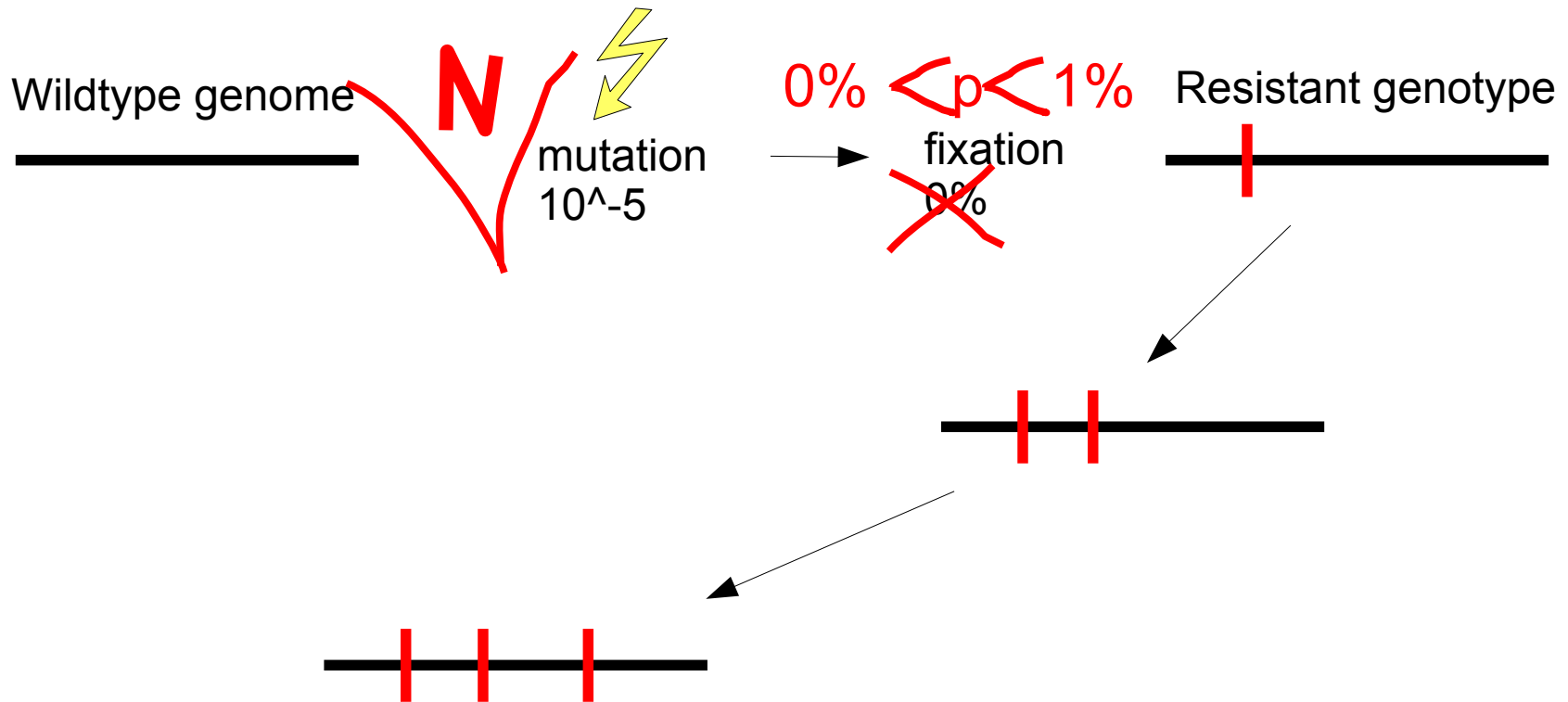


# Why combination therapy works

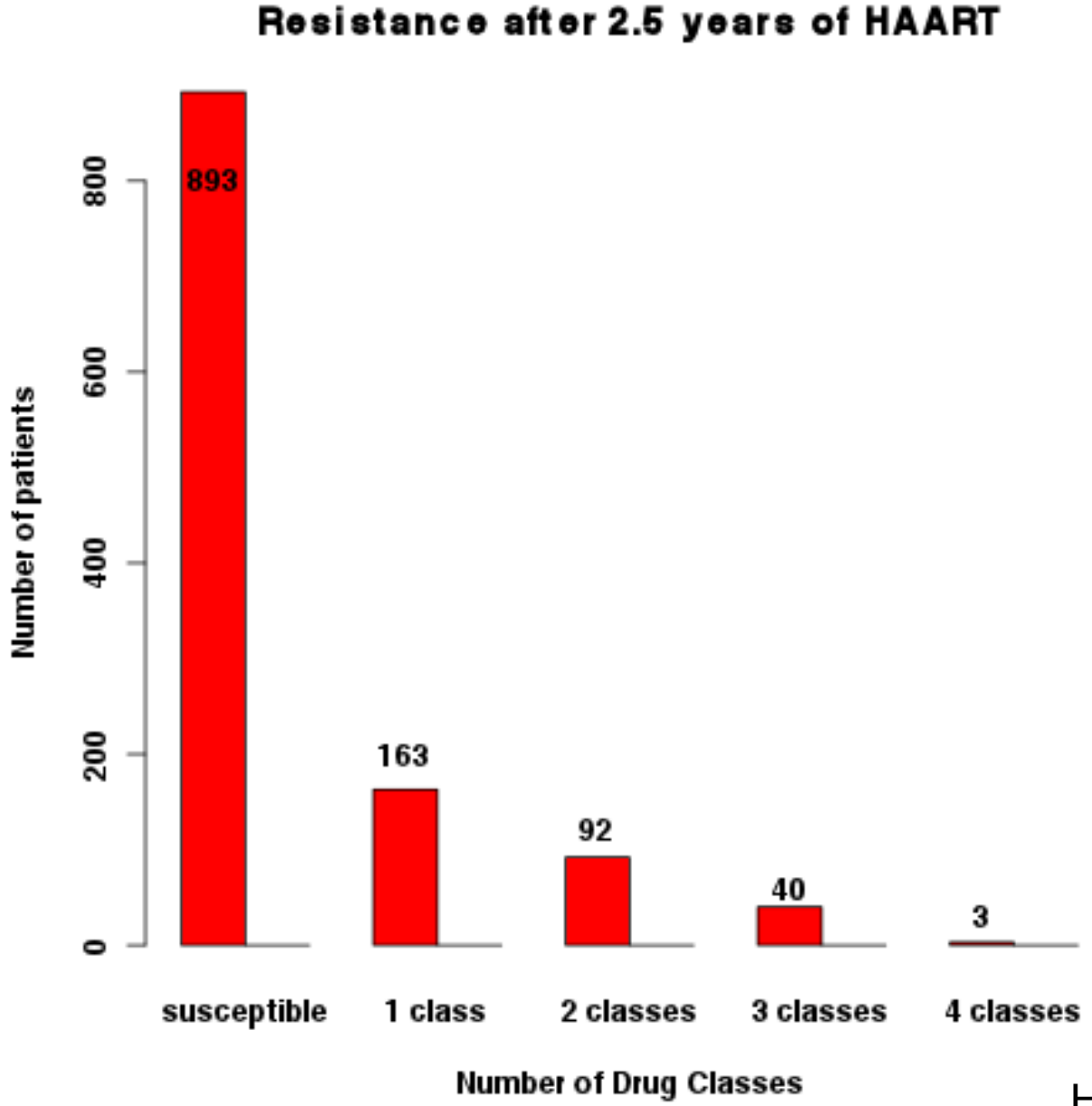
mono  
therapy



comb.  
therapy



# Resistance evolves one drug class at a time

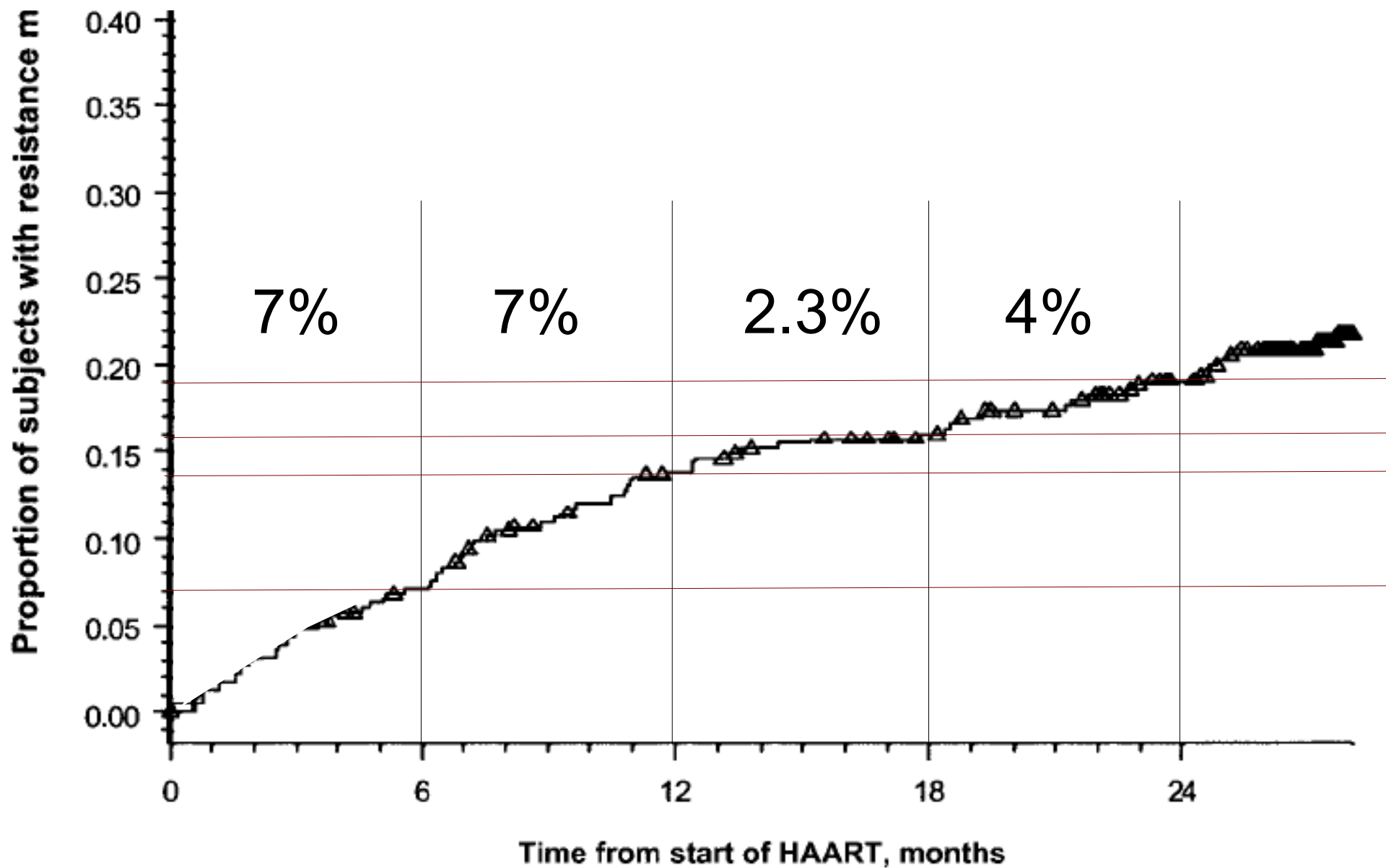


# Summary of introduction

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!

