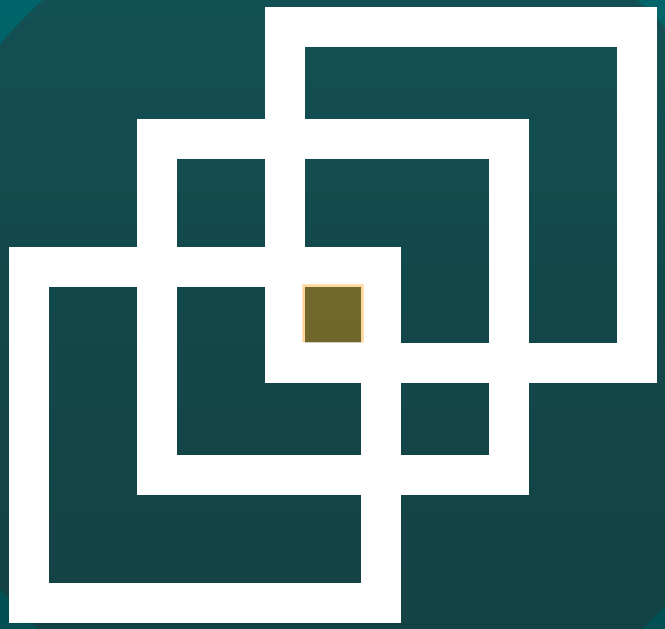
Forum for Collaborative HIV Research

A New Perspective On HCV Drug Resistance Multiple Paths To Sustained Virologic Response: Resistance Can Be Overcome



Slide set prepared by the Forum for Collaborative HIV Research and Hepatitis C Virus Drug Development Advisory Group

The Slide Deck

- These slides may be used in user's own noncommercial presentations, but kindly do not change content and attribution. We ask that you honor this intent.
- These slides are not to be published or posted online without permission from the Forum for Collaborative Research.

Slide Index

- Introduction: Slides 4-7
- Antiviral mechanisms of action: Slides 8-14
- Principles of drug resistance: Slides 15-20
- Resistant variants and treatment response: Slides 21-28
- Factors contributing to treatment response and SVR: Slides 29-45
- IL28B genotype and direct acting antiviral (DAA) treatment response: Slides 46-48
- Interferon-free combination regimens: 49
- Factors maximizing response and minimizing drug resistance: Slides 50-55
- Acknowledgements: Slide 56
- Selected bibliography: Slides 57-58

Goals of the slide deck: Develop perspective on HCV viral resistance and what it means for future HCV therapy

The educational materials in this slide set:

1) Provide context for viral resistance in HCV
2) Address concerns around HCV resistance
3) Educate on prevention and how to overcome resistance to antiviral drugs

This educational material complements:

1) A primer of HCV viral lifecycle
2) A primer on how mutations are created and resistant variants are selected

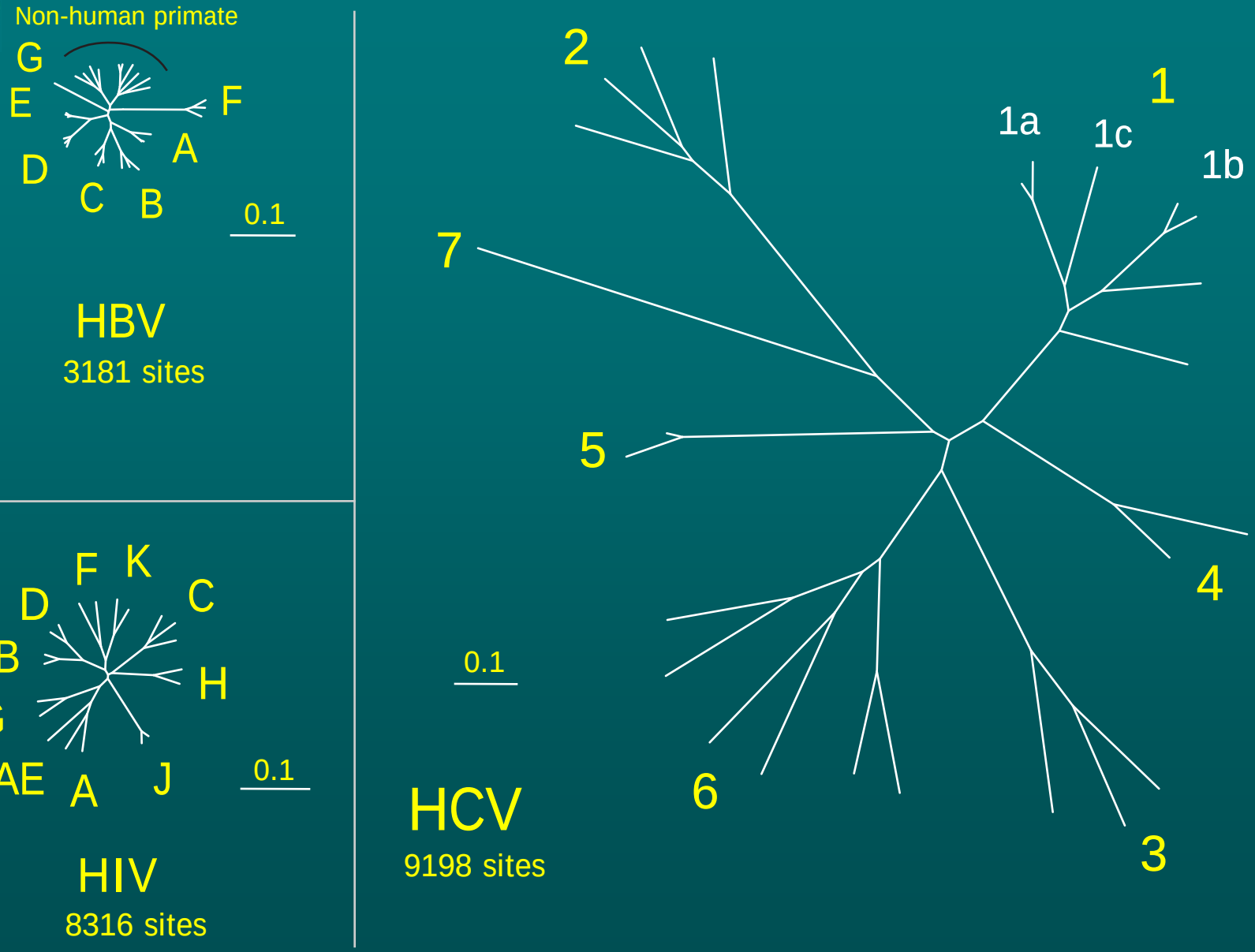
Key points

1. HCV Is Curable
   a) Wild-type and resistant virus can be eliminated
2. Resistant Variants Occur Naturally
   a) Resistant variants to antiviral drugs exist before treatment
   b) Resistant variants can be selected/enriched during treatment
   c) Drug resistance may emerge during treatment with all (or any) antiviral drugs
   d) Resistance is a consequence of treatment failure, but is not always the cause
3. Maximize Response, Minimize Resistance

   Many factors contribute to treatment response: virus, drug and patient

   a) The **genetic barrier** is related to the number and type of mutations required to overcome the clinical activity of a regimen. Mutations that decrease viral fitness (defined in slide #30) increase the resistance barrier.
   b) The **pharmacologic barrier** is increased by higher potency and higher drug levels
   c) Tolerability of a regimen and **patient adherence** are critical for treatment success

HCV sequences are more genetically diverse than HBV or HIV



Unlike HIV and HBV, HCV is curable

Virus	HIV	HBV	HCV
Genome	RNA	DNA	RNA
Mutation Rates	Very High	High	Very High
Virions Produced Daily	10^{10}	10^{13}	10^{12}
Viral Genetic Archiving	YES	YES	NO
Drug Targets	Multiple	One	Multiple
Cure With Current Therapy?	NO (Integrated viral DNA)	NO (cccDNA)	YES
Current Therapeutic Goal	Lifelong suppression	Lifelong suppression	**Cure**: clearance from plasma and liver

HBV, HIV and HCV have targeted drugs approved or in development

HIV

- **Protease**
- **RT** (nucleoside)
- **RT** (non-nucleoside)
- **Co-receptor**
- **Fusion**
- **Integrase**

HBV

- **RT** (nucleoside)

HCV

- **NS3 Protease*** **Telaprevir, Boceprevir**
- **Polymerase** (nucleoside)
- **Polymerase** (non-nucleoside)
- **NS5A**
- **NS4A**
- **NS4B**
- **P7**
- **Cyclophilin**
- **Entry**

* Approved in 2011

HCV enzymes provide good targets for drug development

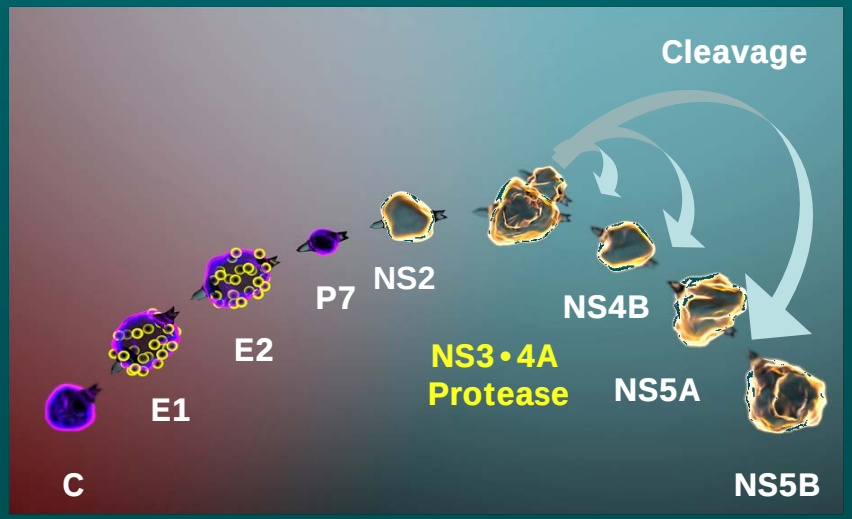
HCV Replicase

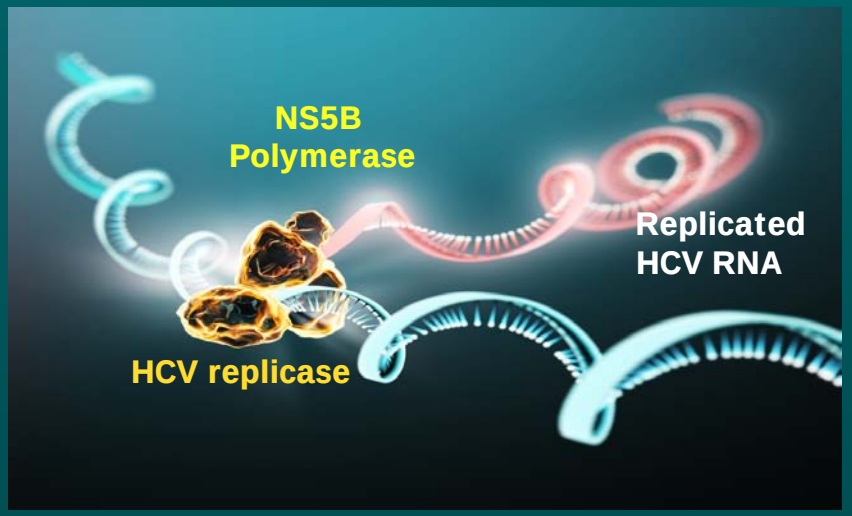
C | E1 | E2 | p7 | NS2 | NS3 | NS4A | NS4B | NS5A | NS5B

