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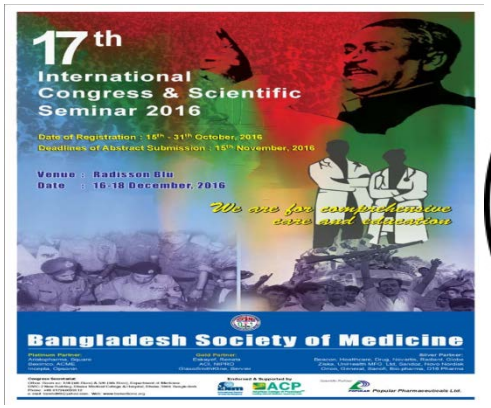

Direct Acting Antivirals in the Treatment of HCV Infection; are they the last Nail in the Coffin?

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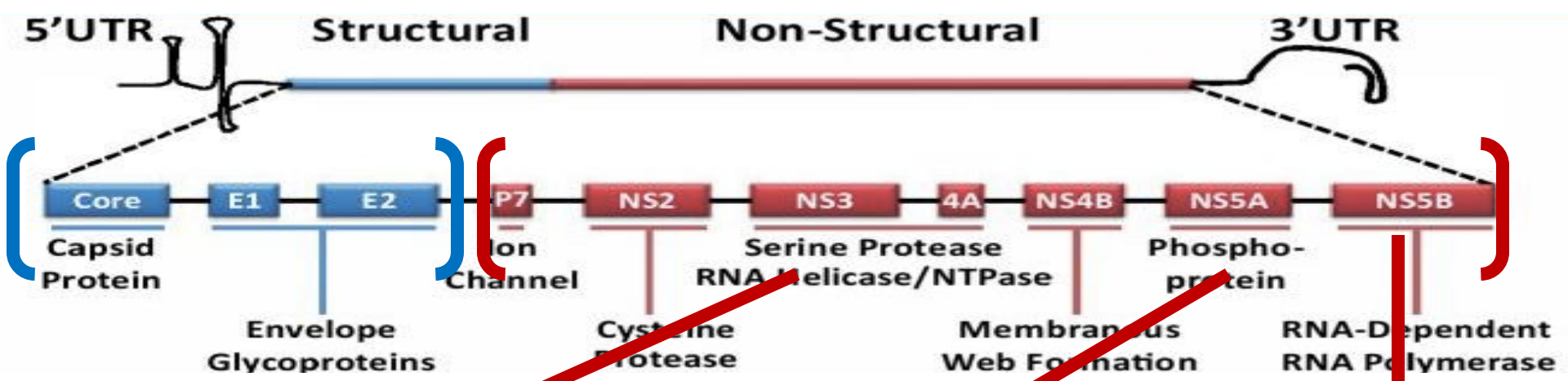
Zagazig Faculty of Medicine, Egypt

President of HWG/ISC

In 2011, the arrival of the 1st generation DAAs profoundly changed the landscape of HCV therapy and SVR rates.

Currently, the treatment for chronic hepatitis C has become possible



<u>Covalent (ketoamides)</u>

Boceprevir

Telaprevir

<u>Non- covalent (tripeptide or macrocyclic)</u>

Fladaprevir

Semiprevir

Paritaprevir

Asunaprevir

Grazoprevir

Ledipasivir

Daclatasvir

Ombitasevir

Albasvir

Samatasvir

PPI- 668

Nucleoside analogue

Sofosbuvir

- Non- nucleoside

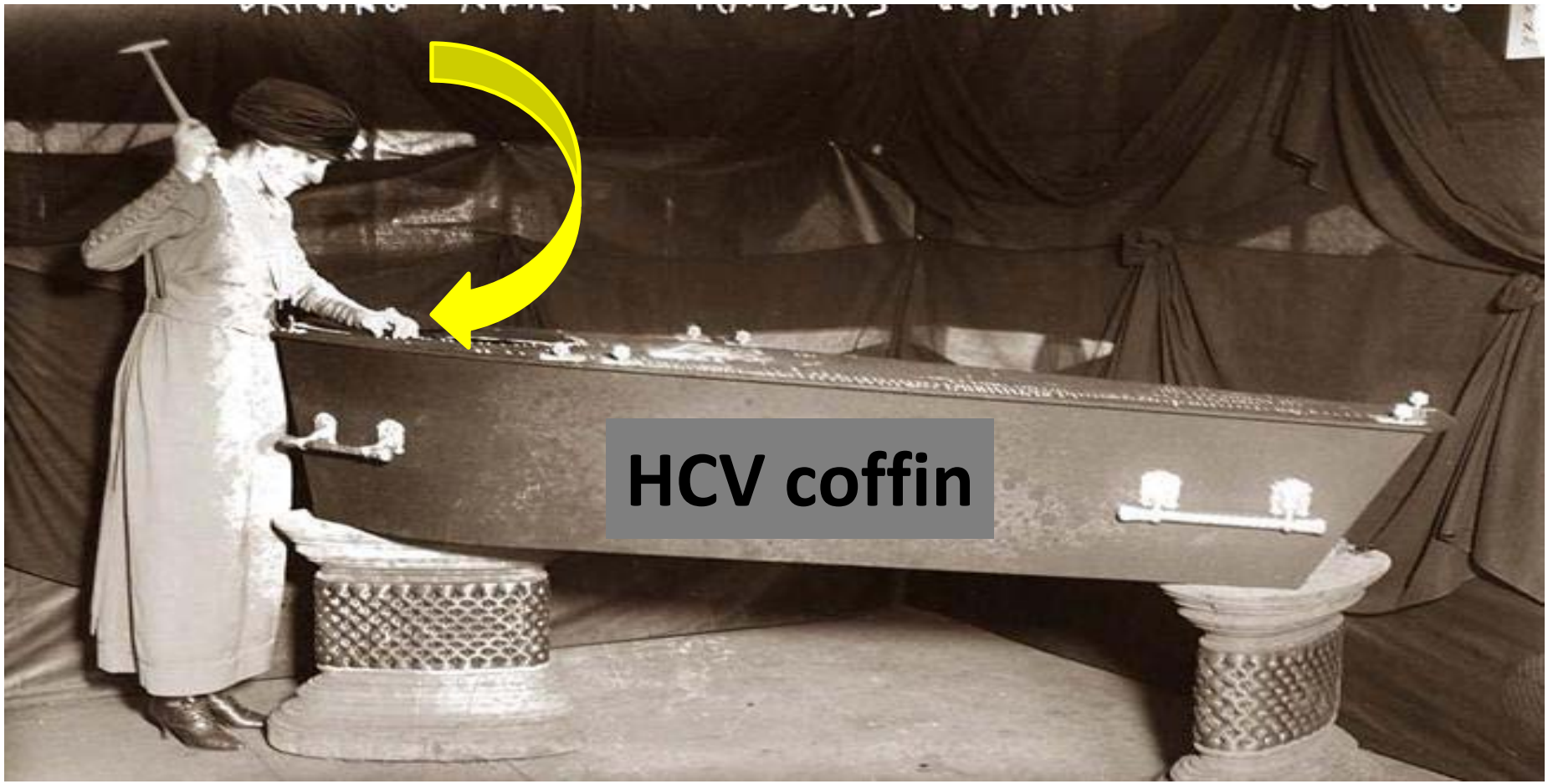
GS 9669

Buclabuvir

Dasabuvir

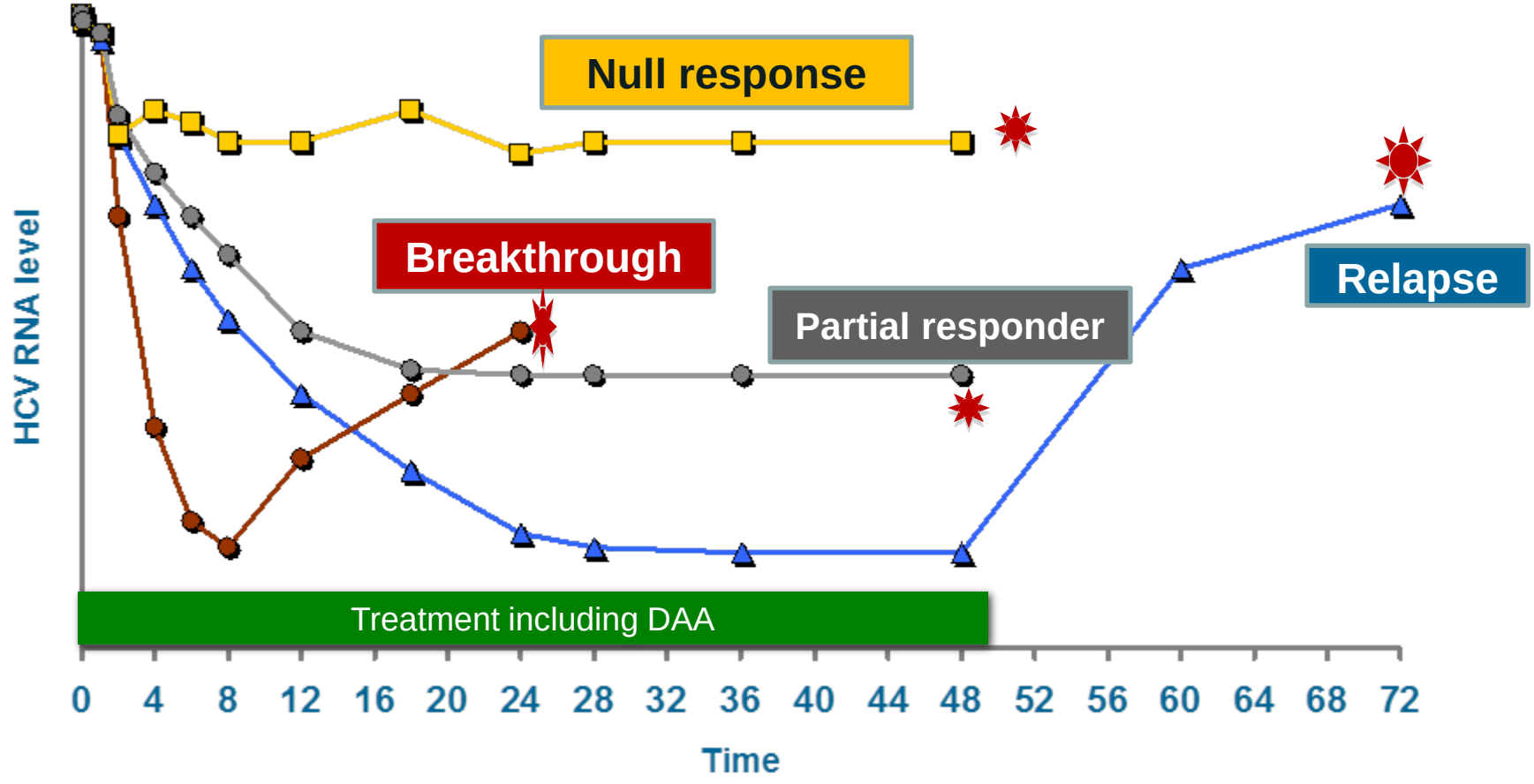
Furthermore, recent drugs in the anti-HCV pipeline have the full capacity, as well as enhanced tolerance and safety profiles.