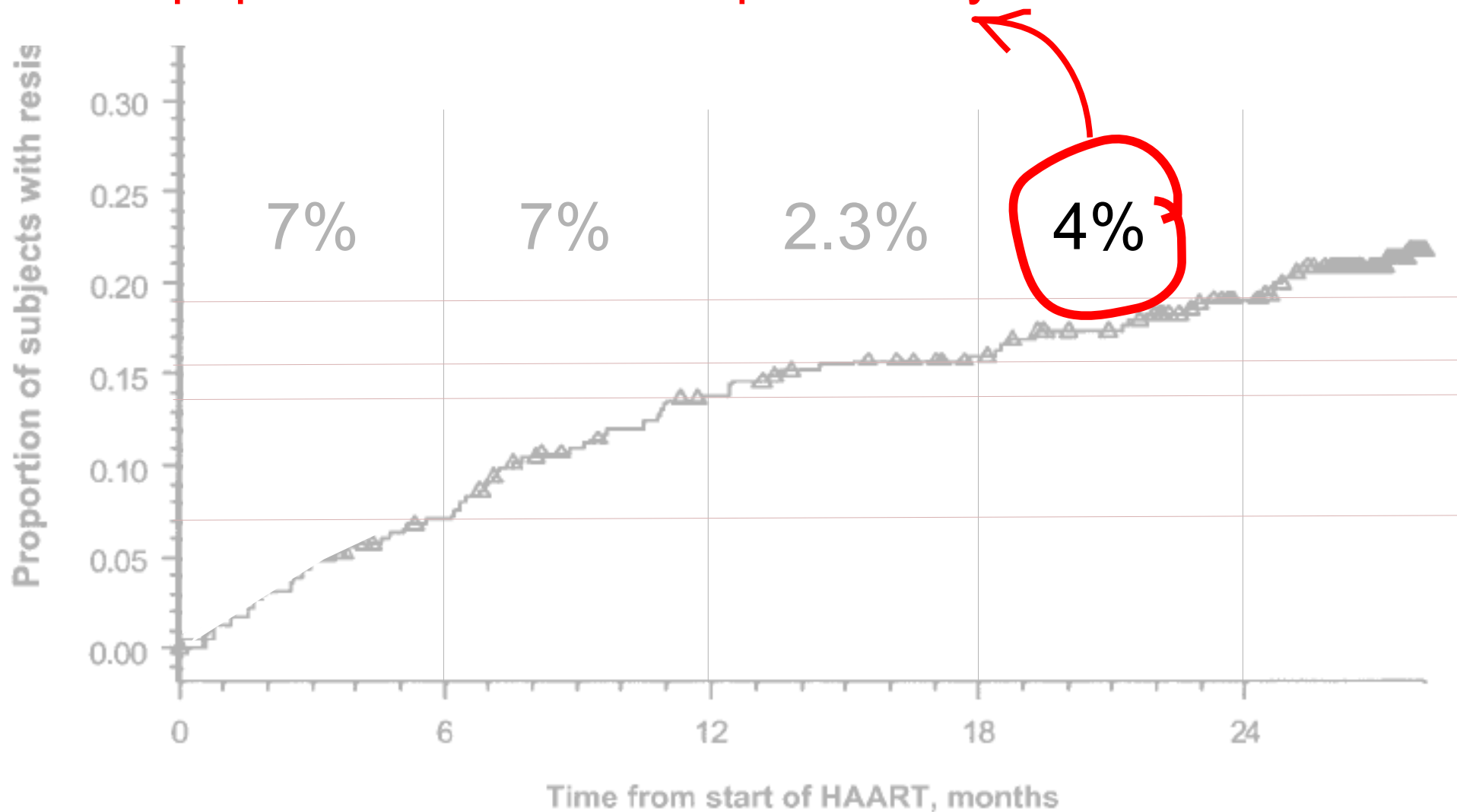
# Example calculation





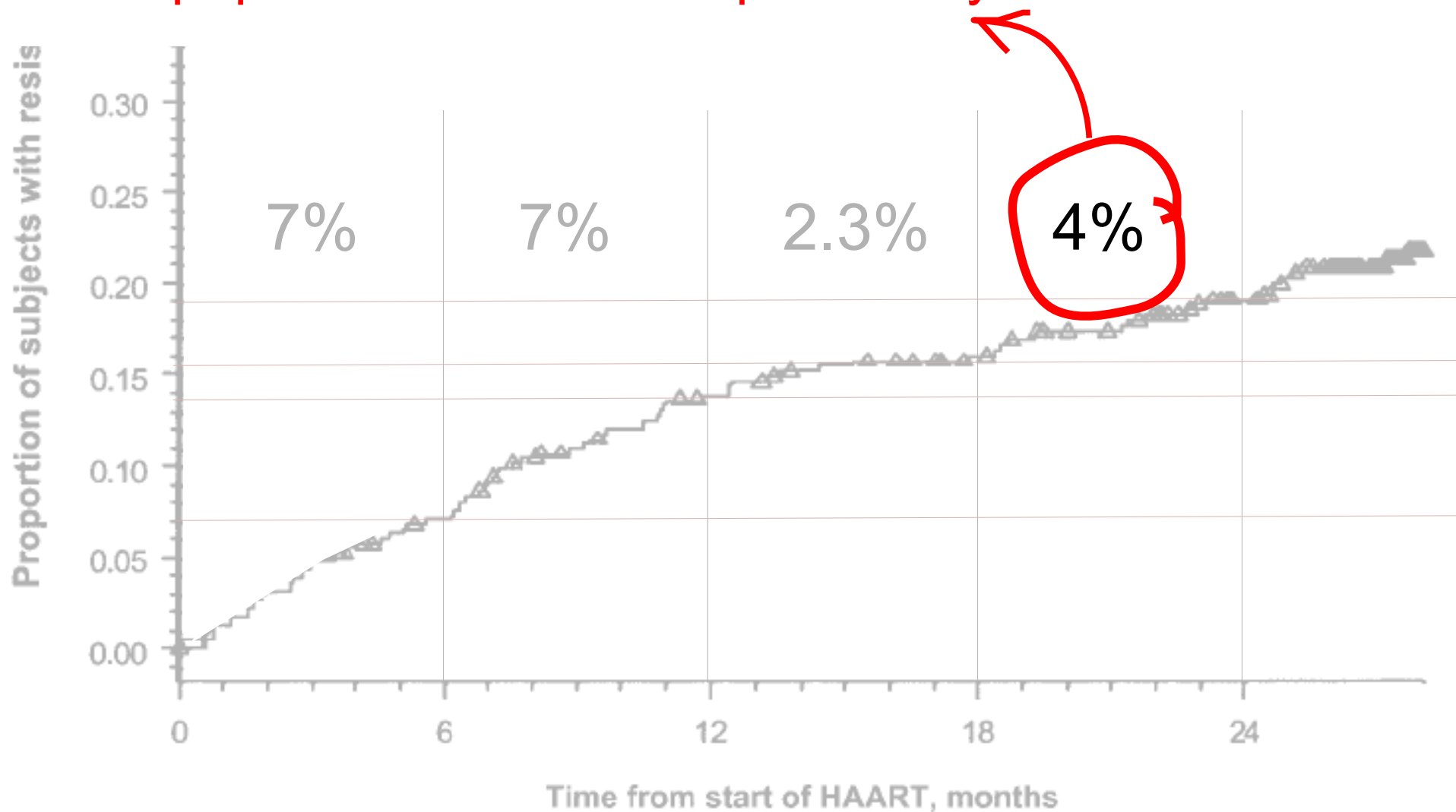
# Example calculation

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

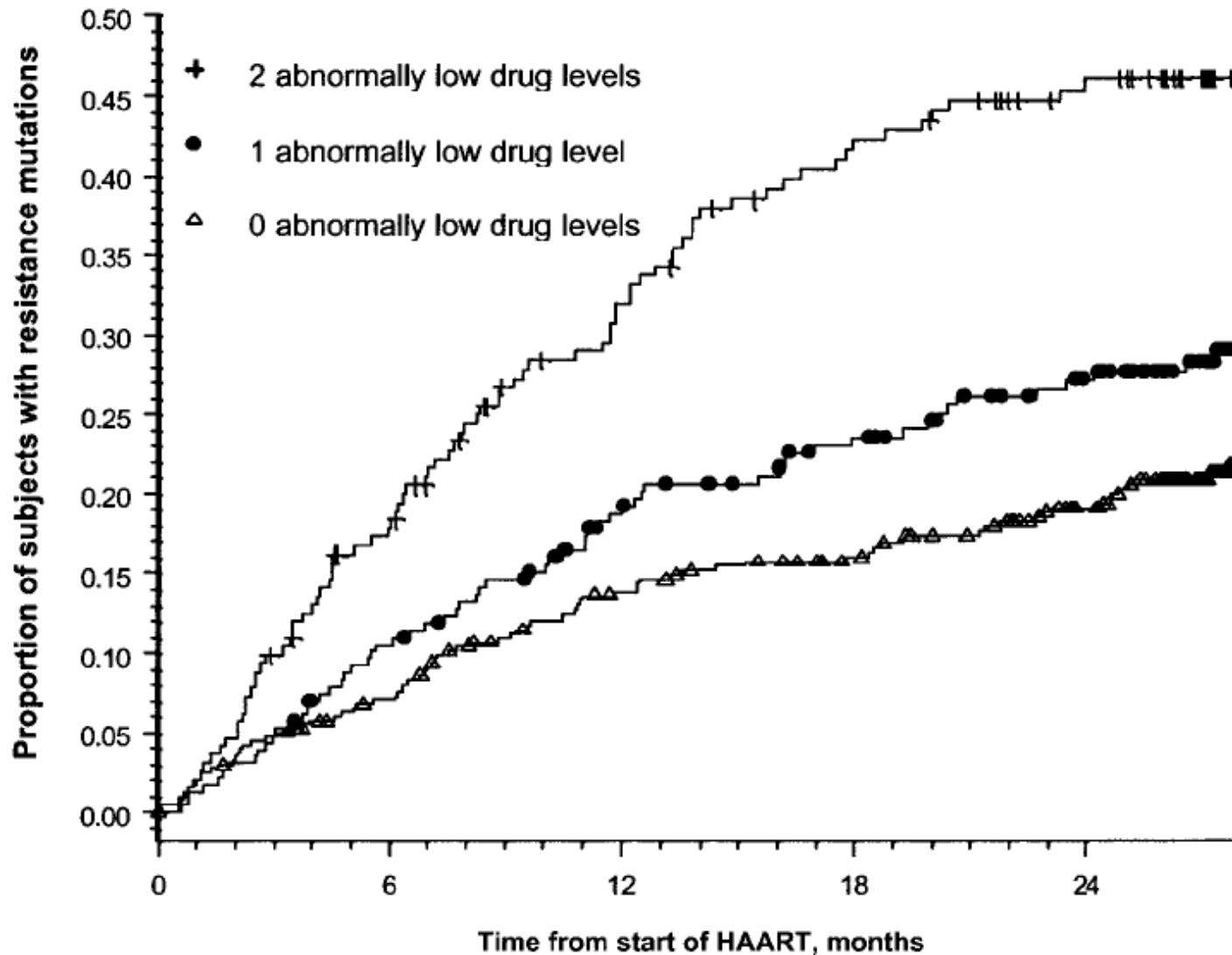


# Example calculation

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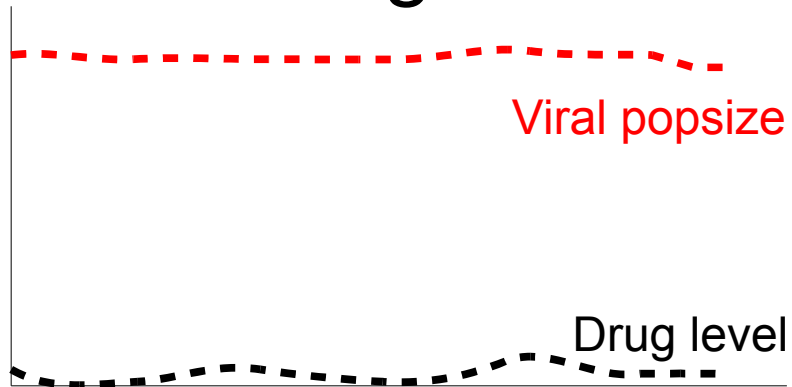