Structural

Protease

RNA Polymerase





Adapted from Kwong AD, et al. *Curr Opin Pharmacol.* 2008; 8(5): 522-31

HCV drug classification and development

Covalent

Slow reversible

e.g. telaprevir, boceprevir*

Irreversible

e. g. AVL-192†

Active site

GS 6620 IDX 184 INX 189
PSI 7977 PSI 938 RG 7128
TMC 649128

NS3 Protease

Non-covalent

Linear

ACH 1625 ABT 450/R
Asunaprevir (BMS 650032)
BI 201335 GS 9451

Macrocyclic

Danoprevir (RG7227/ITMN 191)
GS 9256
MK 5172
TMC 435
Vaniprevir (MK 7009)

NS5A

ABT 267 ACH 2928
AZD 7295 BMS 790052
GS 5585 PPI 461

NS5B Polymerase

Palm

ABT 333
ABT 072
GS 9190
Setrobuvir
(ANA 598)

Thumb 1

BI 207127
BMS 791325
TMC 647055

Thumb 2

BMS 791325
Filibuvir
GS 9669
VX 222

TLR-7

ANA 773

Cyclophilin

Debio 025
SCY 635

* Approved 2011; † Preclinical

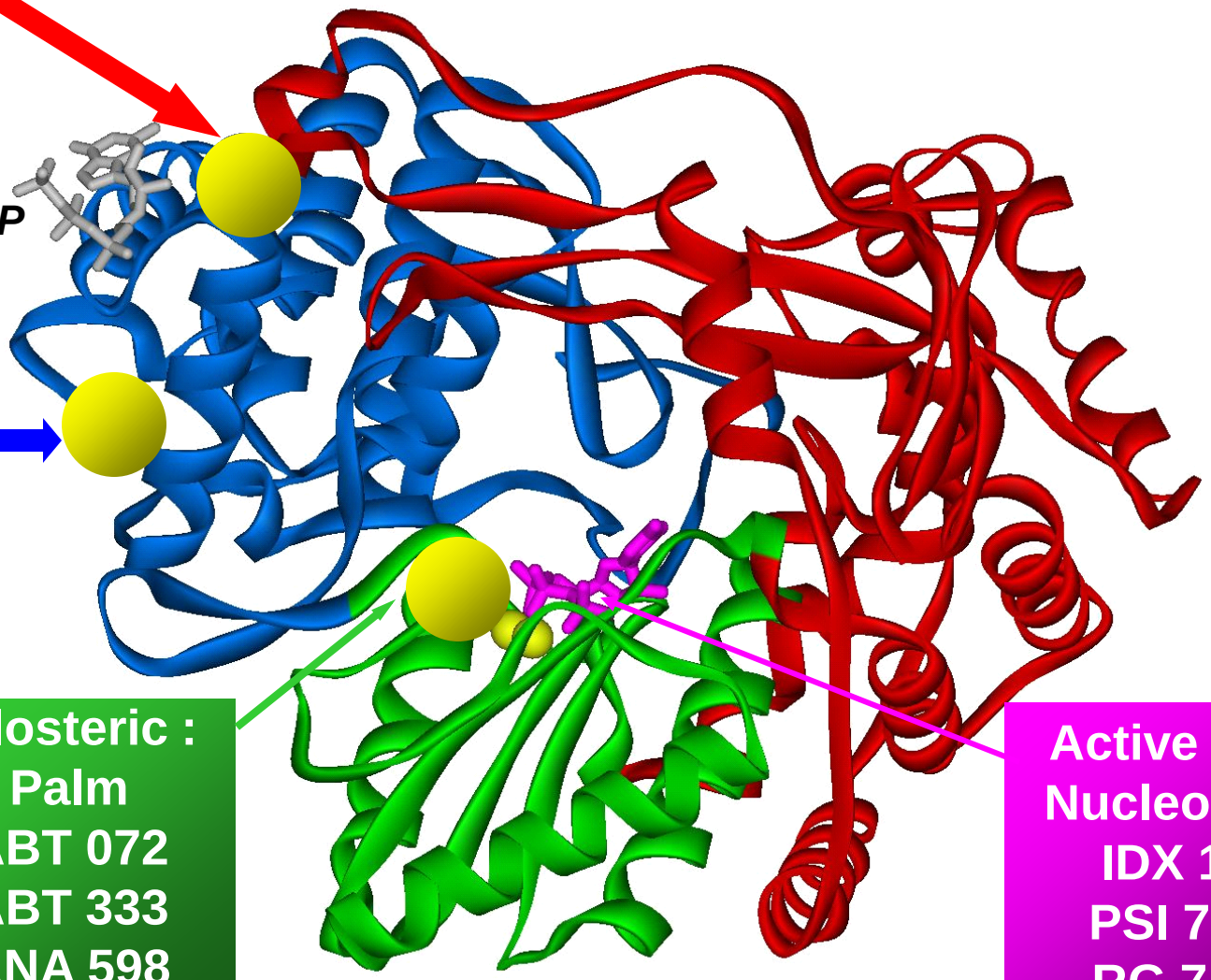
Compounds in Ph 1-3 trials (January 2012)

Examples of HCV NS5B polymerase inhibitors and their binding sites

Allosteric:
Thumb 1
BI 207127
TMC 647055

Allosteric GTP

Allosteric:
Thumb 2
Thiophene
Filibuvir
GS 9669
VX 222

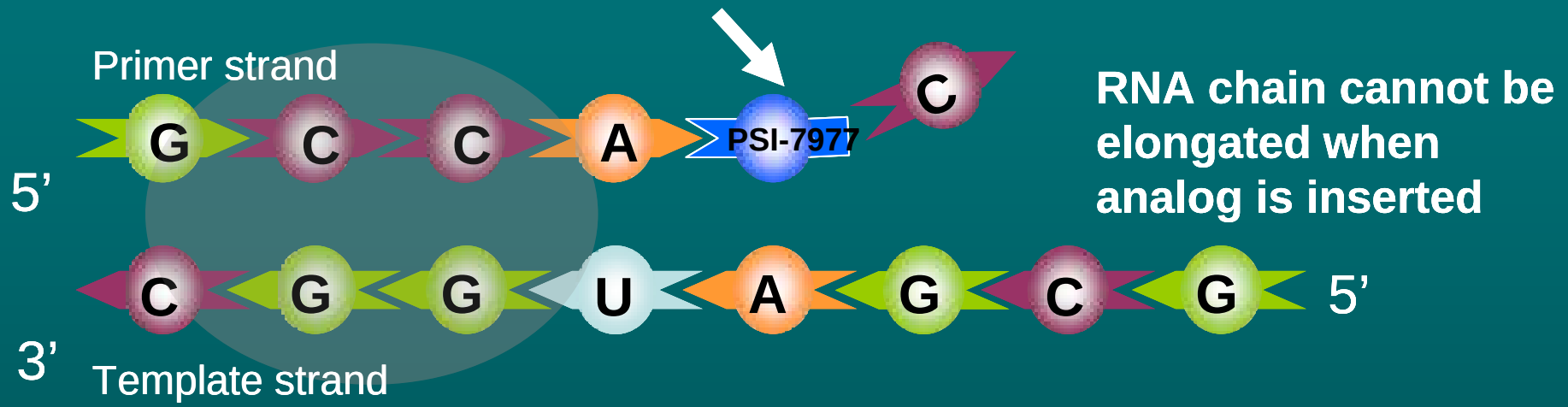


Allosteric :
Palm
ABT 072
ABT 333
ANA 598

Active Site :
Nucleosides
IDX 184
PSI 7977
RG 7128

Nucleotide analogs are chain-terminators

Nucleotide Chain-terminator
(e.g.,PSI-7977)