So, can DAAs be considered the last nail in HCV coffin.



Unfortunately, in real life cohorts 5-10% of patients end up with virological failure

Data from real life setting shows 4 groups of patients failing therapy



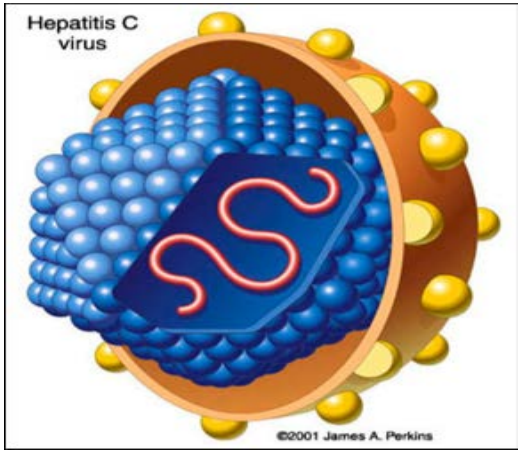
Resistant variants

WHY

WHY?

Why

1. Virus factors



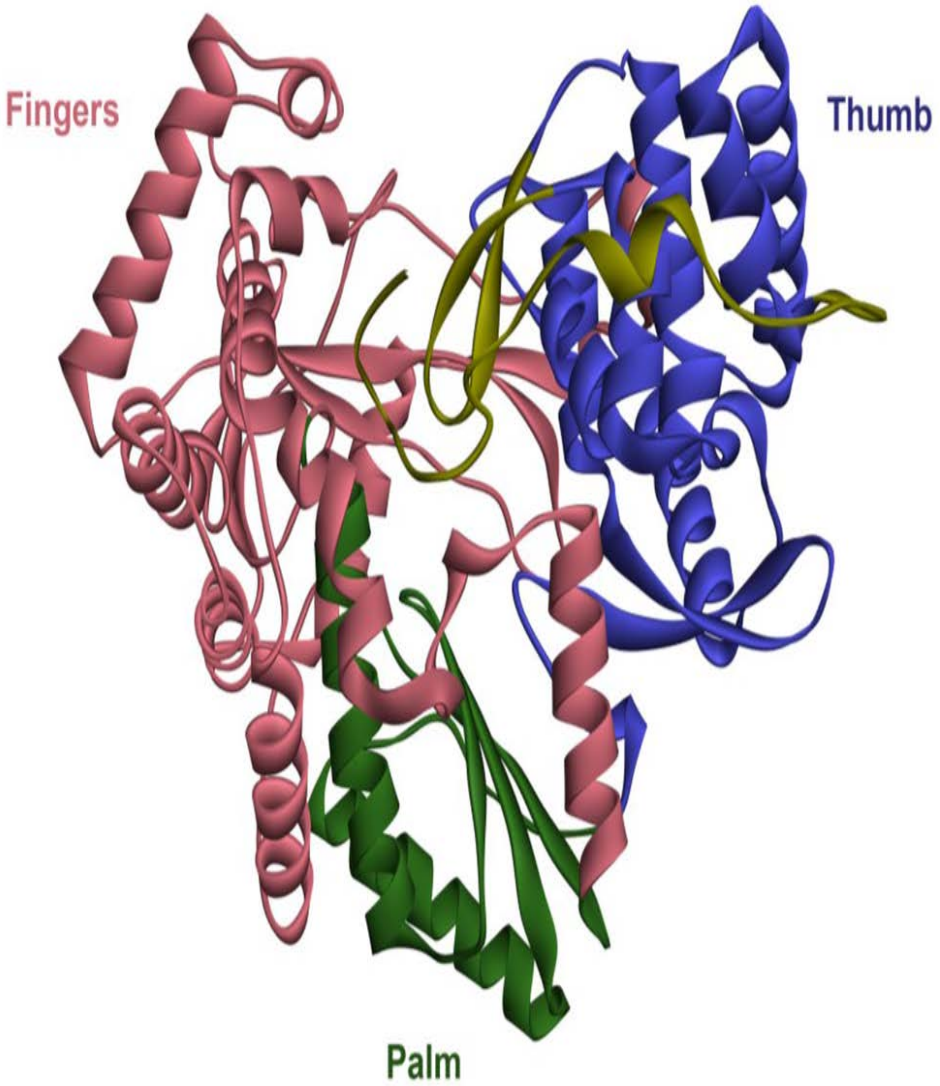
2. Drug factors

1. Viral factors

RNA- dependent RNA polymerase (RdRp)

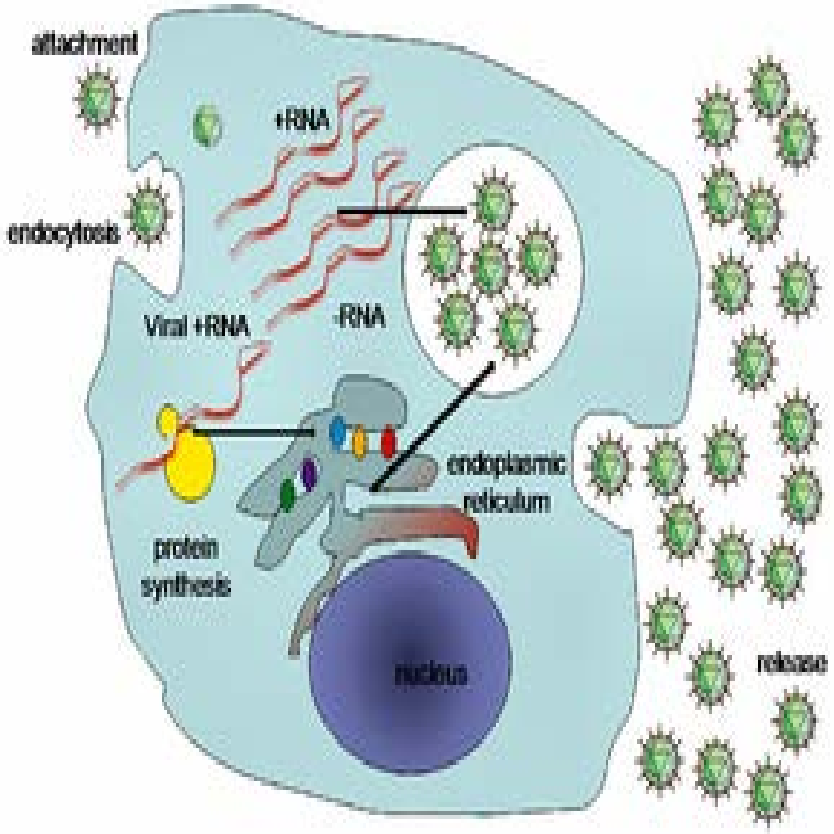
- **Effectuates synthesis of the RNA by catalyzing formation of the complementary RNA strand**