# Non-adherence increases rate of evolution



# Why non-adherence leads to faster evolution?

## 1. No drugs



# Why non-adherence leads to faster evolution?

~~1. No drugs~~

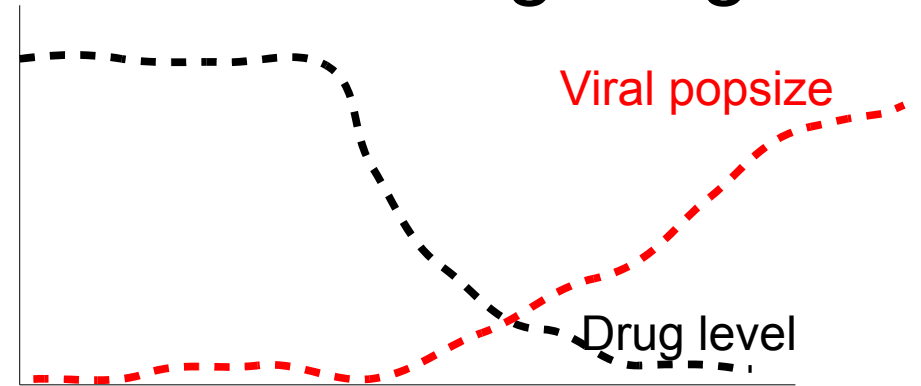
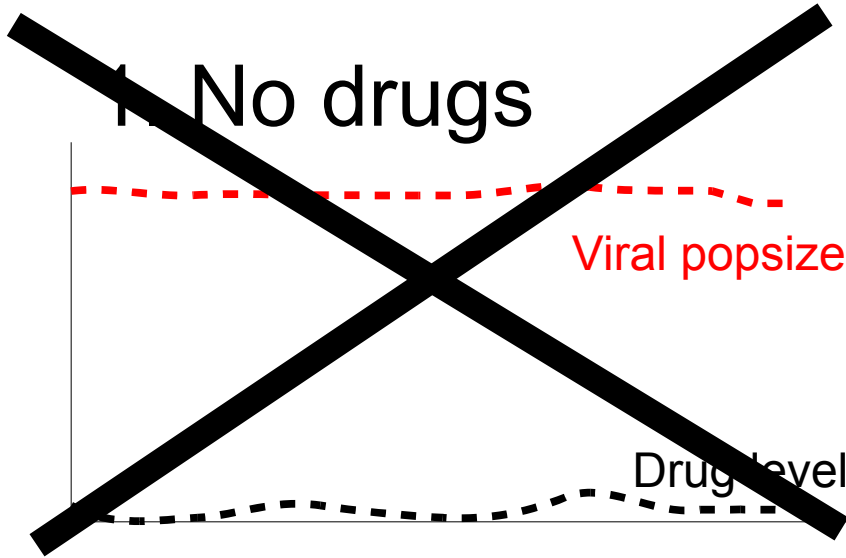
~~Viral popsize~~