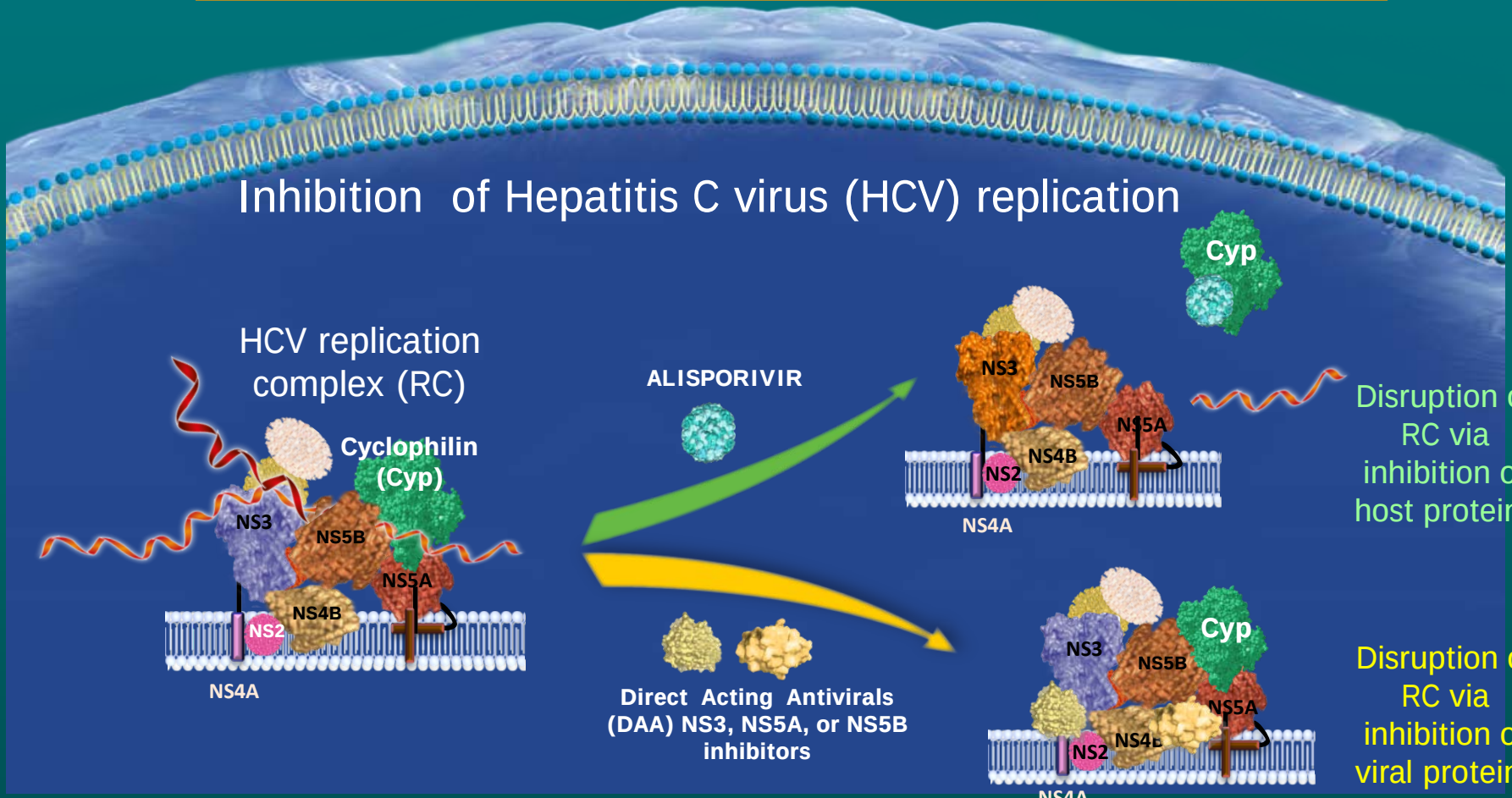


RNA chain cannot be elongated when analog is inserted

- Mechanism of action, e.g., chain termination, does not rely on enzyme homology across HCV genotypes
- Both pyrimidine and purine analogs can inhibit activity
- Antiviral activity of nucleotides is conserved against PI-resistant or non-nuc polymerase inhibitor resistant virus

Carroll S.S. *J Biol C hem,* 2003; 278:11979-11984
Deval , J. *Antimicrob Agents Chemother*, 2007; 51:2920-2928
Klumpp, K.G. *J Biol Chem,* 2006; 283: 3793-3799
Klumpp, K.G. *J Biol Chem,* 2008; 283: 2167-21675
Ma, H. *J Biol C hem,* 2007; 282: 29812-29820
Migliaccio, G. *J Biol Chem,* 2003; 278: 49164-49170
Murakami, E. *Antimicrob Agents Chemother*. 2007; 51:503-509

Mechanism of action and key attributes of cyclophilin inhibitor, alisporivir



Key attributes of host-targeting antiviral (HTA), alisporivir

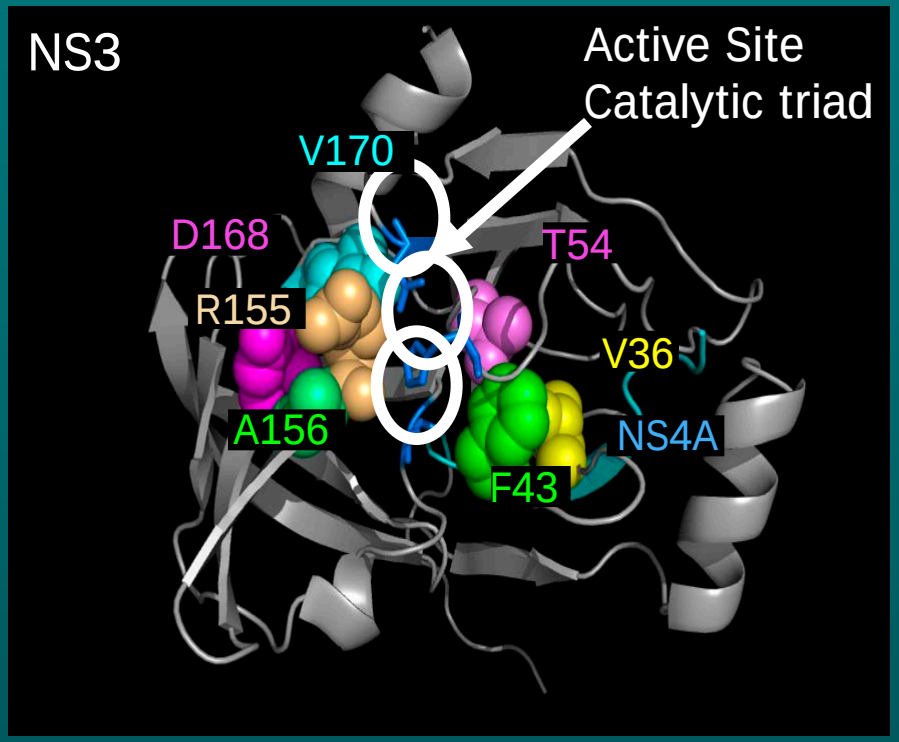
- Mechanism of action different from direct acting antivirals (DAA)
- High barrier for HCV resistance
- Compelling efficacy with pan-genotypic coverage

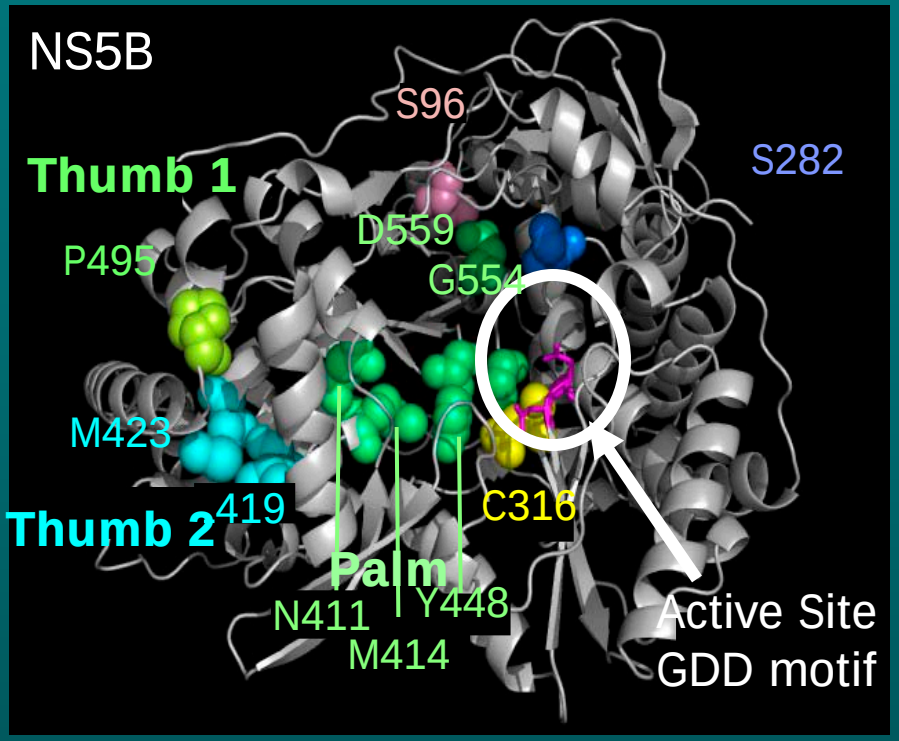
Mechanism of action of NS5A replication complex inhibitors

- Role of NS5A in HCV replication remains elusive
- Precise mechanism of action in HCV replication currently under investigation
- NS5A inhibitor, BMS-790052 and similar chemotypes:
  - Bind to HCV NS5A protein in cell culture[1]
  - Interact with the NS5A N-terminus of Domain 1[2]
  - Block both cis- and trans-acting functions of NS5A[3]
  - Alter the subcellular localization of NS5A into functional replication complexes therefore suppressing HCV RNA replication[4]

1.Gao, M. *Nature,* 2010; **465:** 96-100
2. Lemm, J.A. *J Virol*, 2010; 84 (**1**)**:** 482-491
3. Fridell, R.A. *J Virol* 2011; 85(14): 7312-20
4.Lee, C. *Virol* 2011; 414(1):10-8

All antiviral drugs can select resistant variants





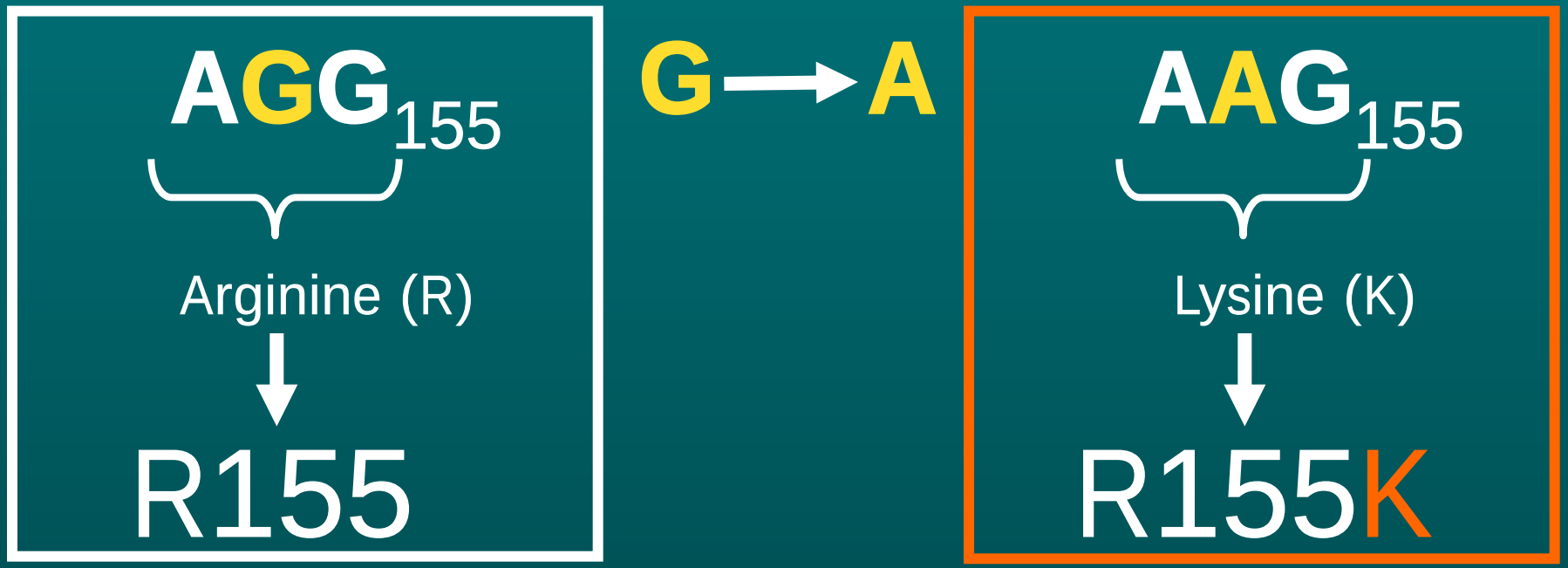
NS3

Amino acid changes conferring resistance to NS3 protease and NS5B polymerase inhibitors