- **Error-prone**
- **Lacks proof-reading activity.**

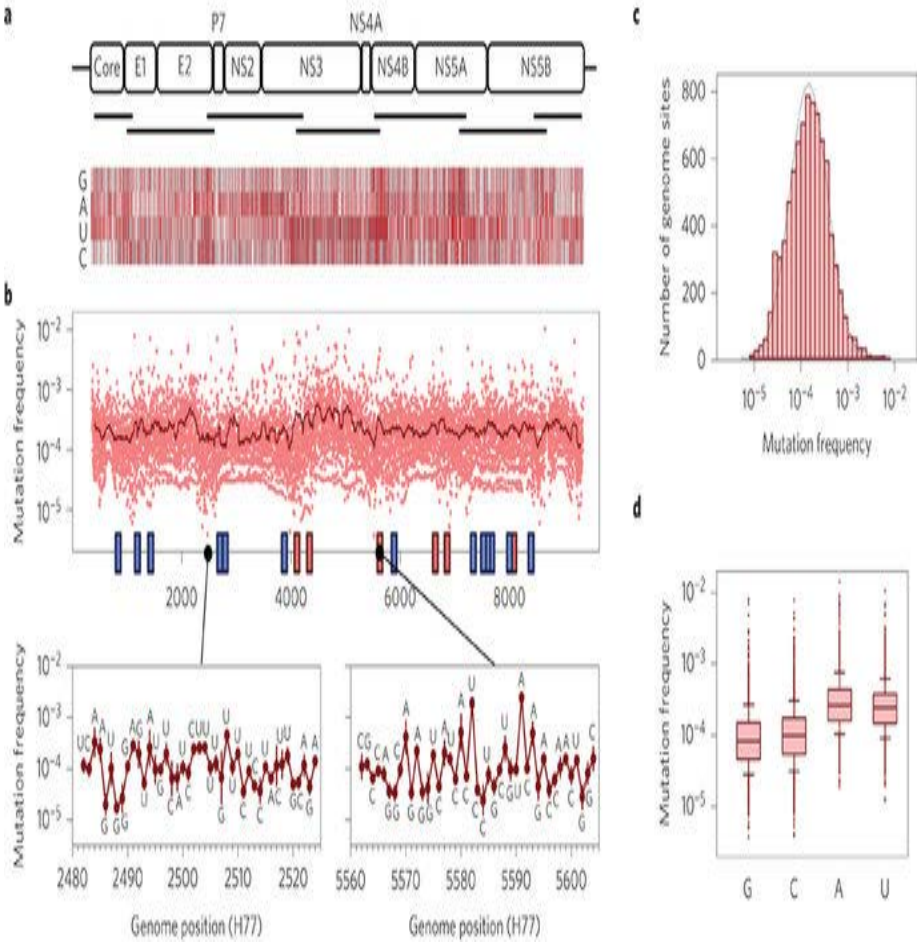


Genetic variability of HCV

High replication rate, 10^{10}-10^{12}, Half-life 2-5 hs

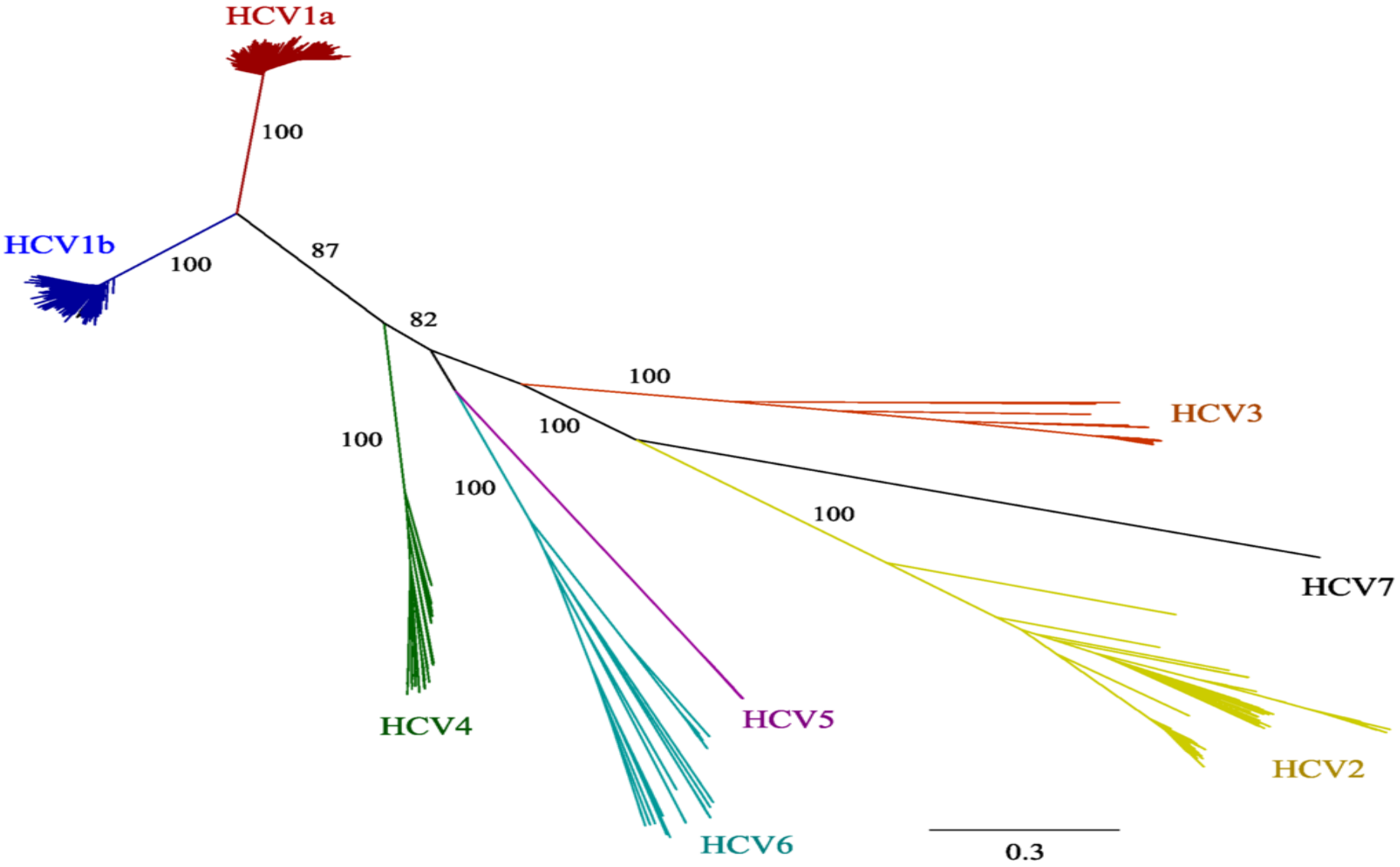


Very high mutation rate of HCV, 10^{-4}–10^{-5} substitutions/ nucleotide/ round of genome replication.