~~Drug level~~

2. Decreasing drug level

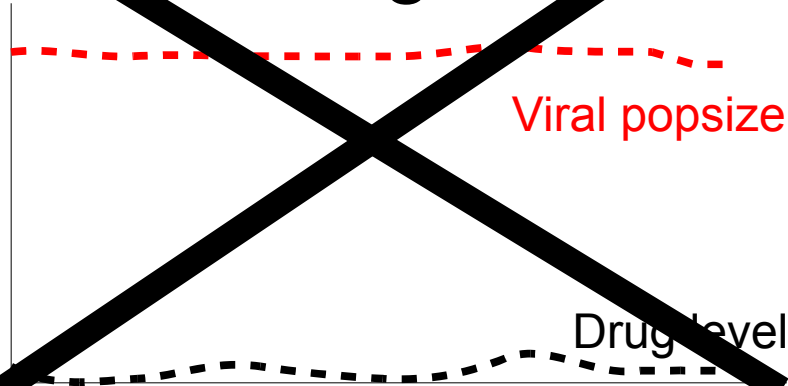
Viral popsize

Drug level

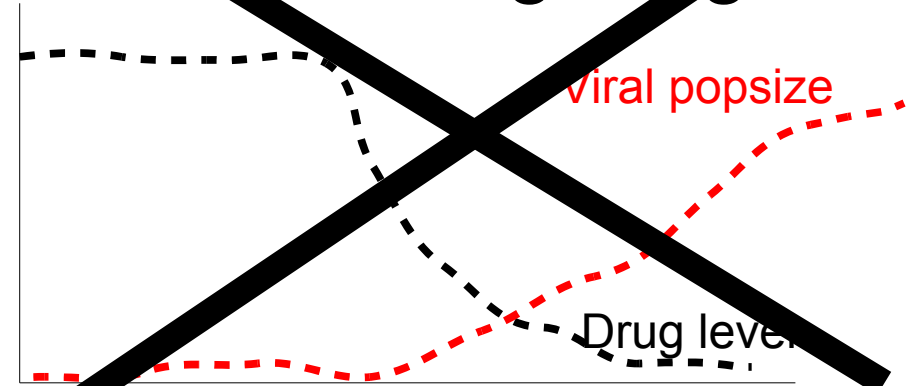


# Why non-adherence leads to faster evolution?

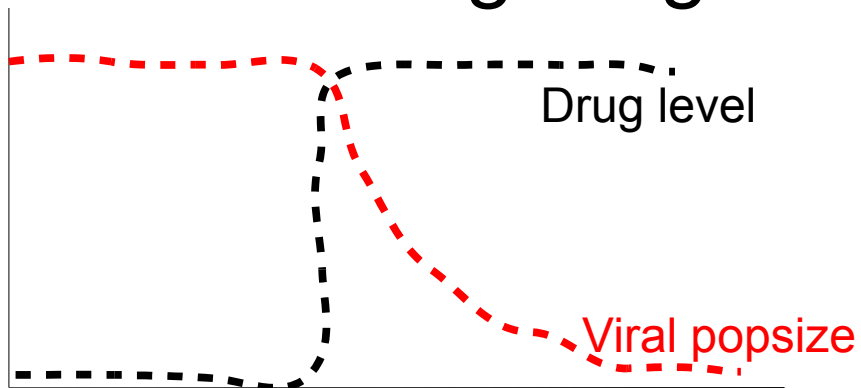
1. No drugs



2. Decreasing drug level

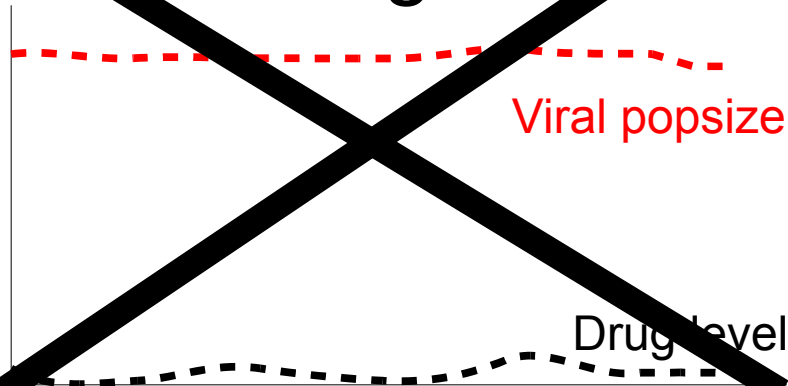


3. Increasing drug level

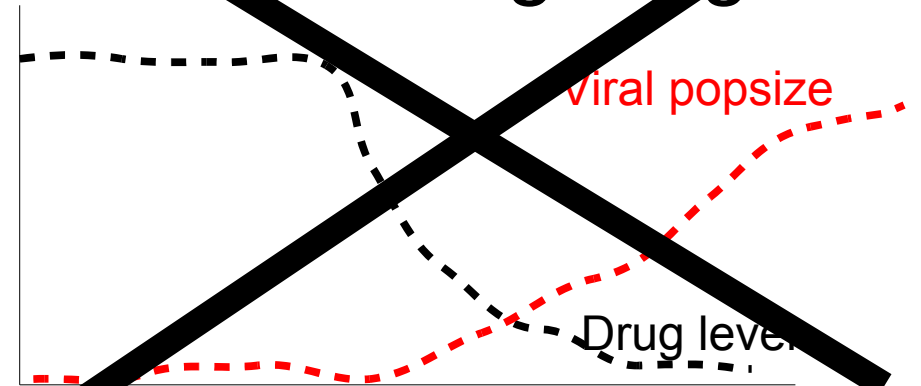


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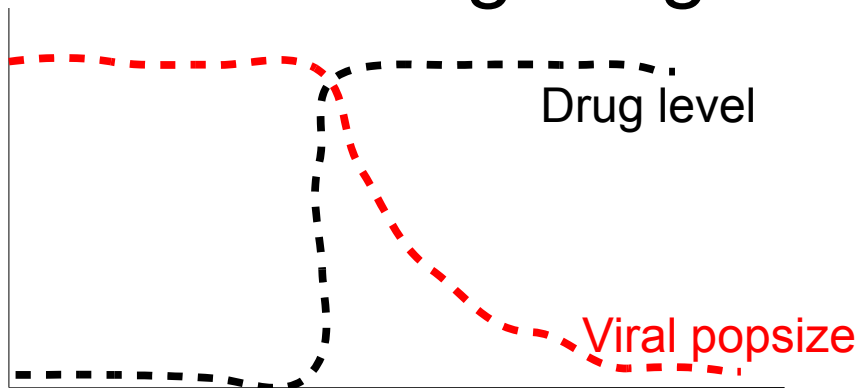
1. No drugs