NS5B

Nucleotide changes result in codon changes that can confer resistance to a drug

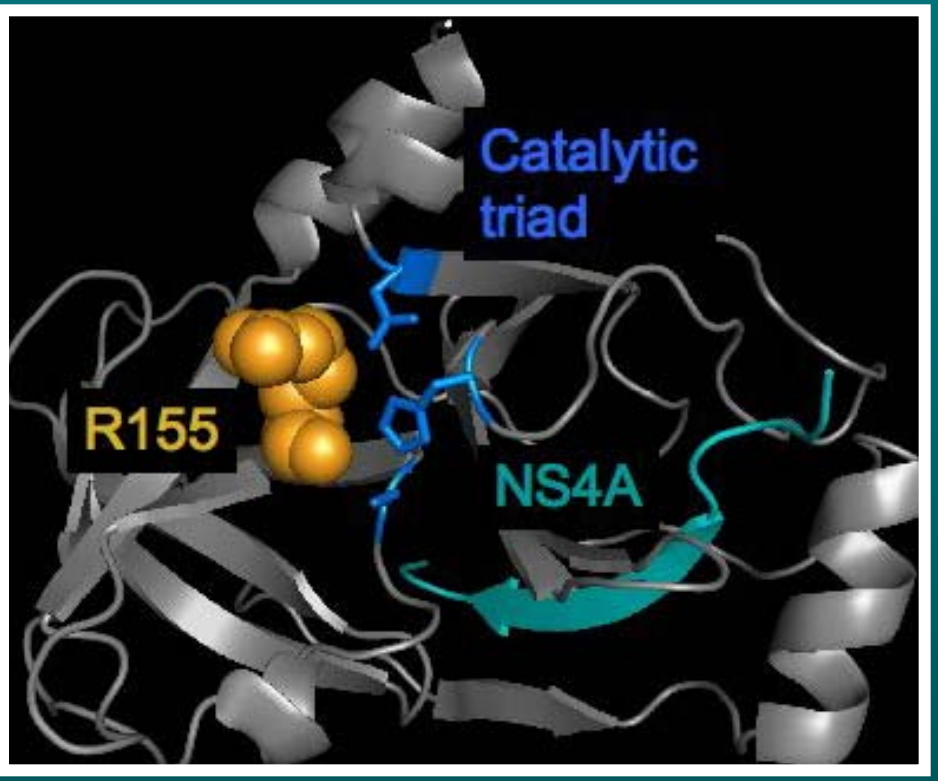
Example: Codon 155 of the HCV Protease



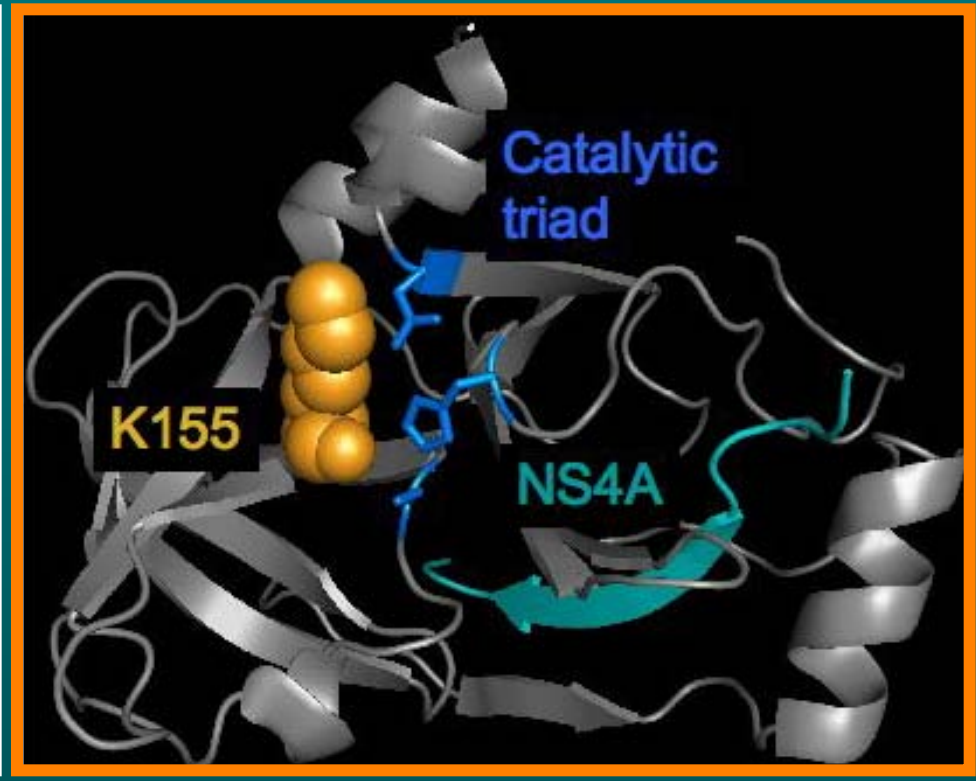
Consensus “wild type” amino acid

Resistant variant amino acid

Codon changes may result in amino acid changes, which can change the interaction with a drug



Wild type NS3

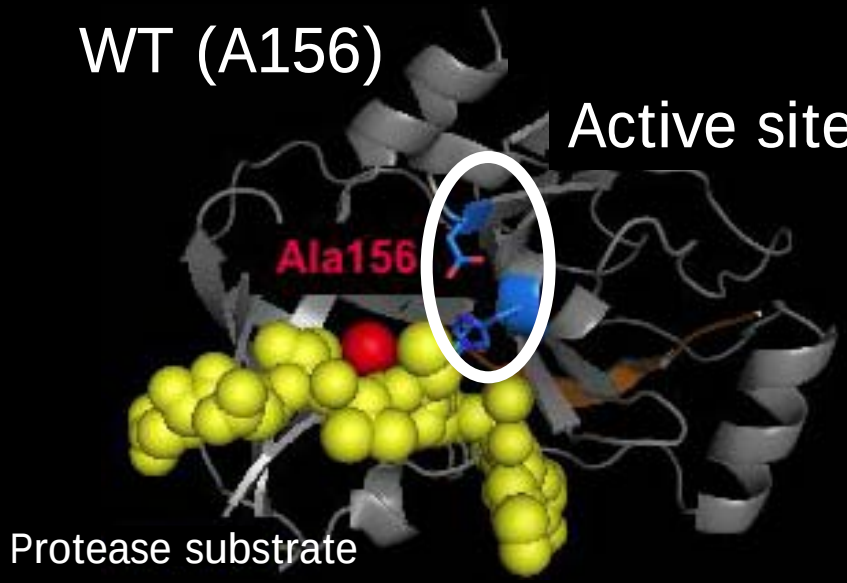


R155K variant NS3

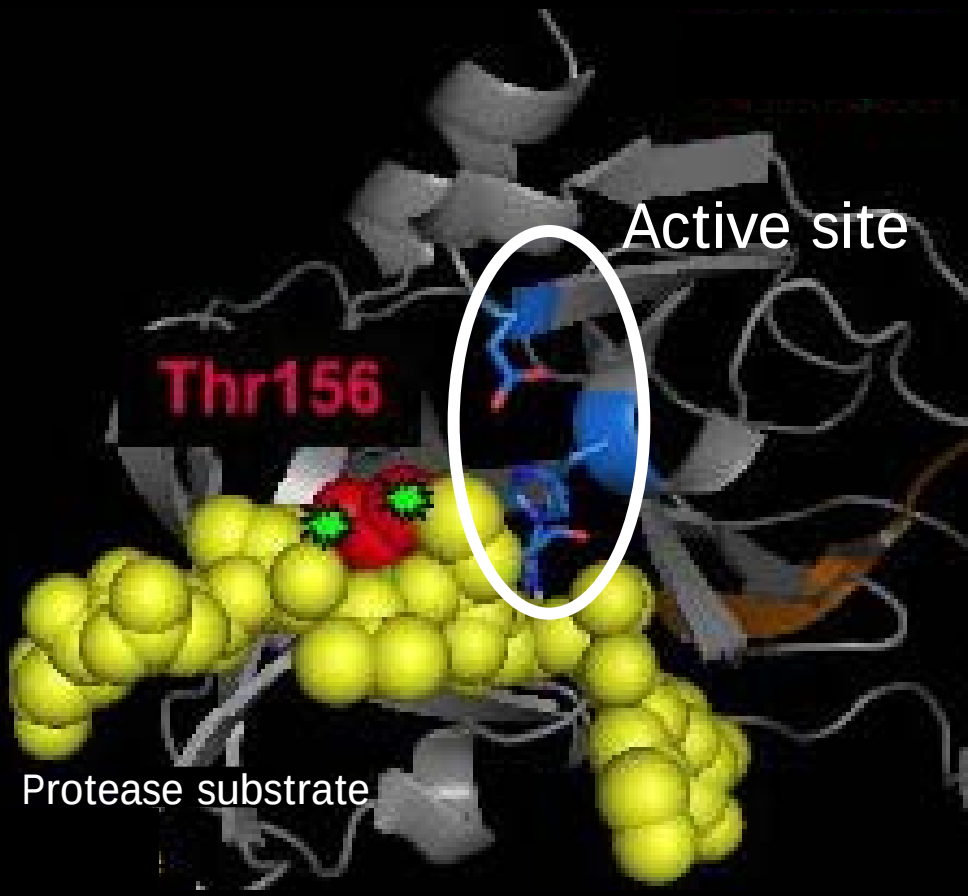
- Decreased binding of a drug results in decreased inhibition of viral replication
- Decreased binding to the natural ligand results in decreased viral replication

Resistance often results in reduced viral fitness

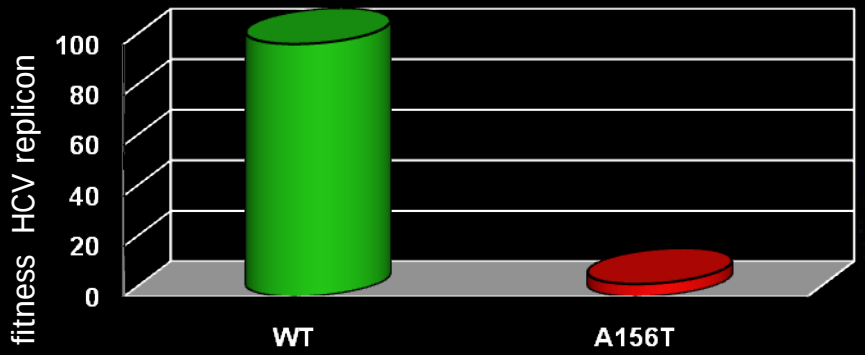
WT (A156)