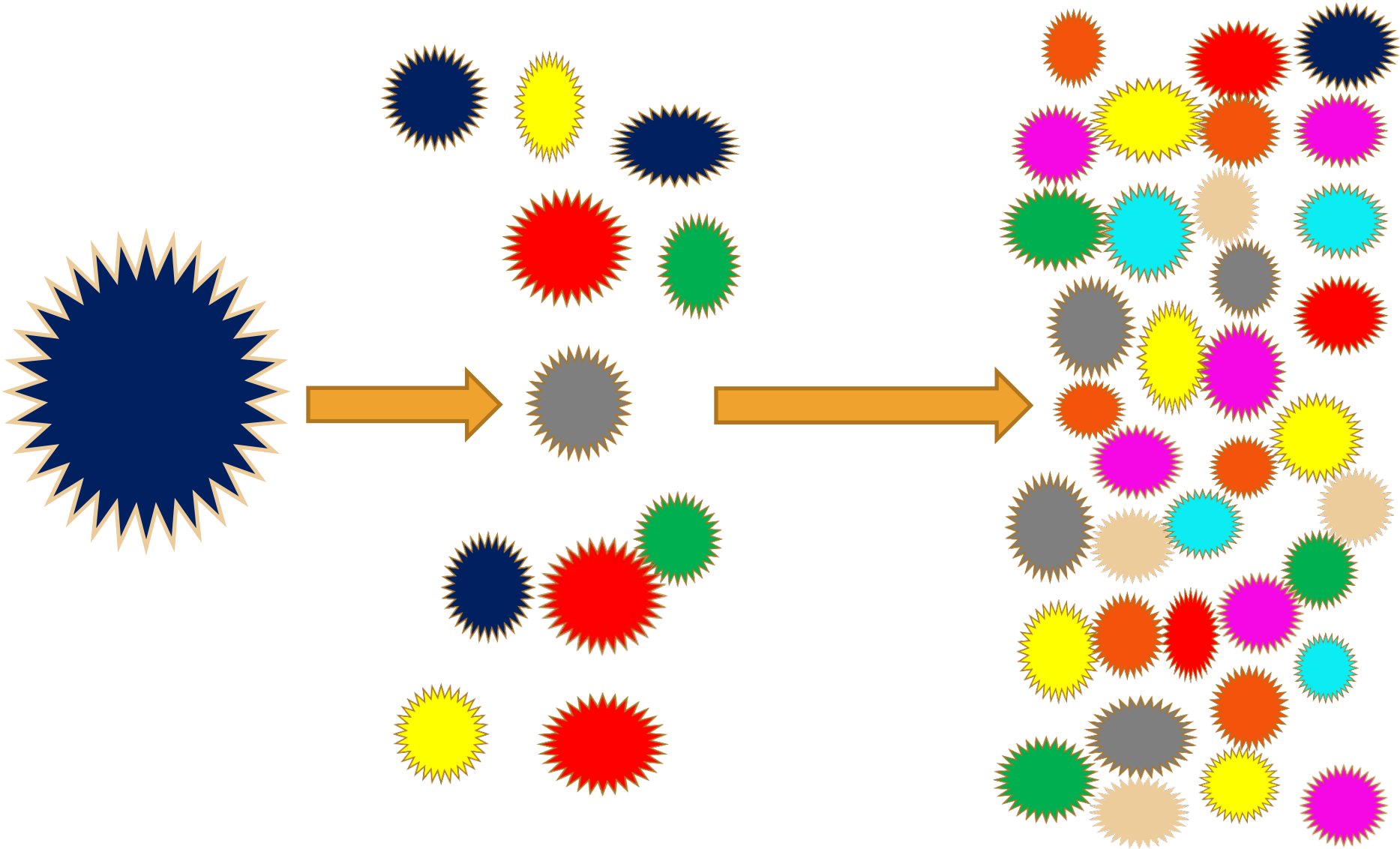


At the level of all infected population

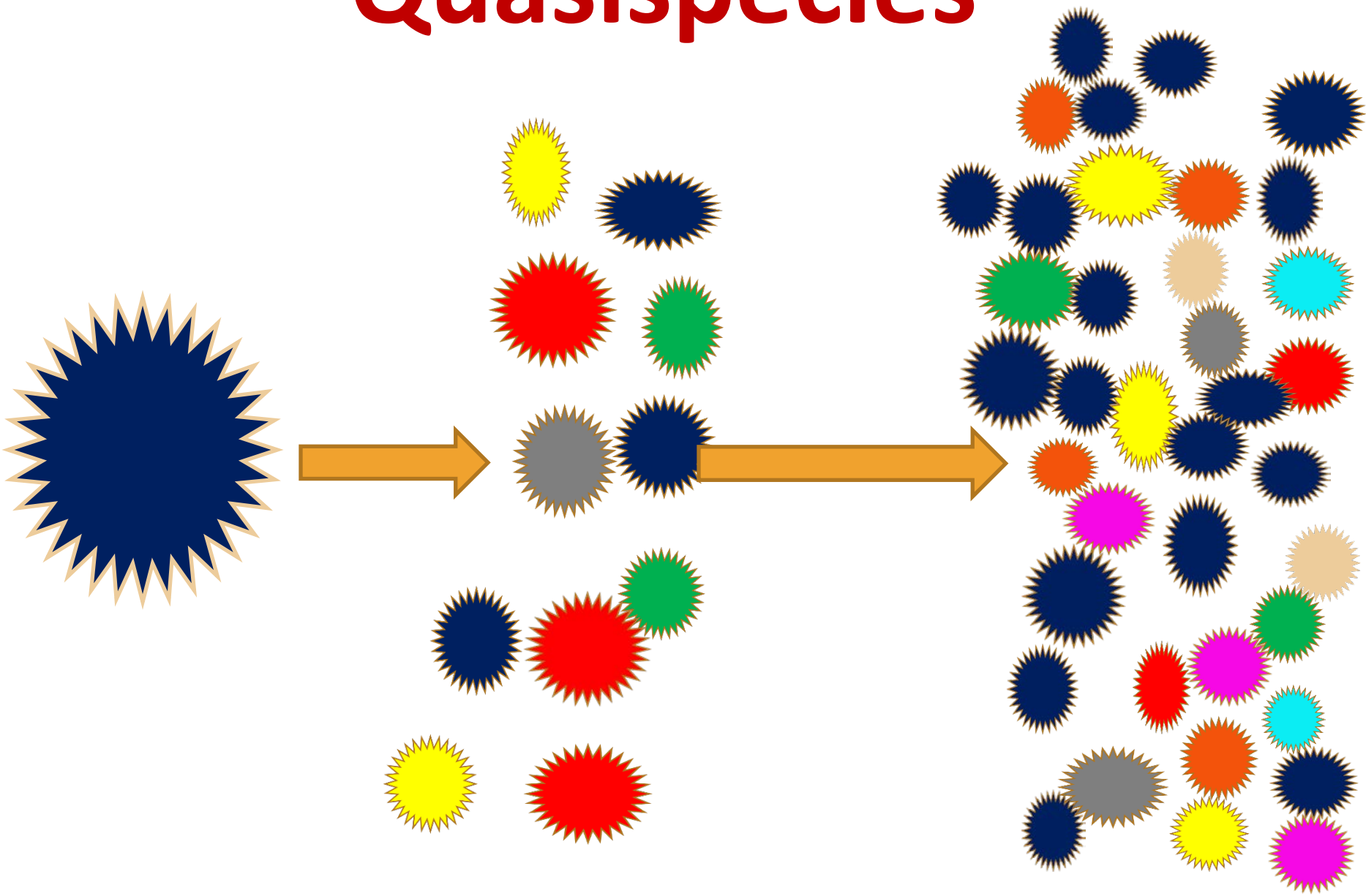
Genotypes and subtypes



At level of an infected individual: Viral quasispecies



Quasispecies



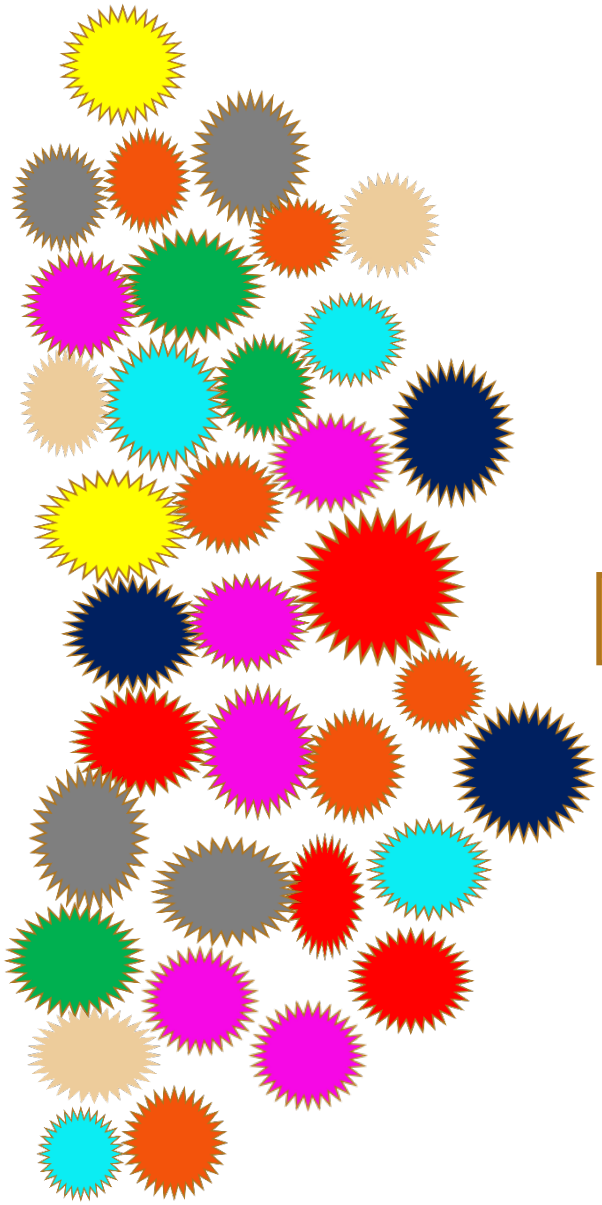
Fitness

fitness-associated substitution(s) in the sequence of HCV genome

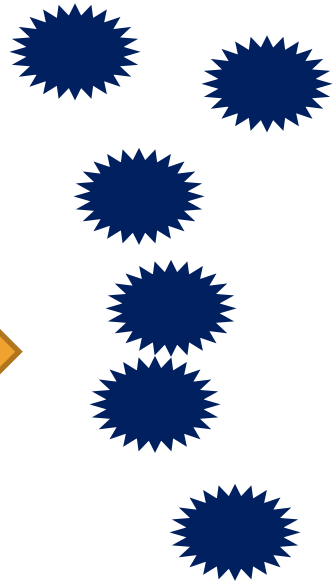
resistance-associated substitution(s) in the sequence of HCV genome

The populations of viral quasispecies within each patient, are under the pressure of Darwinian selection forces which lead to natural selection to optimize fitness.

In the absence of DAAs

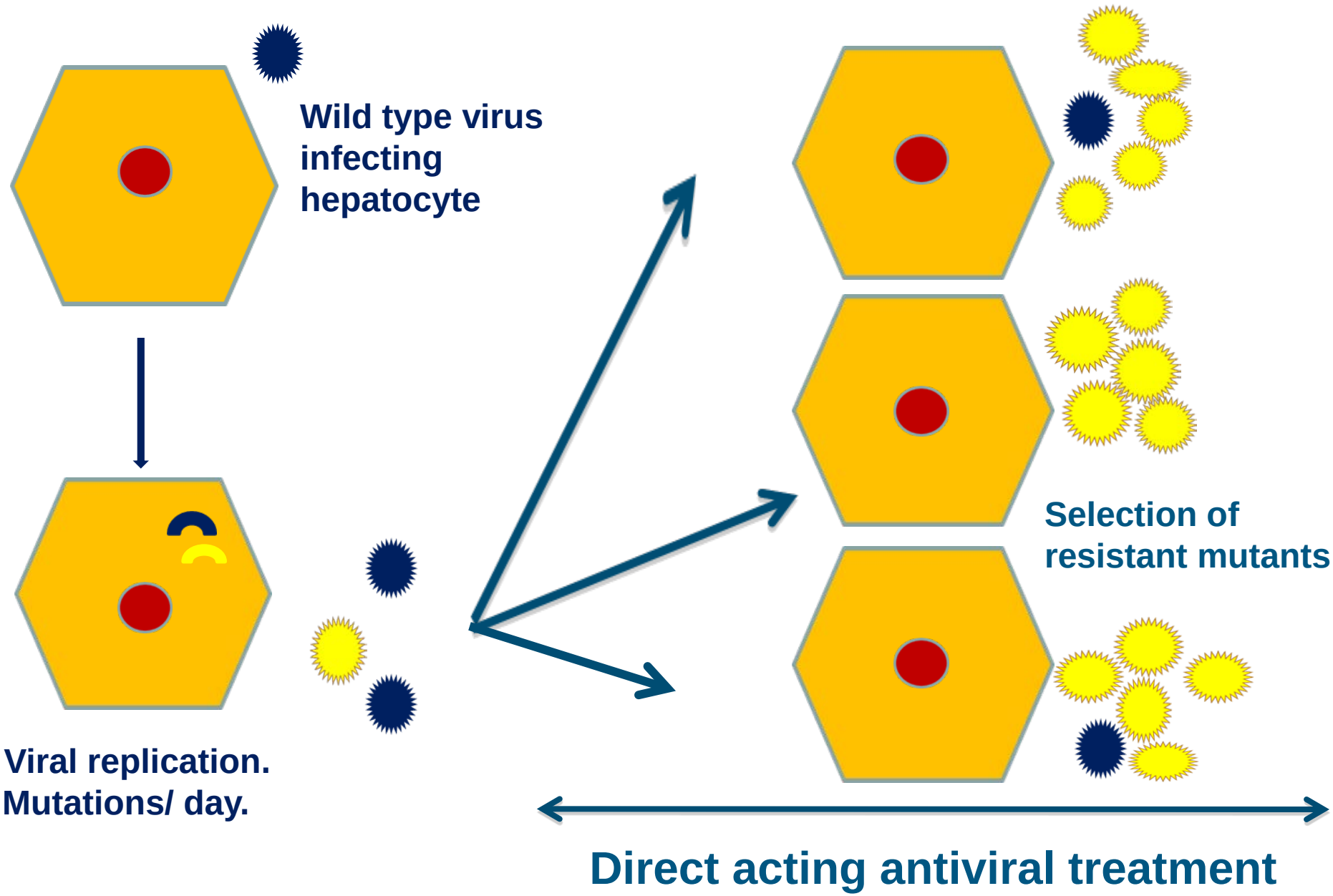


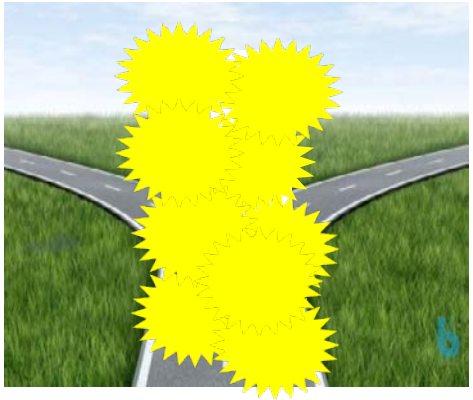
Natural selection
(Darwinian evolution)