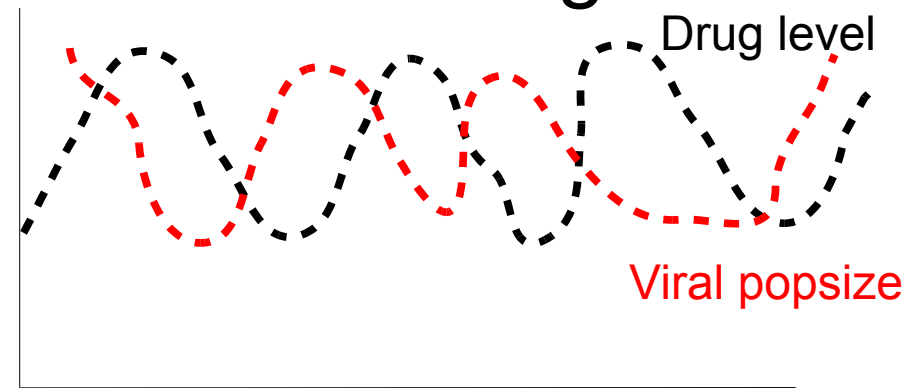
2. Decreasing drug level



3. Increasing drug level

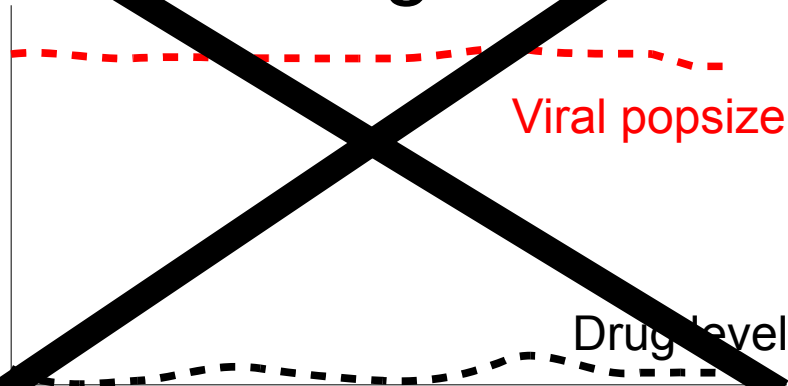


4. Quick changes

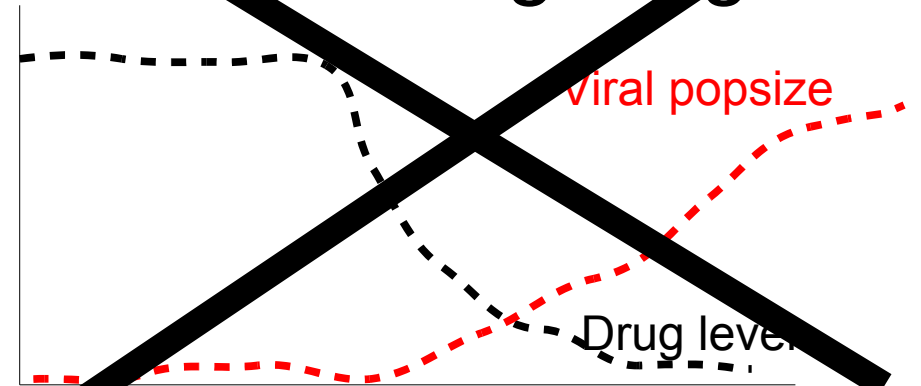


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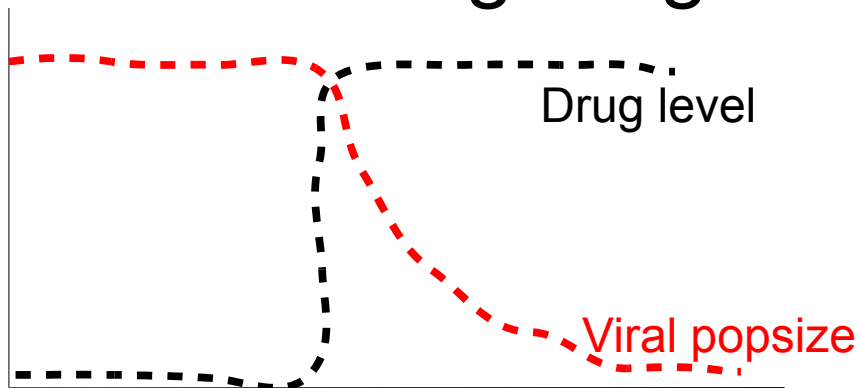
1. No drugs