Resistant Variant (A156T)

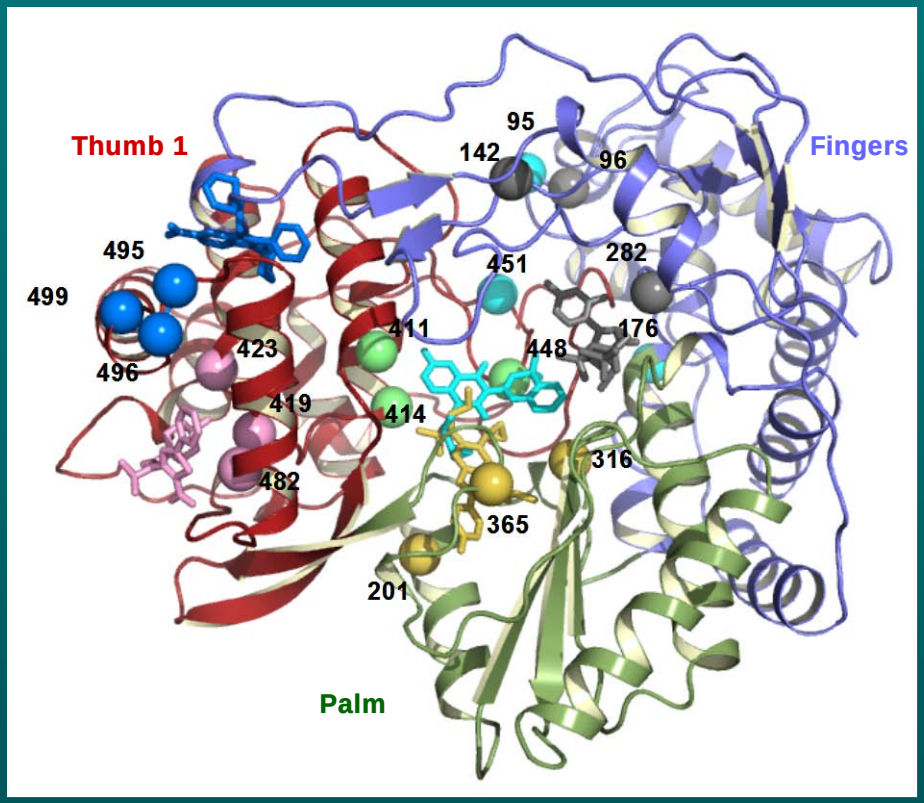


The A156T variant is less fit than WT



Steric hindrance prevents the substrate from efficiently binding to the mutant protease active site

Resistance mutations associated with NS5B polymerase nucleoside and non-nucleoside inhibitors



Nucleoside Inhibitors

- R1626: S96T (*in vitro*)
- R7128: S282T (*in vitro*)

Non-Nucleoside Inhibitors

- Filibuvir: M423T (in patients)
- VCH-759 and VCH-916: M423T/V/I, L419V/M, I482L/V/T, V494A/I) (in patients)
- HCV796: C316Y/N, S365T/A (in patients)
- ABT333: S556G (in patients); C316Y, Y448C (*in vitro*)

- Though *in vitro* studies with **nucleoside analogs** have demonstrated the selection of resistant variants, they have not been observed in patients with HCV infection.
- Wide range in frequency of resistance mutations associated with **non-nucleoside analogs**. While many are only observed *in vitro,* some are also associated with viral breakthrough in clinical trials.

Changes in drug susceptibility: Detection of resistance

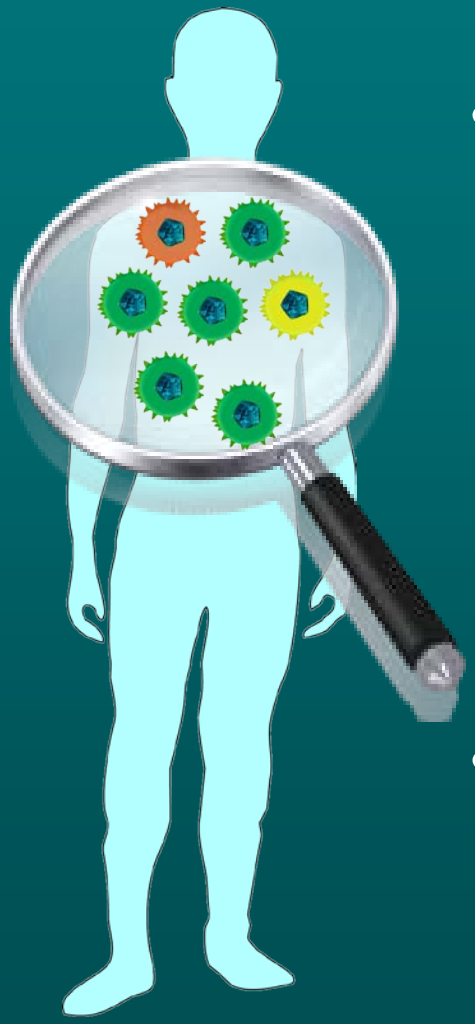
- Sequence analysis and phenotype analysis are used in combination to identify/discover resistance pathways

- **Sequence Analysis**: Detects specific amino acid substitutions relative to a pre-treatment or standard reference sequence that are known to decrease susceptibility to antiviral agents.
  - Can identify substitutions known to impact drug susceptibility
  - Can identify novel drug resistance pathways associated with treatment failure

- **Phenotypic Analysis**: Determines drug concentrations needed to inhibit viral replication.
  - Effective concentration (EC): drug concentration required to inhibit viral replication by 50% or 90% (EC_{50} or EC_{90})
  - Less susceptible (resistant) viruses will require *more* drug to be inhibited, thus an *increase* in EC_{50} or EC_{90}

Resistant Variants Occur Naturally

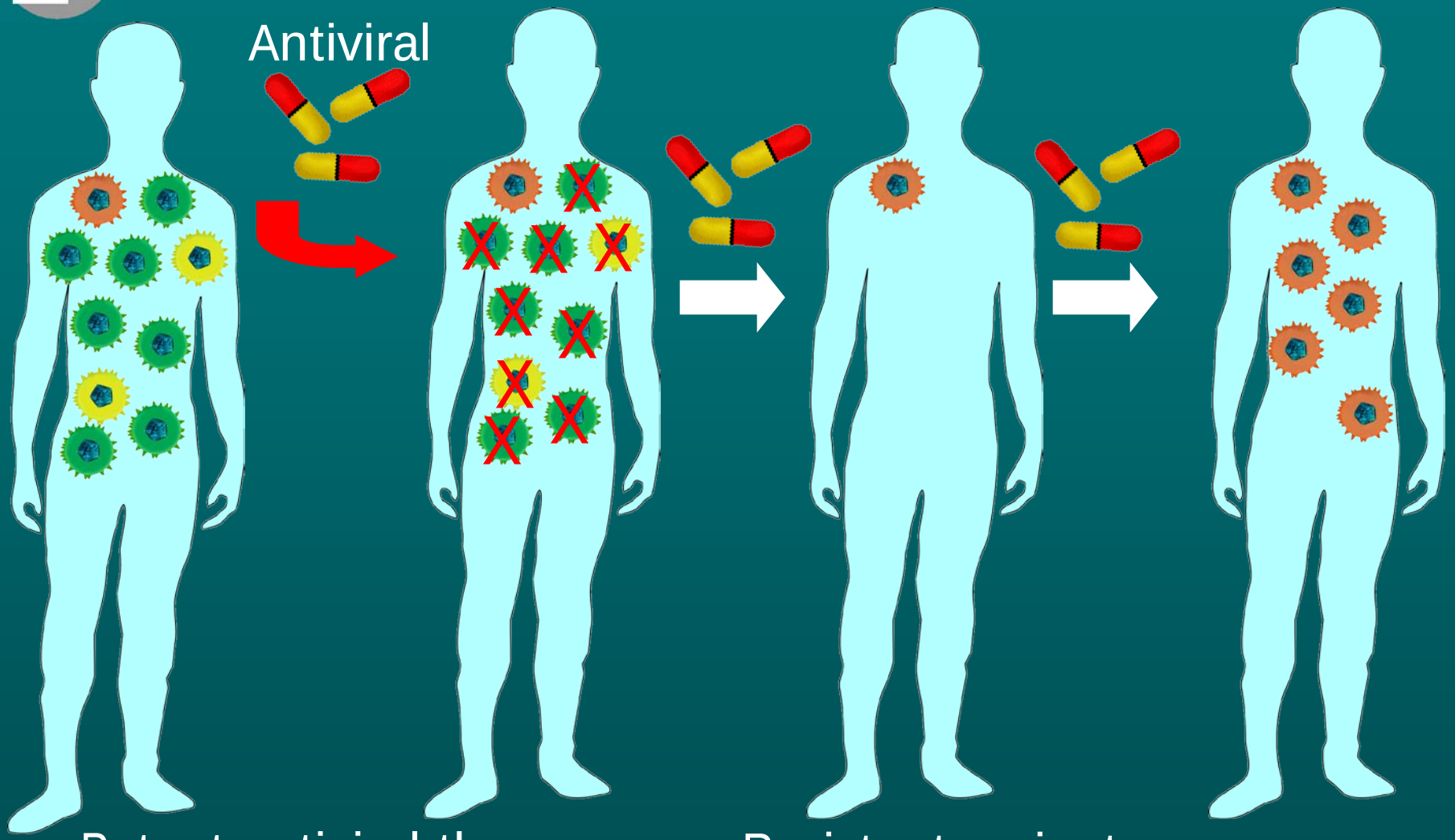
Resistant variants are present before treatment



- HCV exists as a mixture of populations of genetically distinct, but closely related, virions in every patient[1]
  - ~10^{12} viruses produced per day
  - ~1 nucleotide mutation per virus produced
  - All possible single nucleotide-mutant viruses, and all combinations of double nucleotide-mutant viruses, are thought to preexist before treatment in most patients[2]
- Most resistant variants are relatively unfit and are undetectable prior to therapy with current technology[3,4]

1. Pawlotsky JM. *Clin Liver Dis* , 2003; 7:45-66
2. Rong L. *Sci Transl Med* , 2010: 2 (30):30ra32
3. Kuntzen. *Hepatology* , 2008; 48(6):1769-78
4. Bartels DJ. *J I nfec Dis,* 2008; 198: 797-9