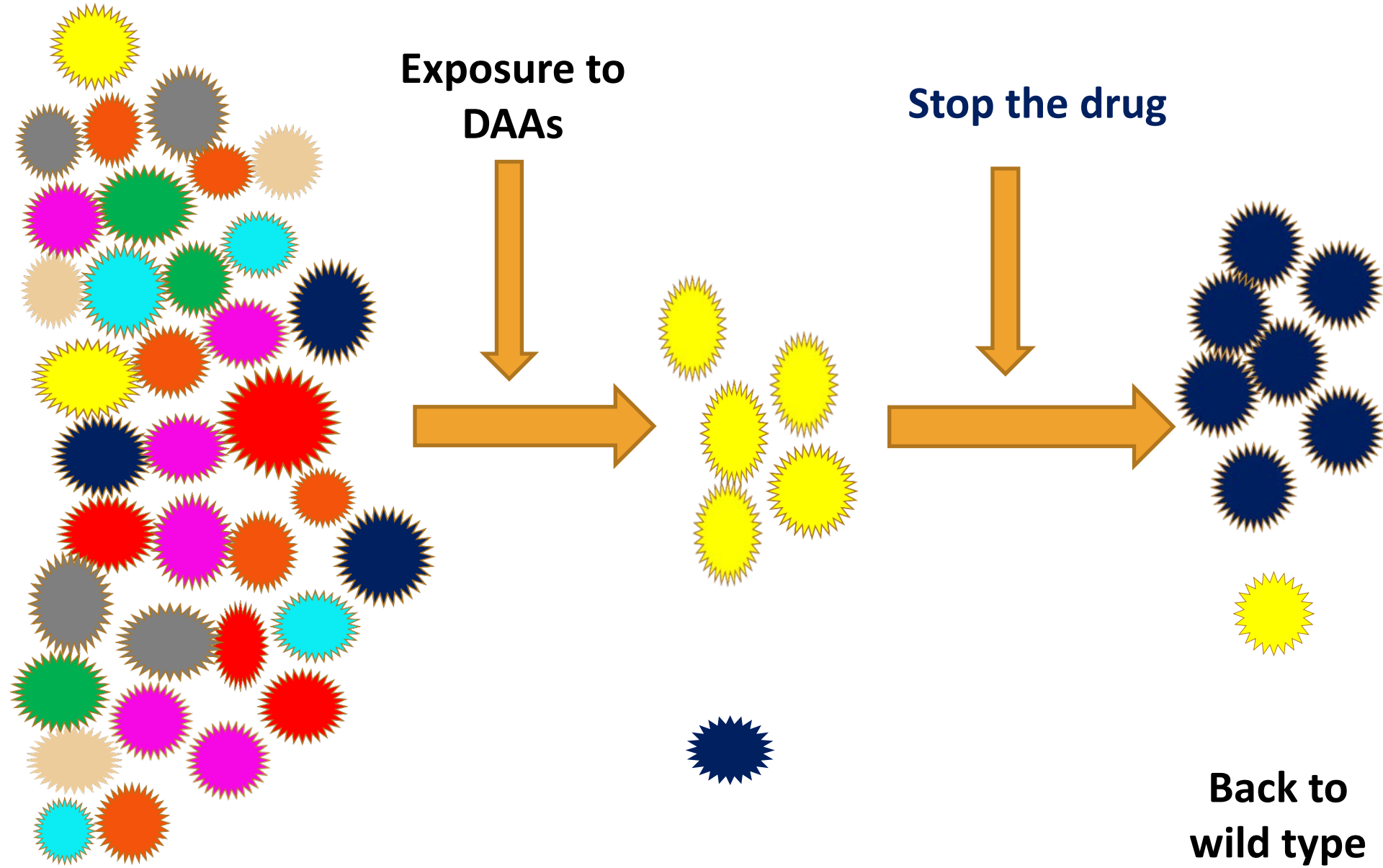
The fittest

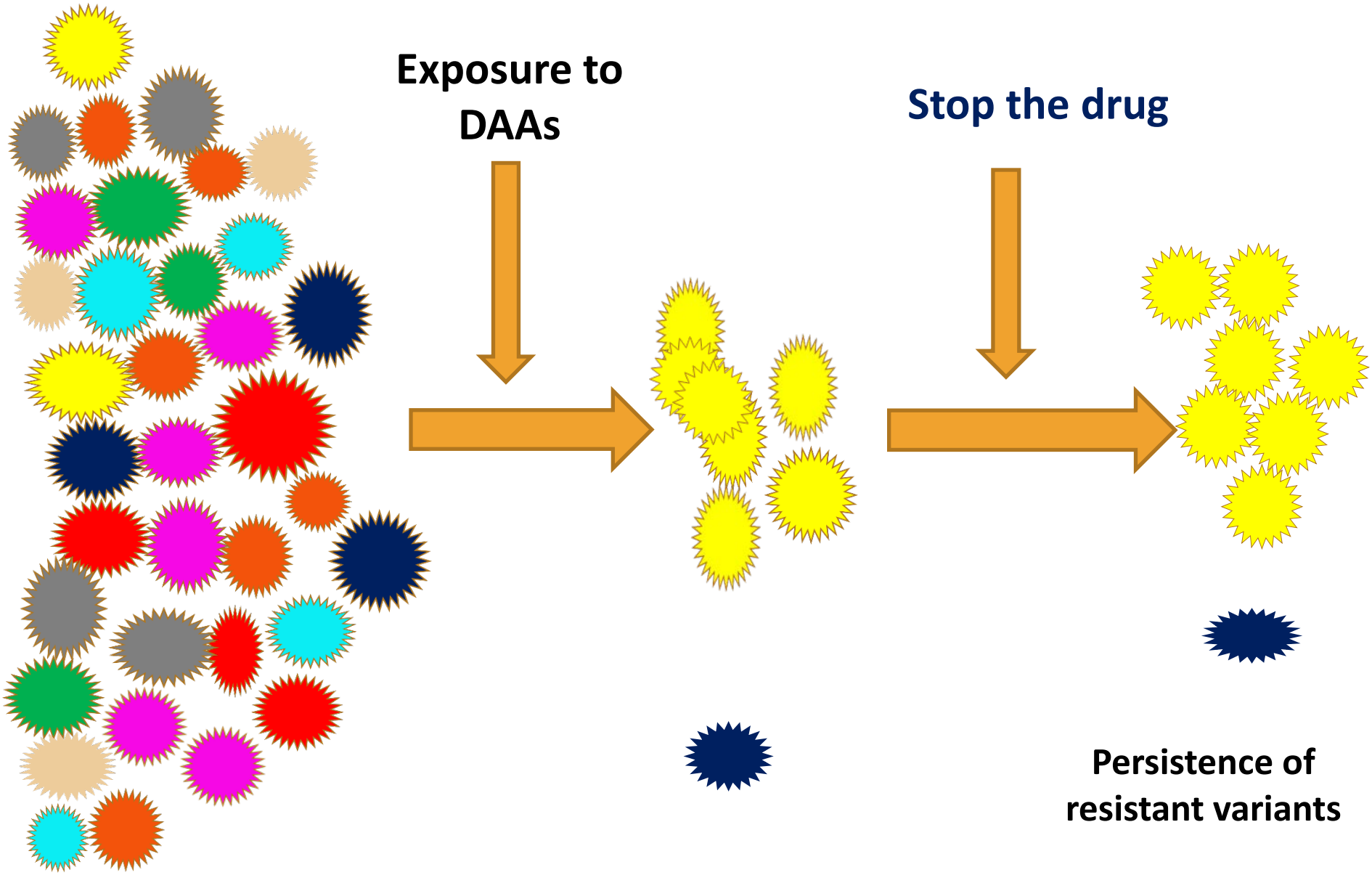
DAAs selective pressure





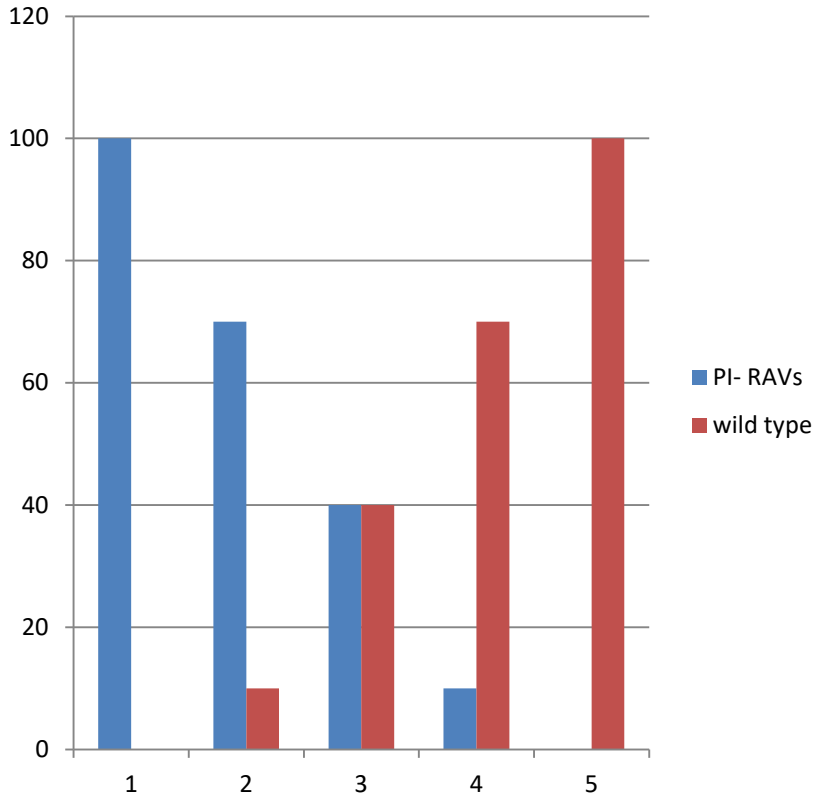
Potential fate of resistant variants after stopping DAAs