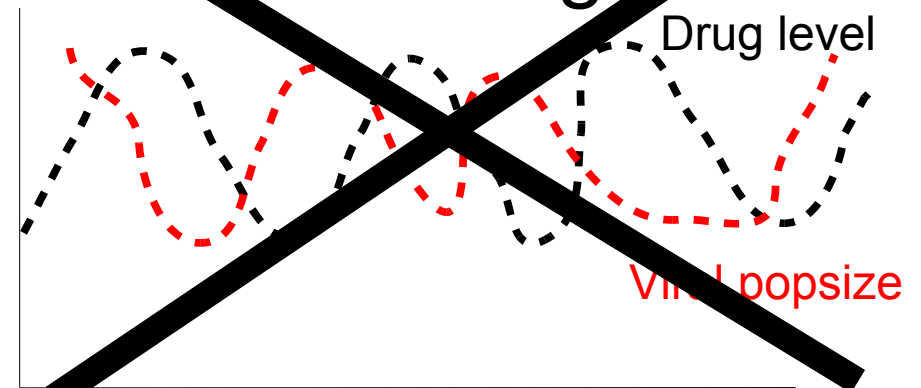
2. Decreasing drug level



3. Increasing drug level



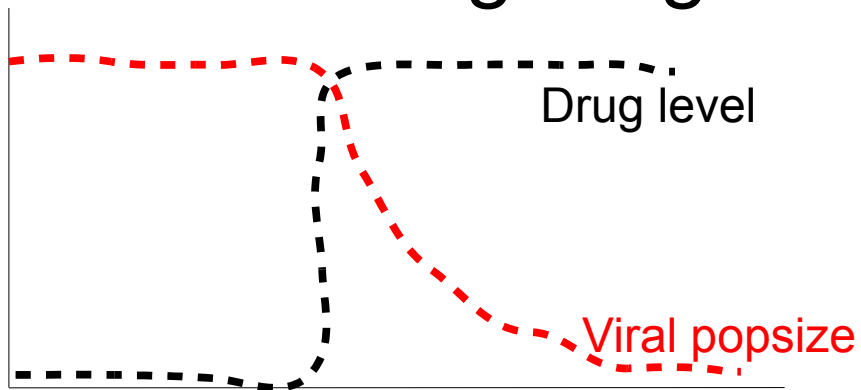
4. Quick changes



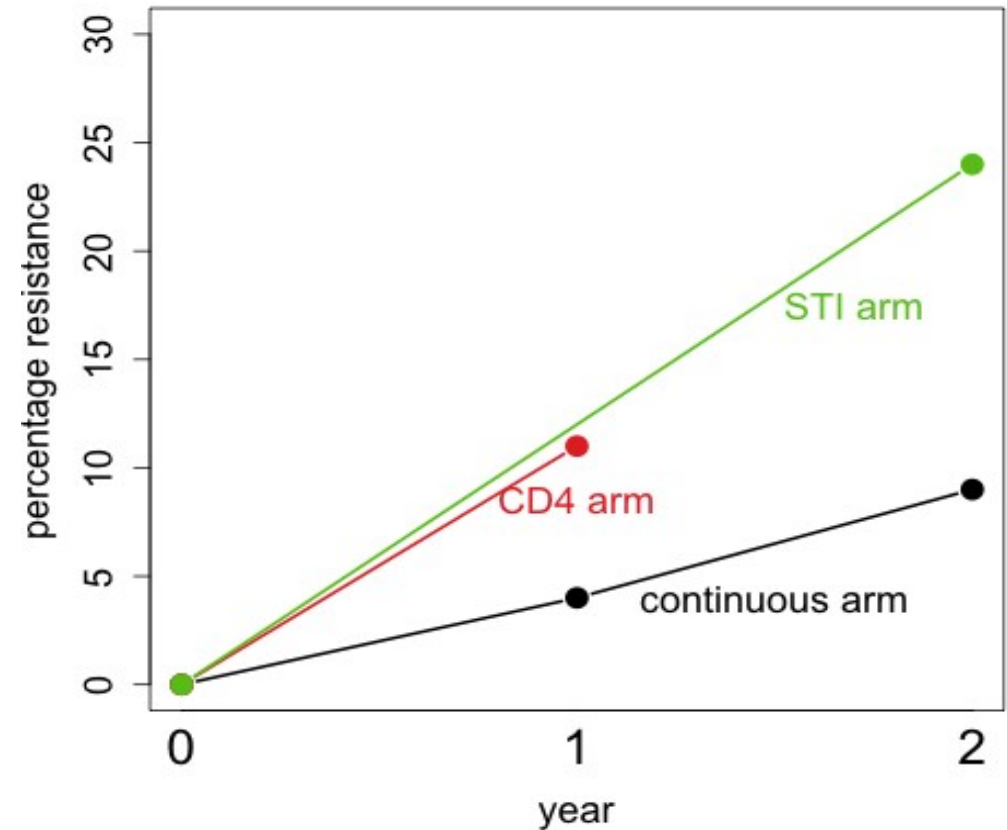


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