Resistant variants can be selected during treatment



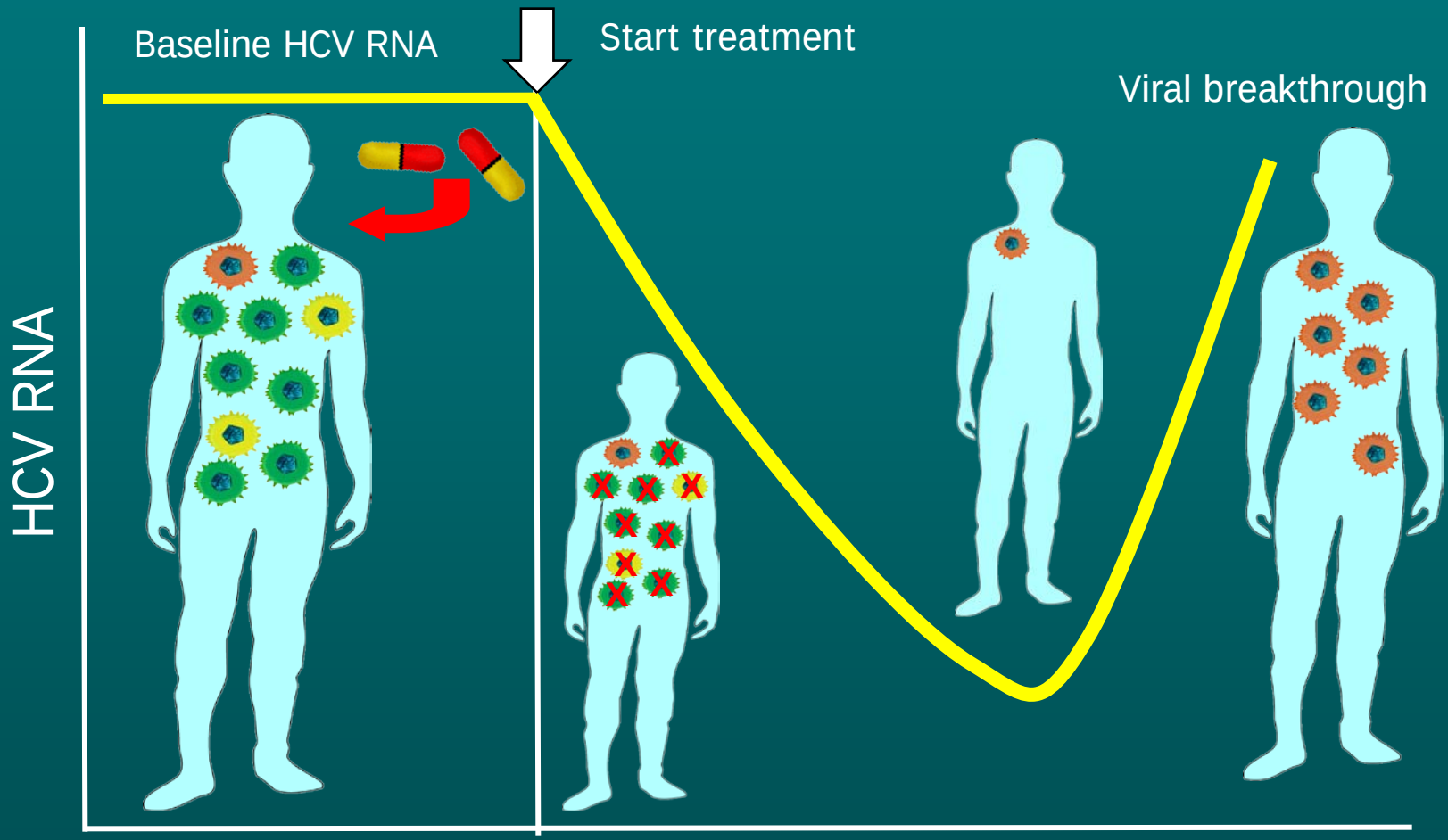
Potent antiviral therapy eliminates sensitive variants

Resistant variants are uncovered which can then expand

Resistant virus

Sensitive virus

Frequent monitoring of HCV RNA levels can detect treatment failure and resistance



Patients have viral variants with different levels of resistance to a drug

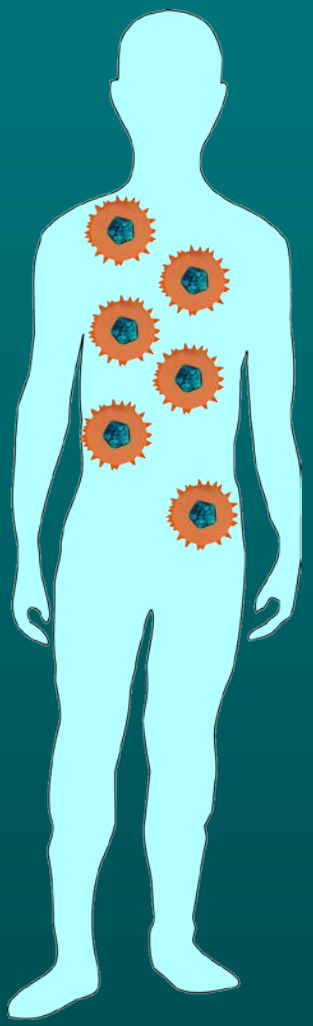
Resistant virus

Sensitive virus

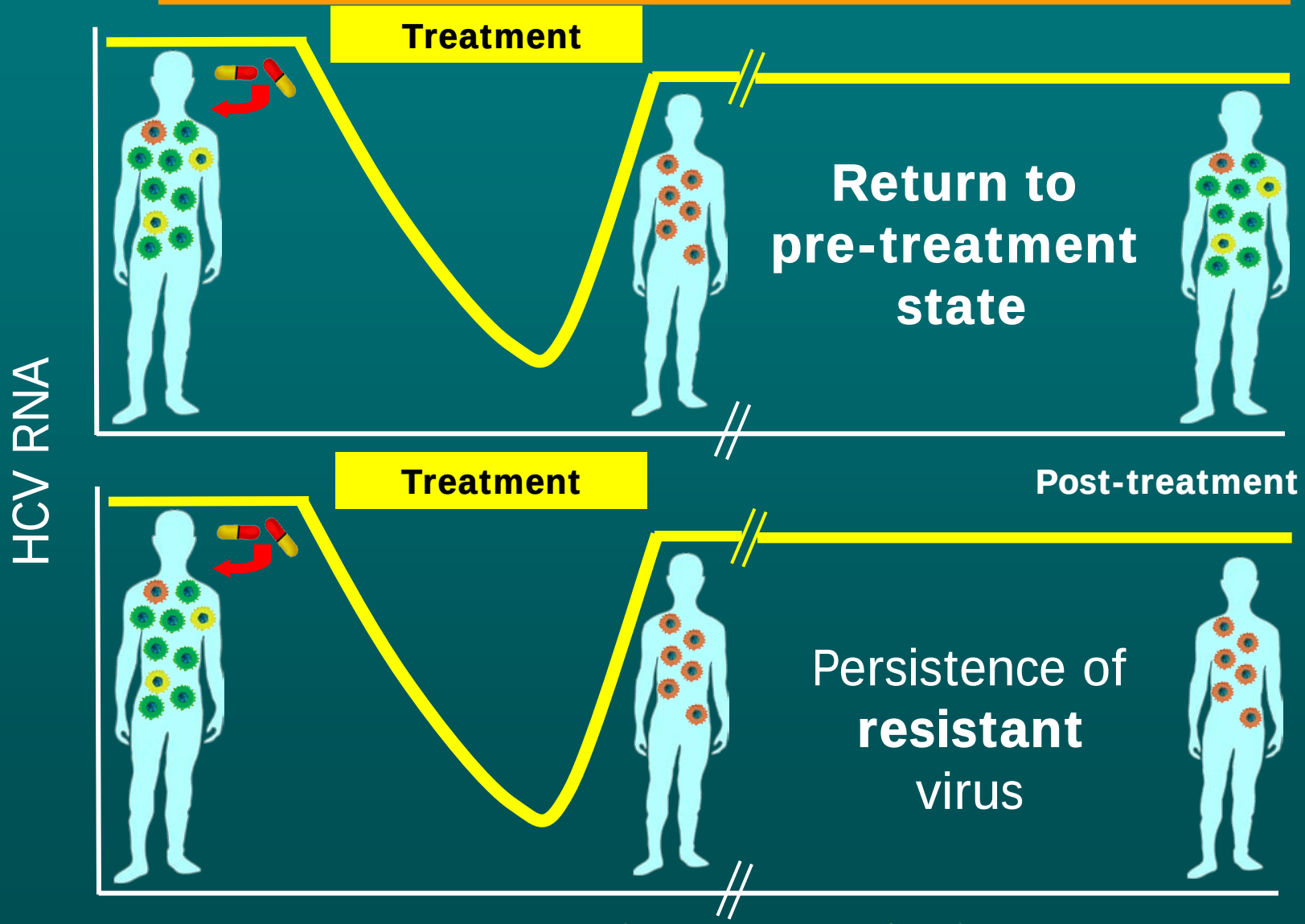
Say “NO” to **CRAP** therapy

Continued **R**eplication under **A**ntiviral **P**ressure

- Continued replication in the presence of drug will likely lead to further evolution of the viral population.
- In theory, further evolution can result in a more fit, drug-resistant viral population that may remain enriched in the patient, even in the absence of drug pressure.
- This should be prevented by discontinuing the direct acting antiviral if a patient has a confirmed increase in HCV RNA levels while adhering to therapy.