Exposure to DAAs
Stop the drug
Back to wild type

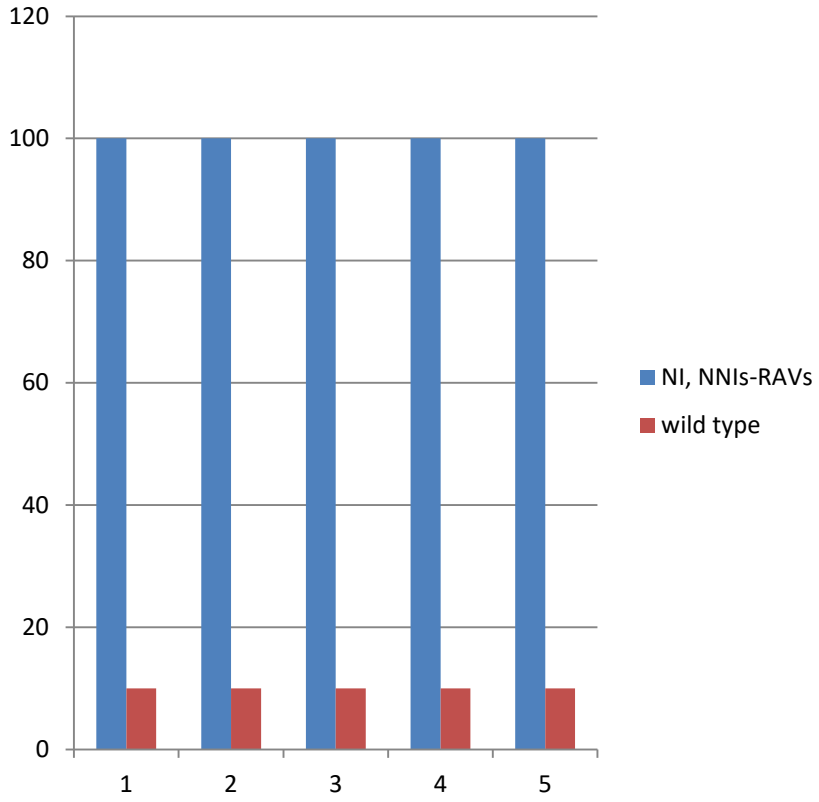

Exposure to DAAs
Stop the drug
Persistence of resistant variants

Application in real life settings

Protease inhibitors (RAVs)



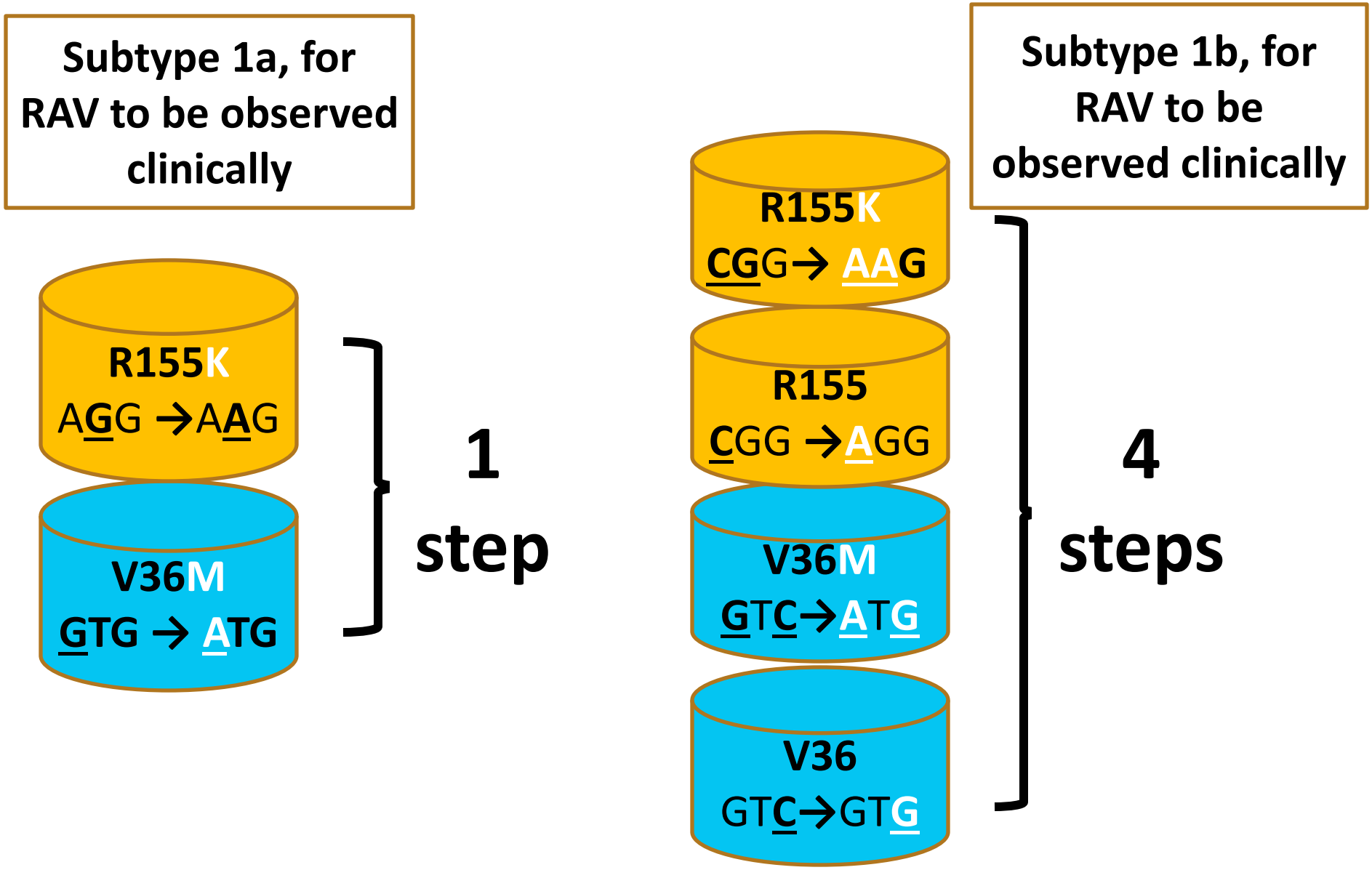
NS5AI & NNIs (RAVs)



2. Drug factors

Genetic barrier to resistance

The number of viral mutations required for replication in the presence of drug-selective pressure.



Clinical implications of genetic barrier to resistance acquisition by protease inhibitor resistant variant V36M+R155K

McHutchison J.G., et al. N Engl J Med, 2009; 360; 18 1827-1838. Hezode C. , et al. N Engl J Med, 2009; 360; 18 1839-1850