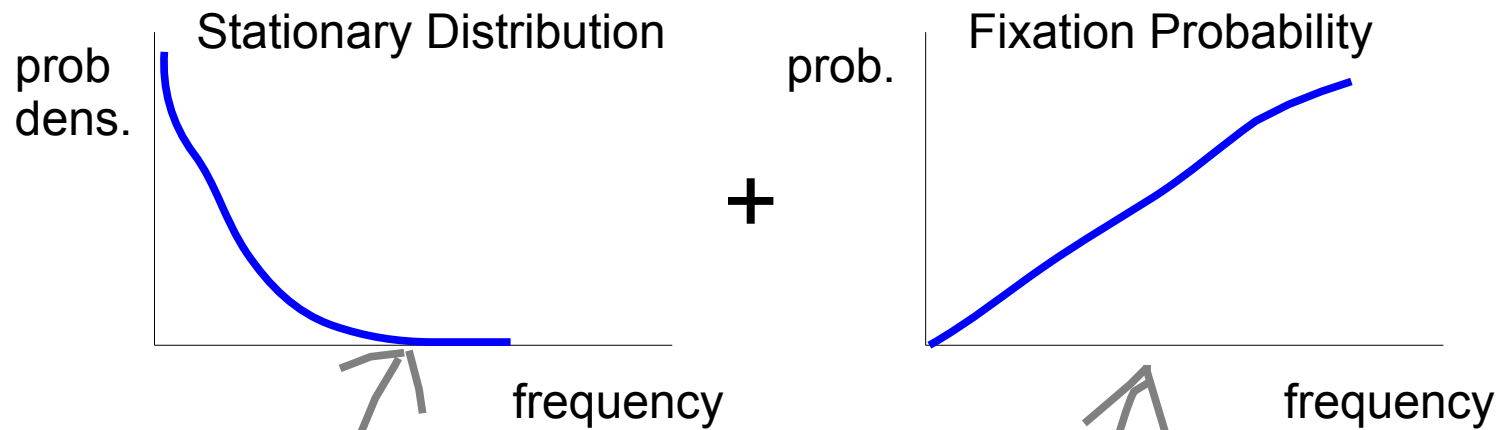
## 3. Increasing drug level



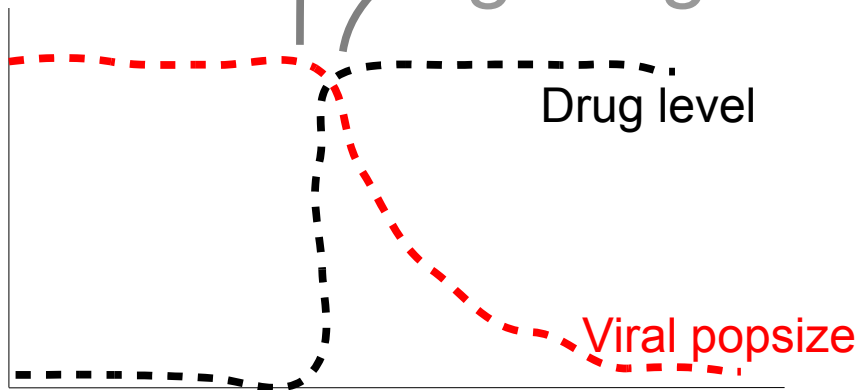
Rate of evolution of resistance Trivacan trial



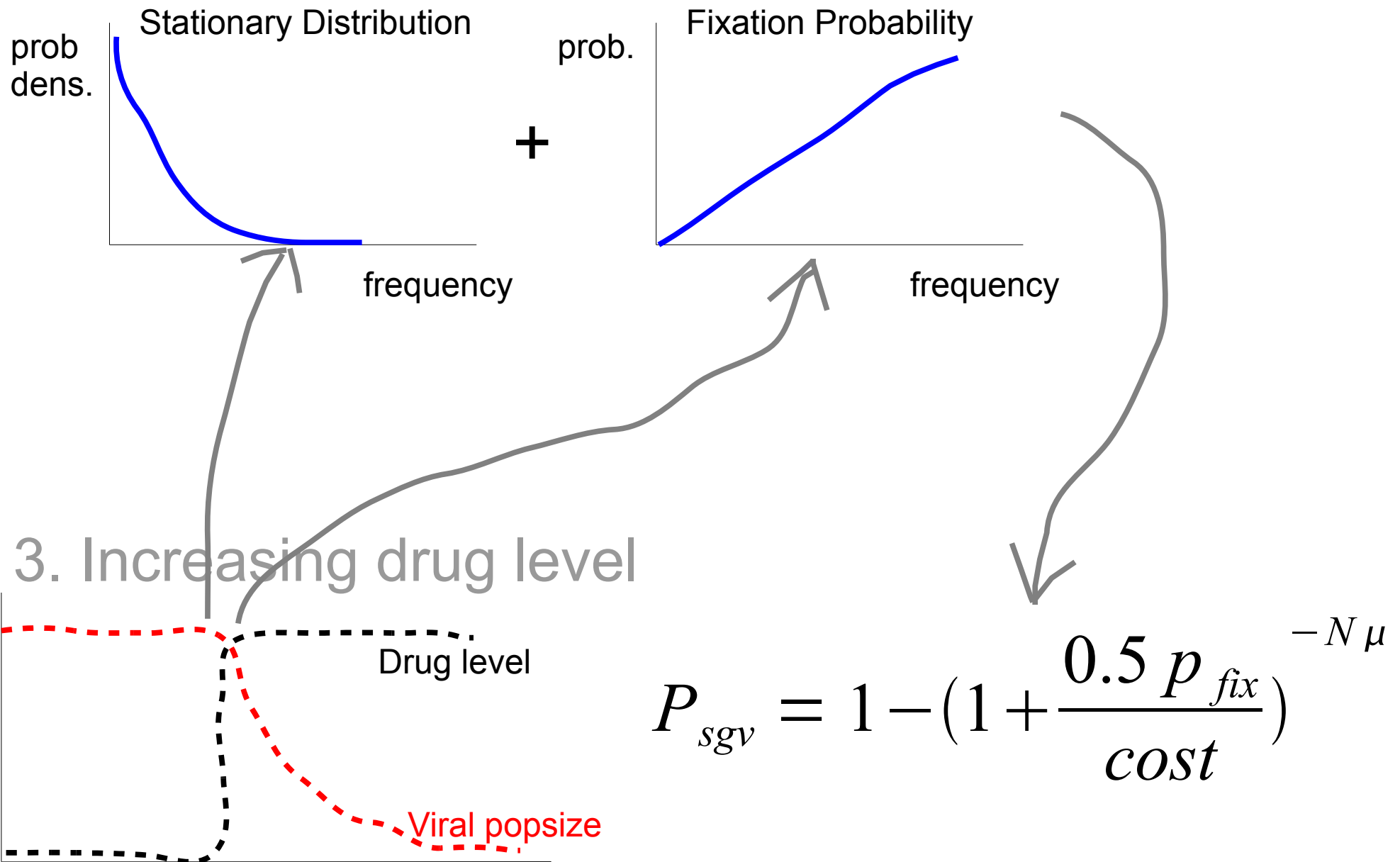
# Adaptation from standing genetic variation