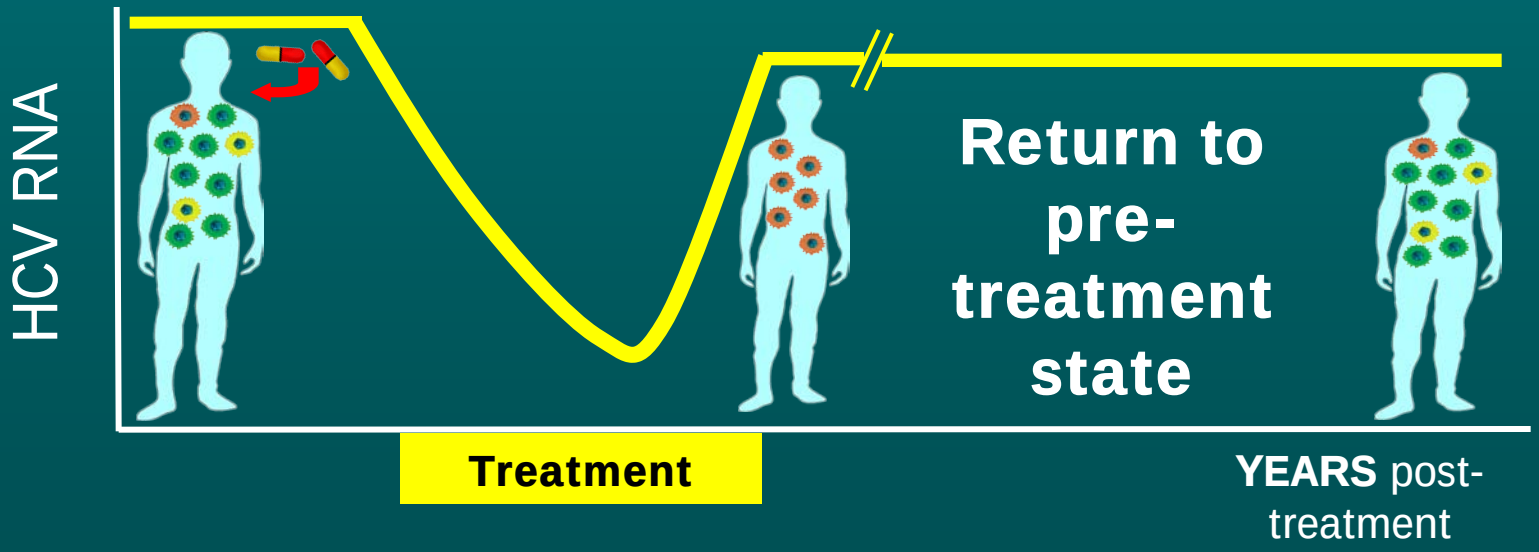


Potential fate of resistant variants after treatment



Long-term follow-up of patients with resistant variants after failing treatment

- Population and clonal amino acid analyses of HCV from patients with protease inhibitor resistance indicate that drug-resistant patient viral populations ***may*** return to pre-treatment levels over time in many patients



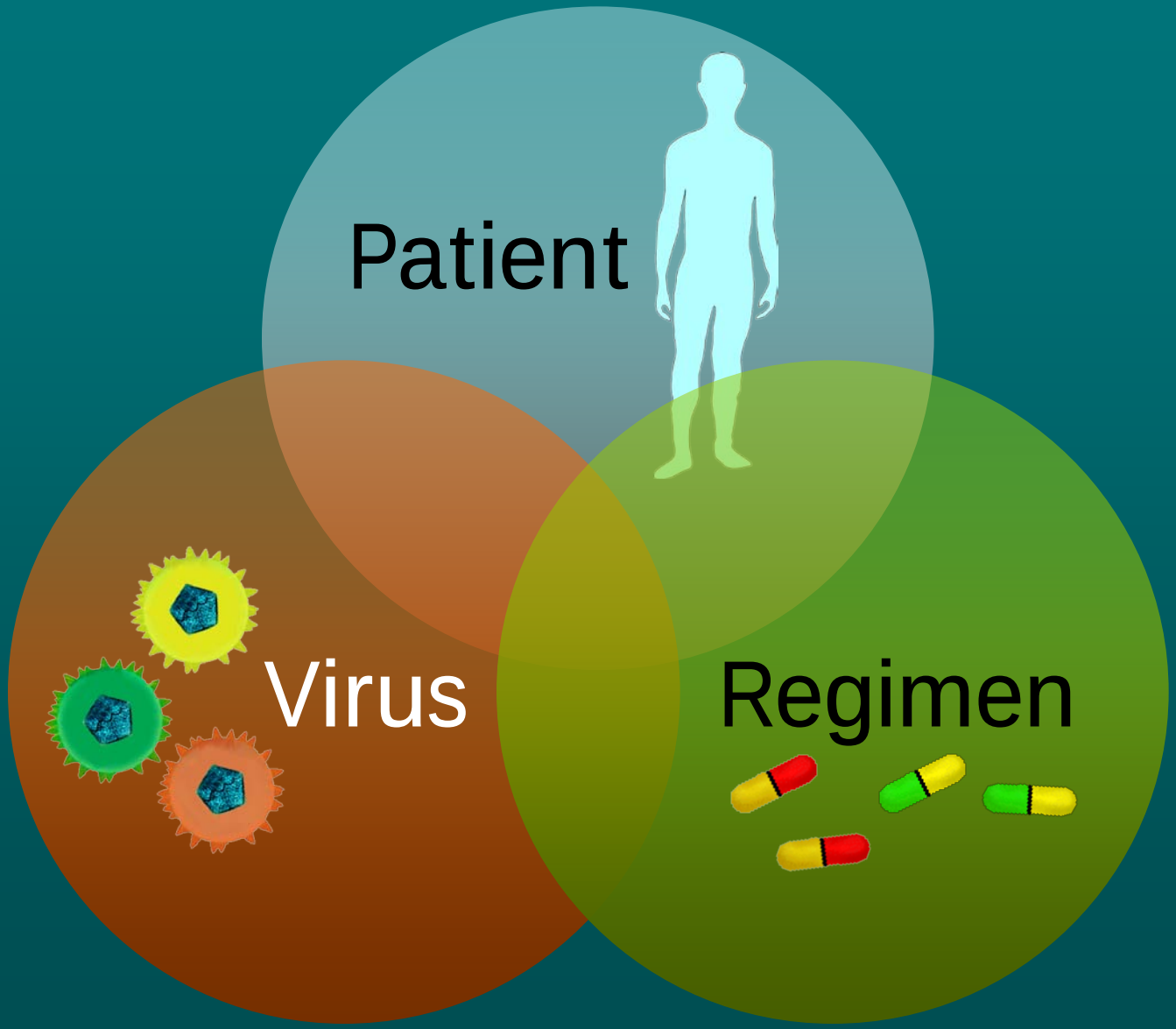
Kieffer T., et al . *AASLD,* 2010, Abstract # LB11

Patient viral populations may return to pre-treatment state over time

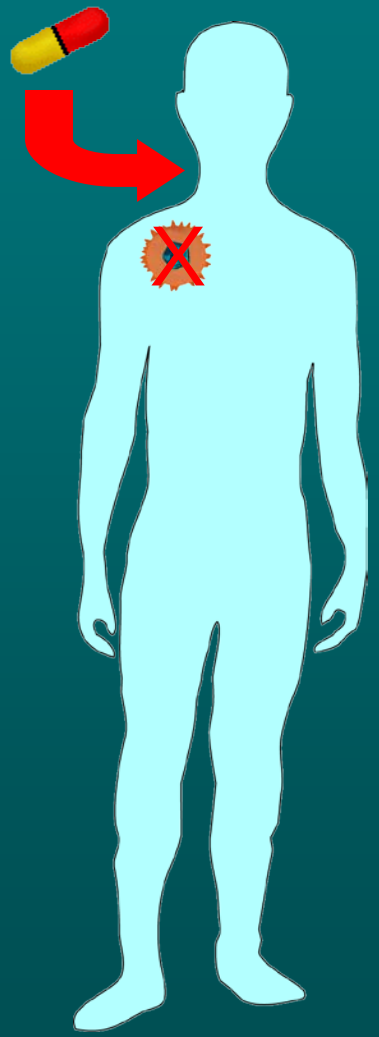
- For protease inhibitors (telaprevir or boceprevir), 59-89% of patients no longer had detectable resistant variants after a median follow-up time of 25-29 months

- Understanding the clinical significance of treatment-acquired resistance requires studies in which patients who experienced virologic failure while on a direct acting antiviral (DAA), are re-treated with a DAA regimen

Many factors contribute to response



Virologic barriers to resistance



Genetic barrier

- Number and type of nucleotide changes required for a virus to acquire clinical resistance to an antiviral regimen[1]

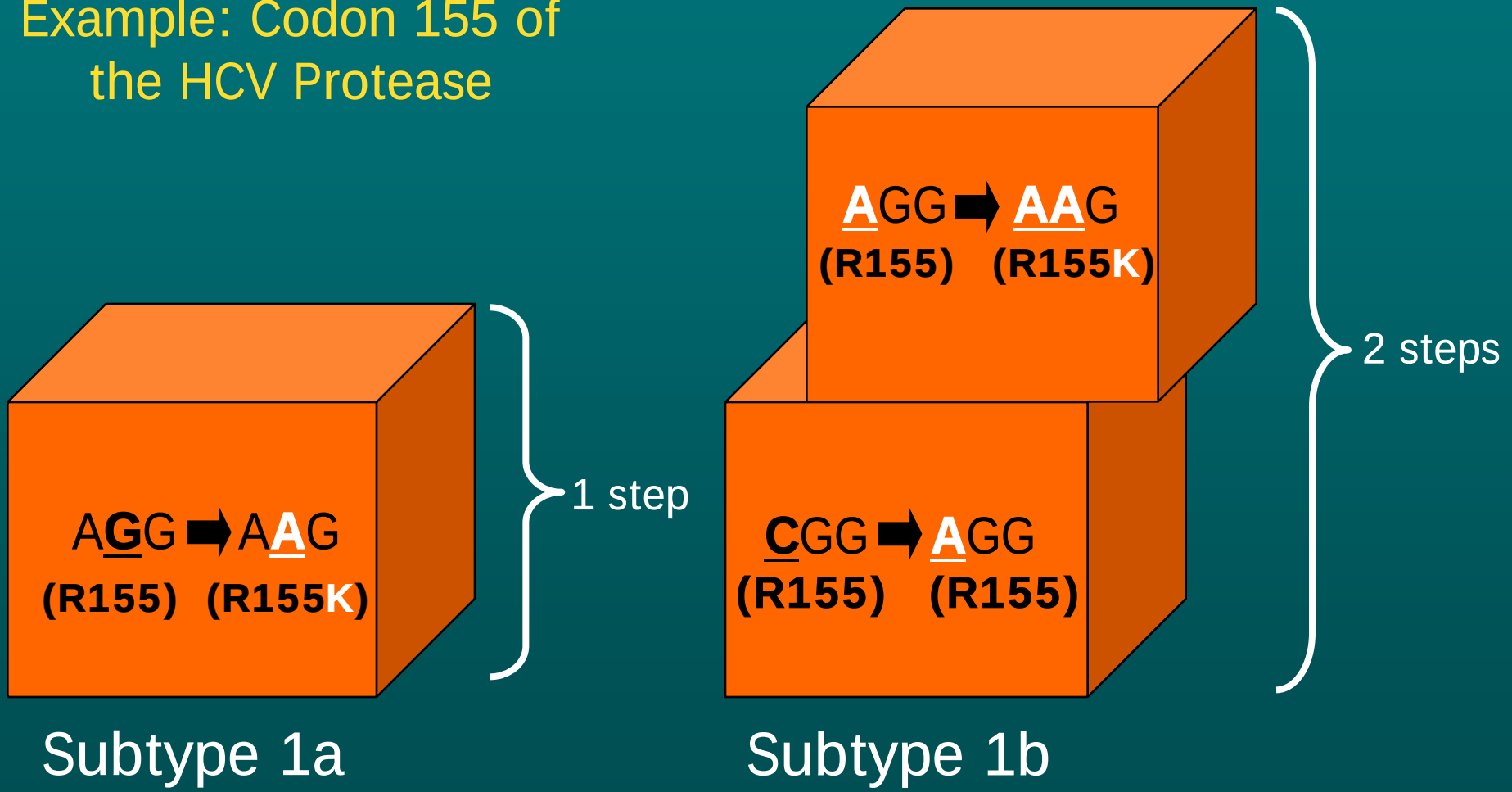
Viral fitness

- Relative capacity of a viral variant to replicate in a given environment
- Resistance mutations frequently compromise viral function and thus reduce viral fitness compared to wild-type in a drug-free environment