DAAs and resistance barriers

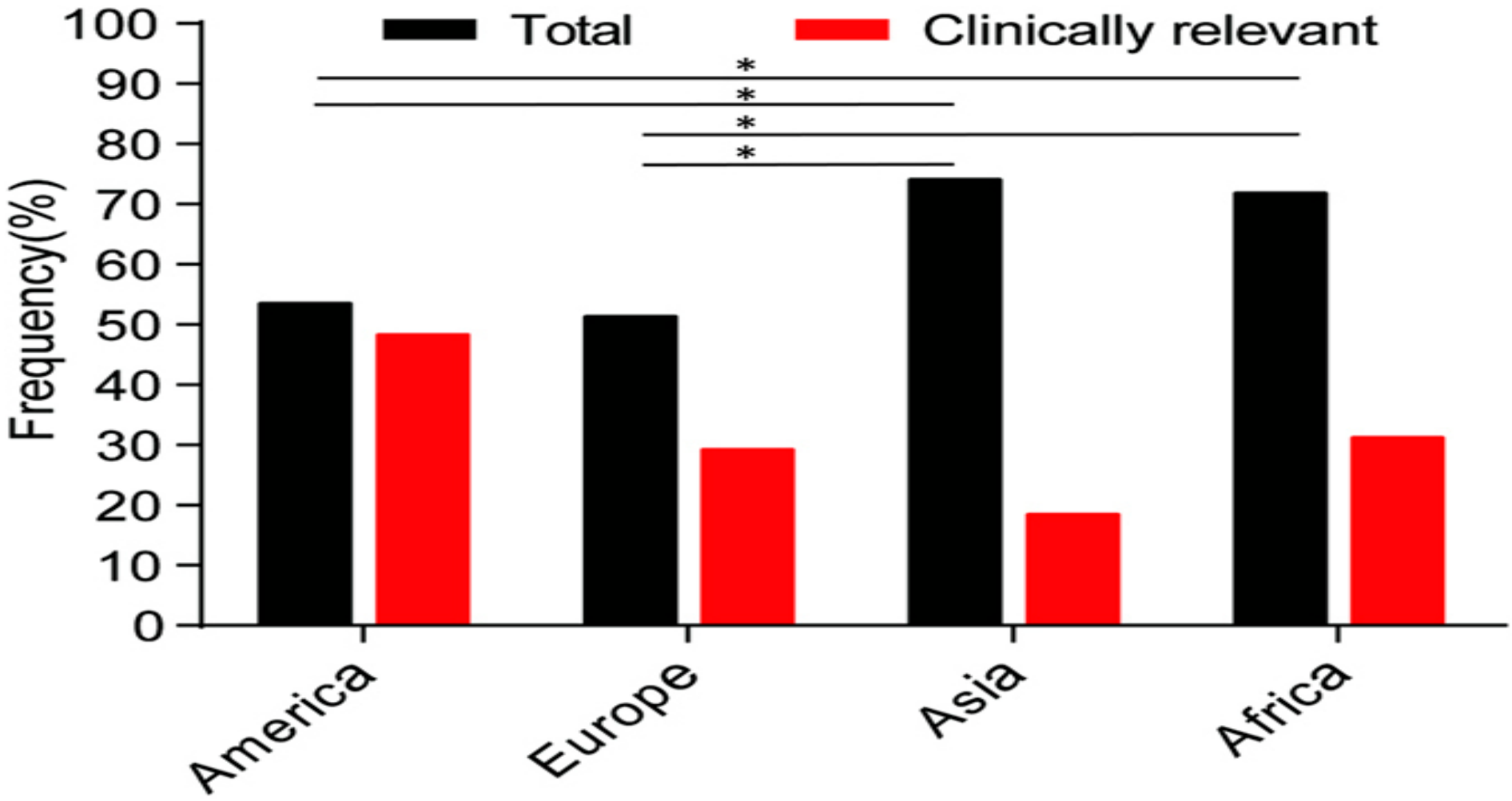
Low barrier drugs

- NS3 protease inhibitors
- NS5A inhibitors
- Non-nucleoside RdRp inhibitors

High barrier drugs

Nucleotide analogues

Using published GenBank data; global prevalence of DAAs RAVs determined

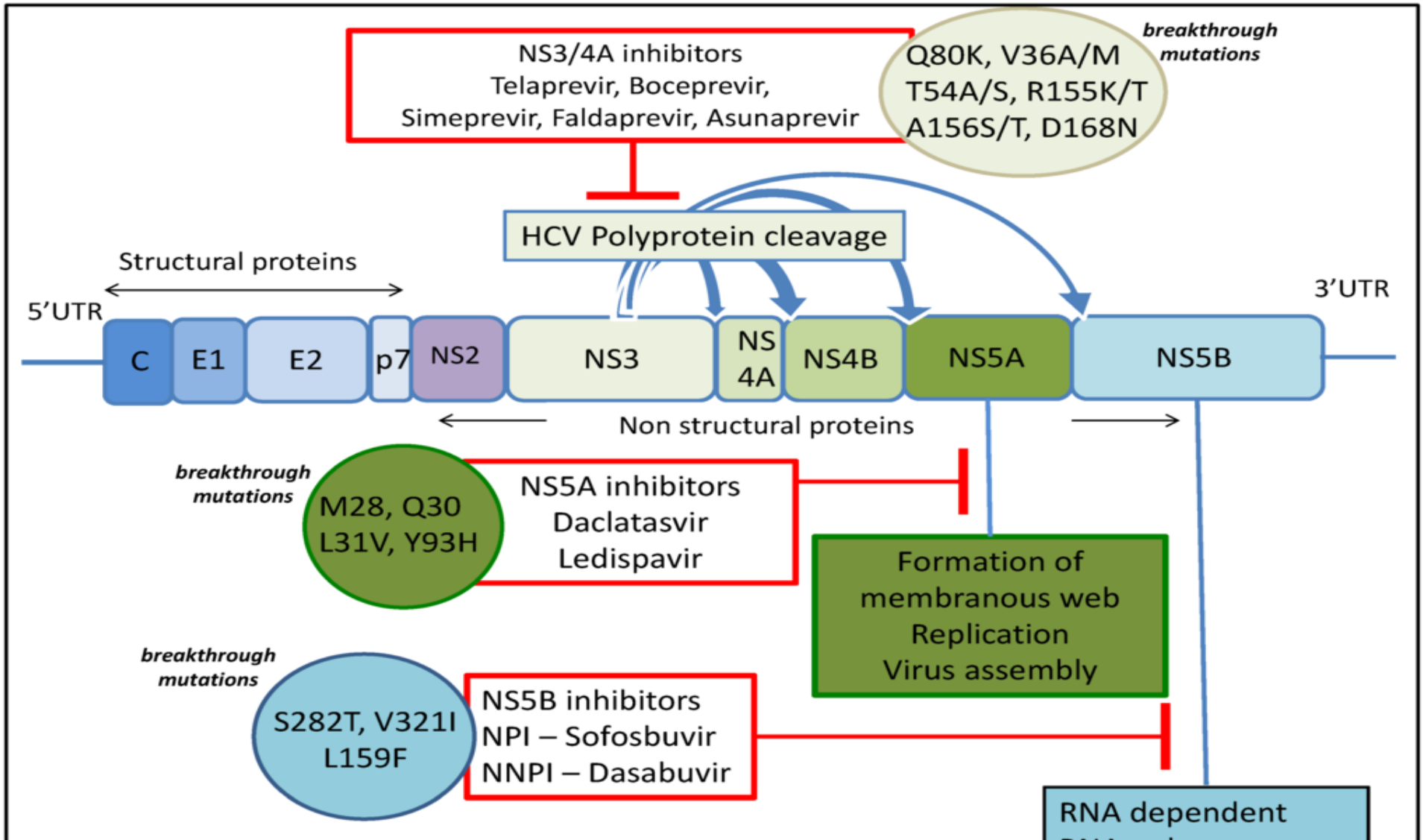


The geographic prevalence of total and clinically relevant DAA resistance associated variants. Oceania was not assessed due to the low number of available samples (four sequences). *p < 0.05.

Chen Z, et al. Global prevalence of pre-existing HCV variants resistant to direct-acting antiviral agents (DAAs): mining the GenBank HCV genome data. 2016

DAAs resistance in real world

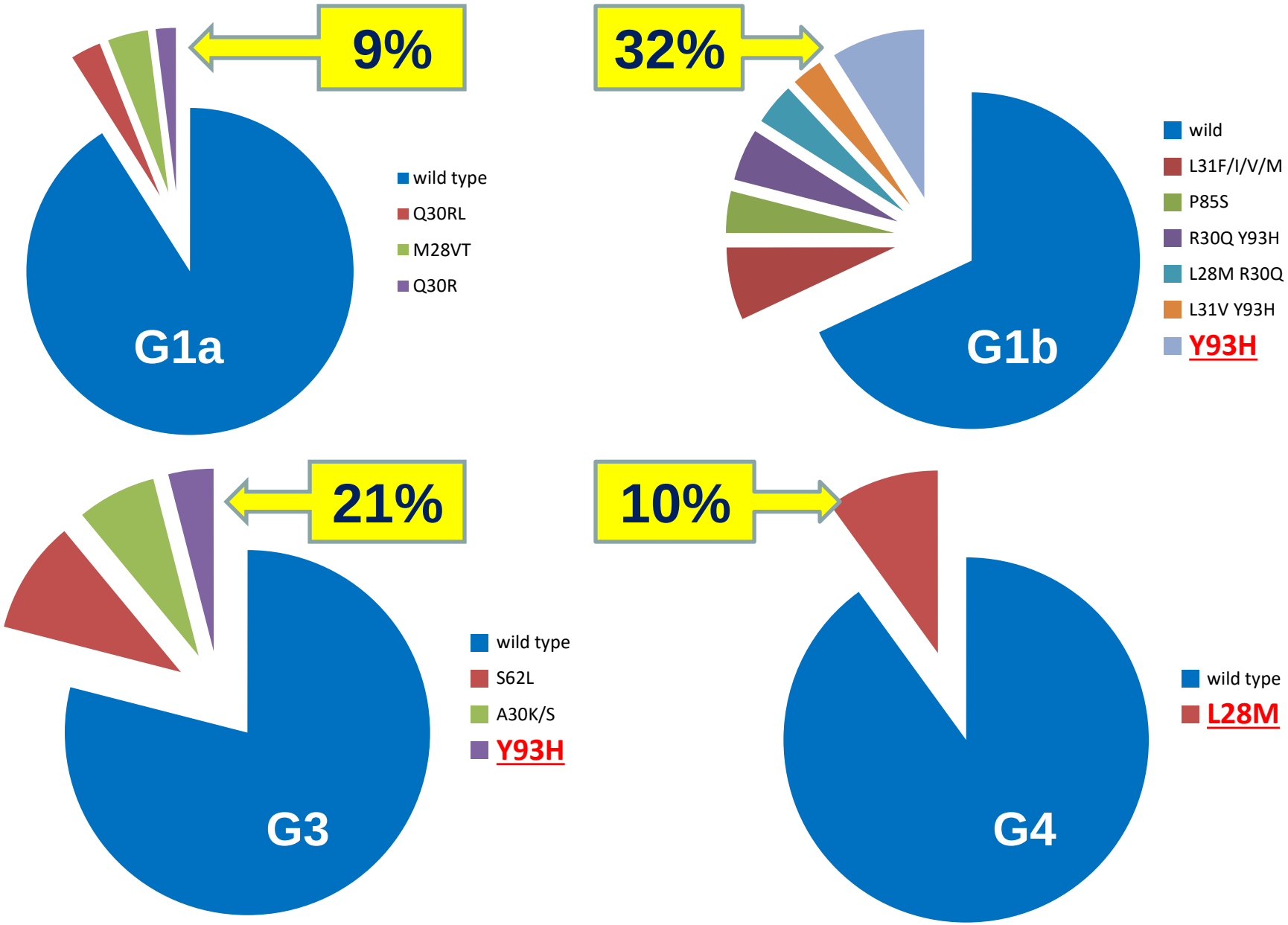
For all licensed DAAs RAVs have been identified in vivo



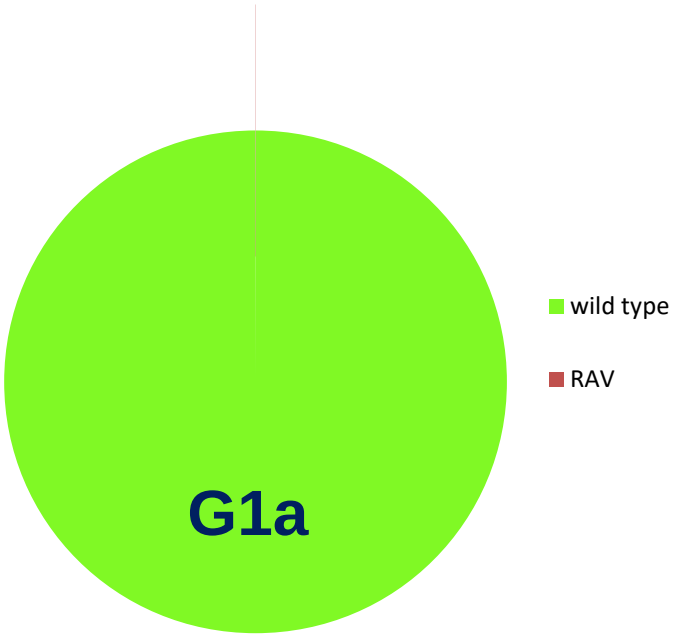
CROI 2016
Conference on Retroviruses and Opportunistic Infections
Boston, USA, 22-25 February 2016