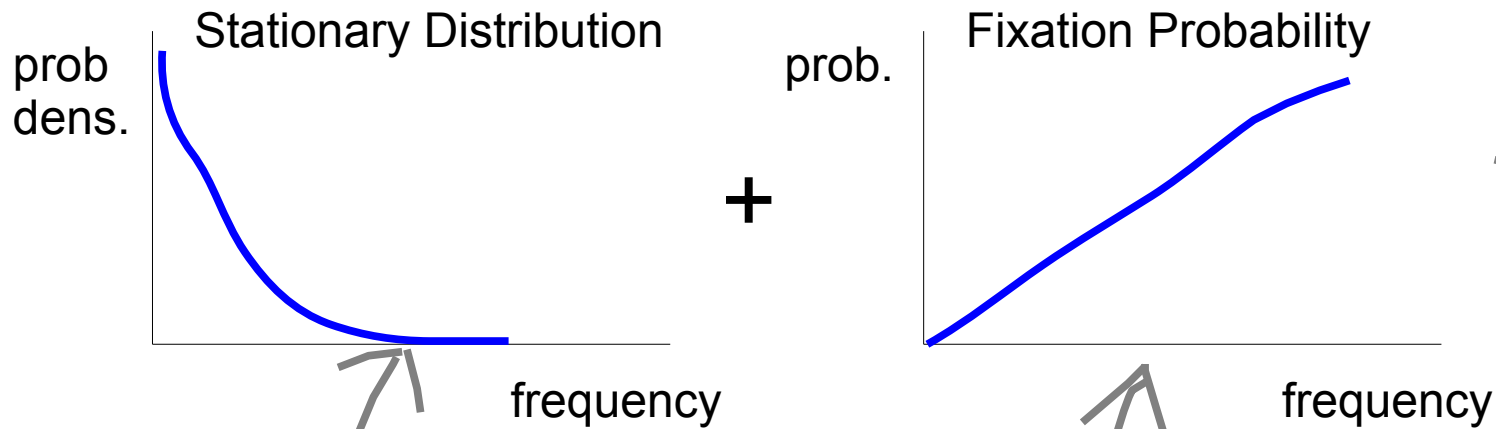
3. Increasing drug level



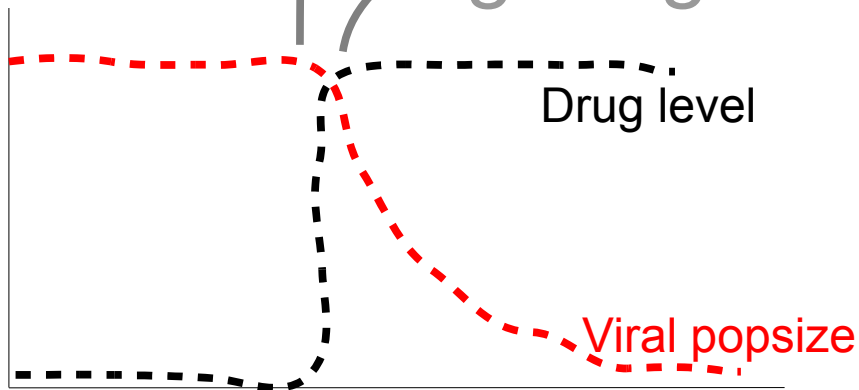
# Adaptation from standing genetic variation



# Adaptation from standing genetic variation



3. Increasing drug level



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

# Data

7 trials of “Structured Treatment Interruptions”

Example: Swiss-Spanish Intermittent Treatment Trial

87 patients (-7)

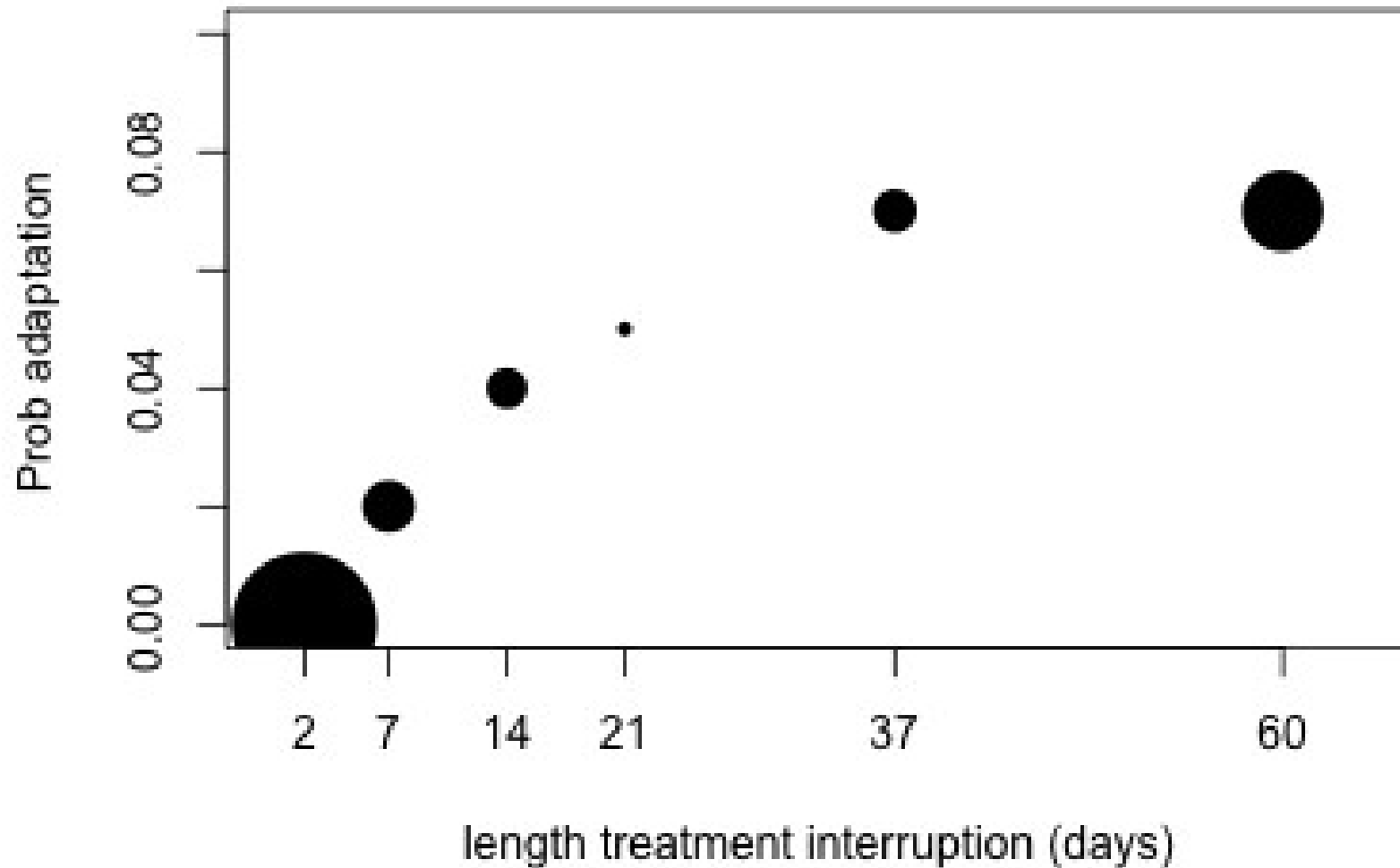
4 interruptions of 14 days

11 patients had resistance

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

# Data

Prob of evolution resistance per interruption



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

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

10<sup>-5</sup>mut/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  $N_e$  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