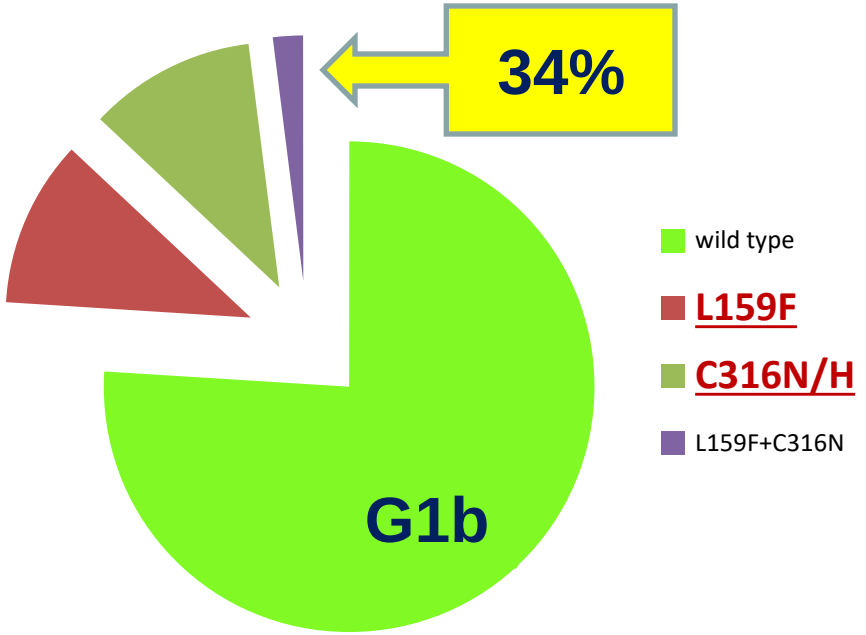
Analysis of HCV resistance to Daclatasvir (NS5A)/Sofosbuvir (NS5B) across different genotypes in the real life at baseline and after virological failure (n=177, 8 respectively)

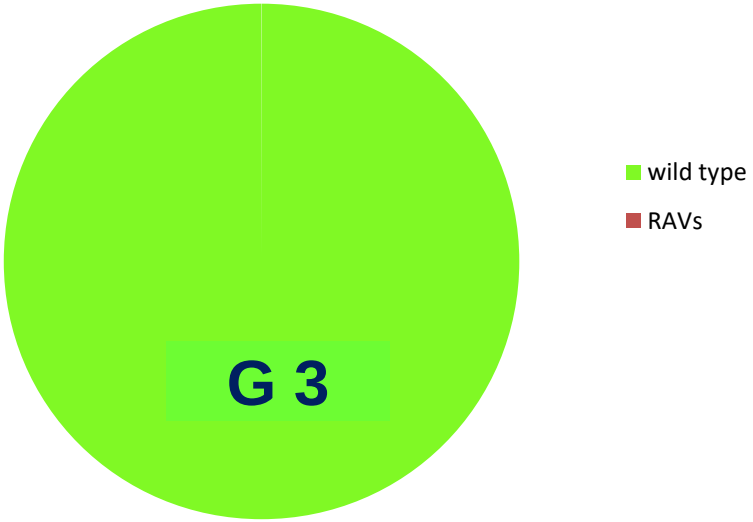
Base line NS5A RAVs (population sequencing)

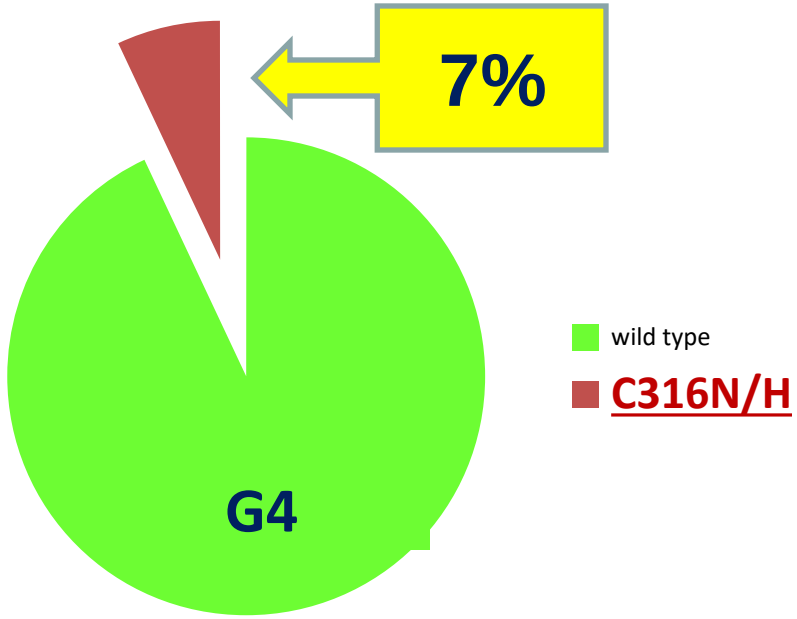


Base line NS5B RAVs (population sequencing)









Impact of RAVs at base line on SVR

Figure 9a: Impact of any RAV but Y93H

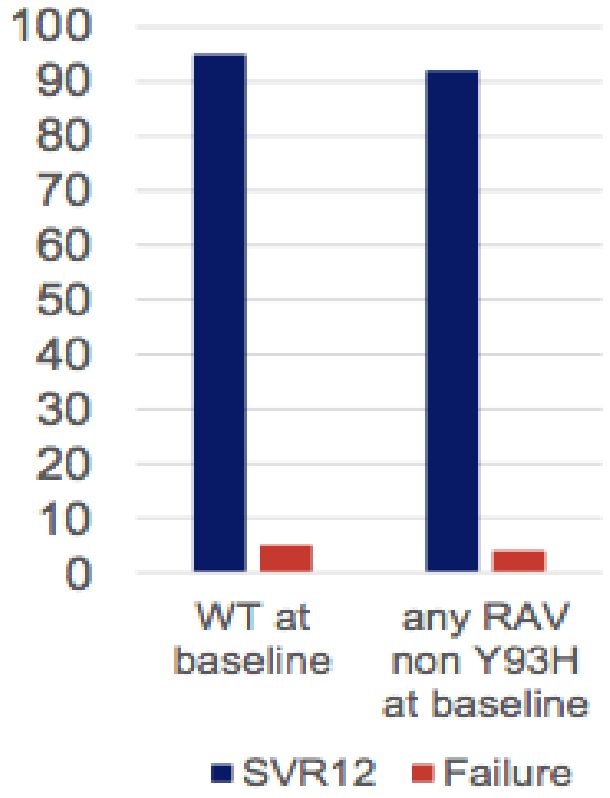
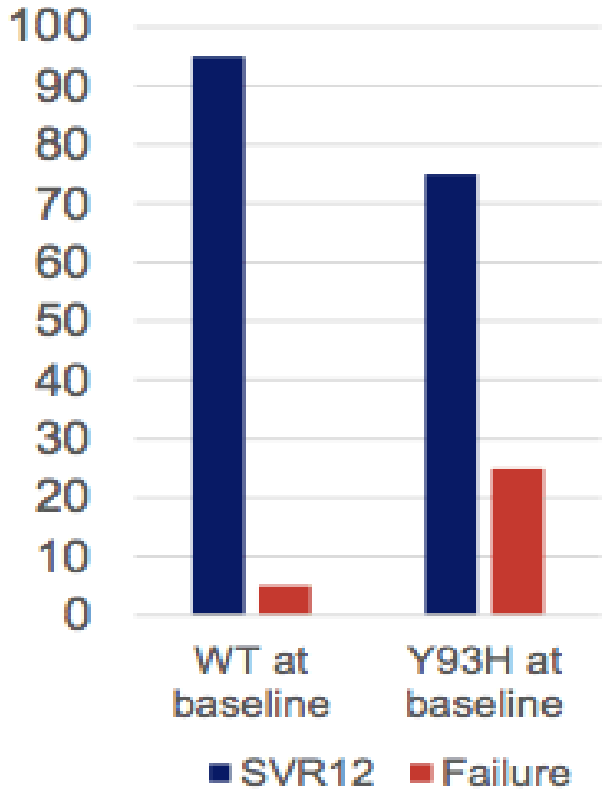


Figure 9b: Impact of Y93H on SVR rate



Virological failure tended to be more frequent when an NS5A Y93H substitution was present at baseline (p=0.067).

Patients with virologic failure

Patient	Genotype	Cirrhosis	NS5A			NS5B	
			Baseline	Virological failure	Virological failure unknown mutations	Baseline	Virologic failure
A	1a	Yes	/	M28T	/	/	/
B	1b	Yes	Y93H	Y93H, L31V	/	/	/
C	3a	No	/	Y93H	/	/	/
D	3a	Yes	/	Y93H	/	/	/
E	3a	Yes	/	Y93H	H85Y	/	/
F	3a	Yes	/	Y93H	/	/	/
G	3a	Yes	Y93H	Y93H	/	/	/
H	4	Yes	L28M	L28M	/	/	/

DAAs resistance testing

Phenotypic tests:

- The rate at which a virus replicates in the presence of different drug concentrations.
- Amount of drug needed to inhibit sample virus is quantified and compared with that of wild type:
  - Reported as a fold change
  - When amount is greater for sample virus, it is considered resistant

Genotypic resistance testing

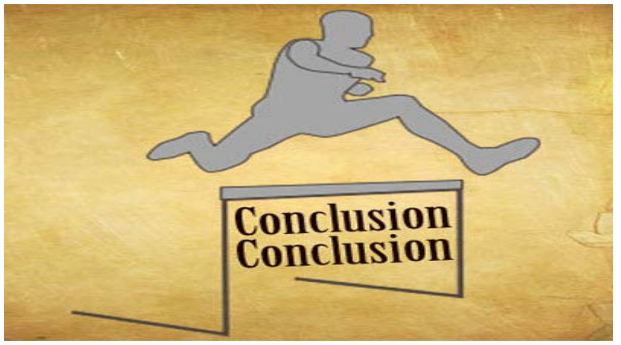
Sequencing

- **Population sequencing:**

determines variants at less than 20% prevalence.

- **Clonal sequencing:** determines variants at lower prevalence
- **Next generation sequencing:** cost-effective - unique level of detail. better interpretation of results due to recent computational and statistical advances.

Conclusions



- DAAs have revolutionized the treatment of HCV infection.
- However, they are not the last nail in the coffin. Emergence of resistance pose a great risk.
- Both virus and drug factors contribute to the treatment failure.
- Guidelines for re- treatment after DAA therapy failure are available, but still it is an area of emerging research.

Thank you
তোমাকে ধন্যবাদ