1. Rong L. Sci Trans Med, 2010: 2(30): 30ra32

Multiple nucleotide changes maybe required to create a single amino acid change

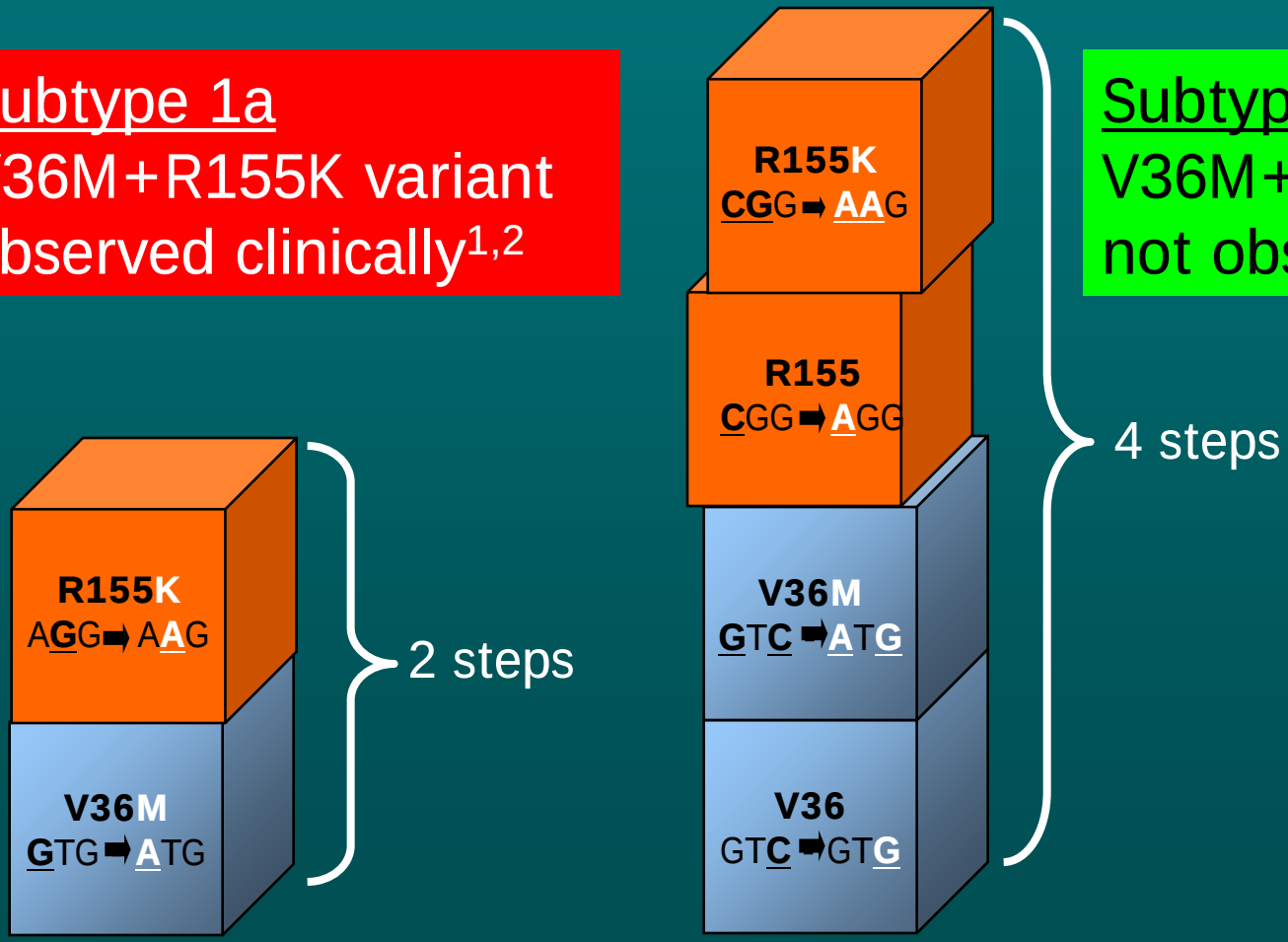
Example: Codon 155 of the HCV Protease



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

Subtype 1a
V36M+R155K variant observed clinically[1,2]

Subtype 1b
V36M+R155K variant not observed clinically



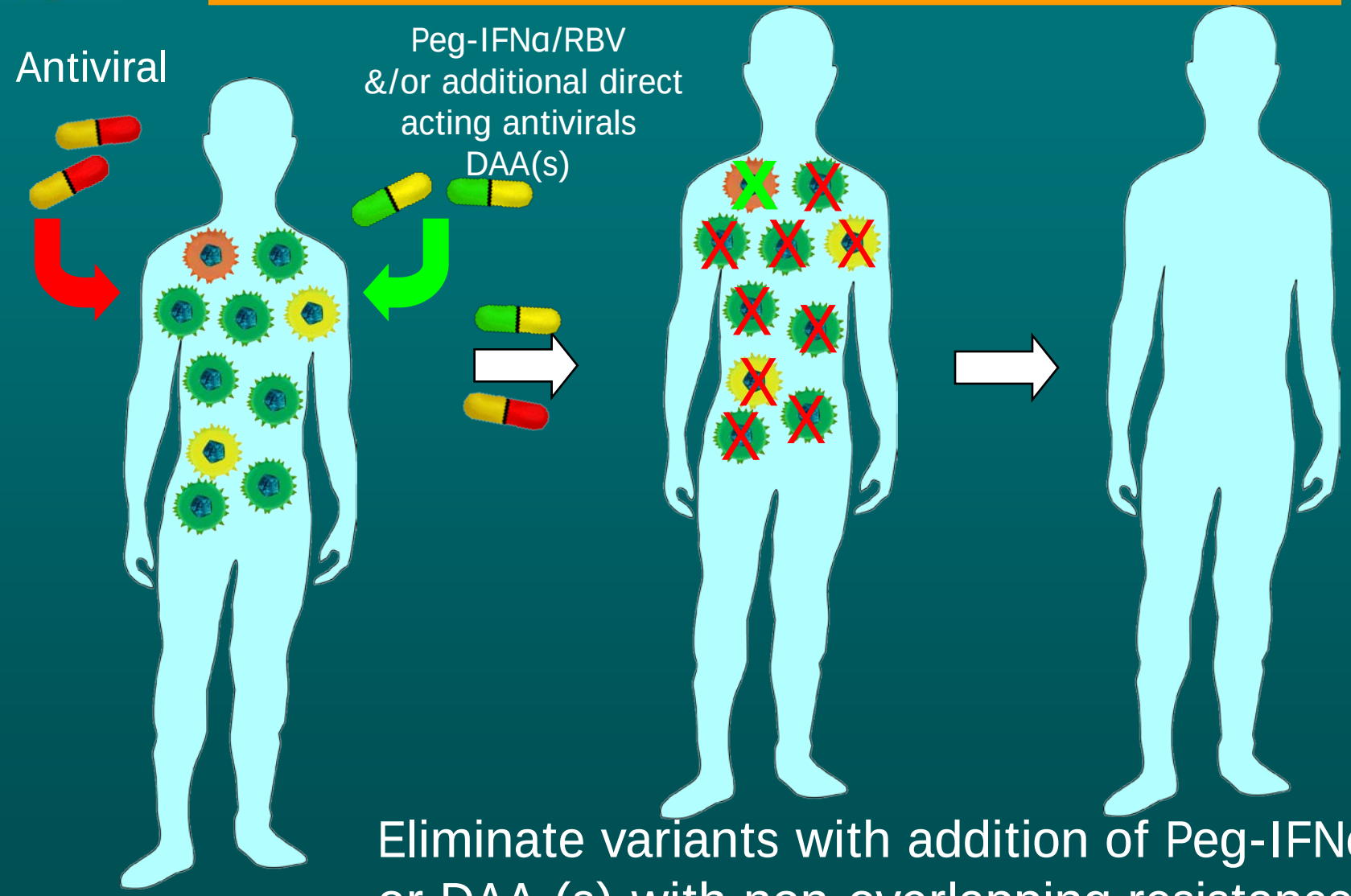
McHutchison J.G., *et al. N Engl J Med,* 2009; 360; 18 1827-1838
Hezode C. , *et al. N Engl J Med,* 2009; 360; 18 1839-1850

Resistant profiles in non-SVR patients

Variant	% of sequenced patients	
	Subtype 1a	Subtype1b
WT	16 %	46 %
V36M	10 %	3 %
R155K	20 %	0 %
V36M+R155K	46 %	0 %
V36A	3 %	16 %
T54A	<1 %	22 %
A156S/T	3 %	13 %

Note: : Information from a subset of patients in trials. Not a complete list of treatment-emergent substitutions observed in clinical trials. See drug Prescribing Information for a complete list.

Combination drug regimens increase the genetic barrier to resistance



Eliminate variants with addition of Peg-IFNα/RBV or DAA (s) with non-overlapping resistance

Resistant virus

Sensitive virus

Lack of cross-resistance between Peg-IFNα/RBV &/or a combination of antiviral agents may provide an opportunity for elimination of resistant variants

Target	Variant	NS3 Covalent: Slow Reversible	NS3 Non-covalent: Linear and Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb 1	NS5B Thumb 2	Peg-IFN	RBV
NS3 Protease	V36M	R	S	S	S	S	S	S	S	S
	T54A	R	S	S	S	S	S	S	S	S
	R155K	R	R	S	S	S	S	S	S	S
	A156T	R	R	S	S	S	S	S	S	S
	D168V	S	R	S	S	S	S	S	S	S
NS5A	L31V	S		R	S	S	S	S	S	S
	Y93H	S		R	S	S	S	S	S	S
NS5B	S282T	S		S	R	S	S	S	S	S
	C316Y	S		S	S	R	S	S	S	S
	M414T	S		S	S	R	S	S	S	S
	R422K	S		S	S	S	S	R	S	S
	M423T	S		S	S	S	S	R	S	S
	P495S	S		S	S	S	R	S	S	S

Note this is not a comprehensive list of known HCV direct acting antivirals (DAA) resistance pathways. 4 fold shift represents arbitrary cutoffs for illustrative purposes only

S = Susceptible
(< 4 fold shift in HCV replicon EC50)

R = Resistant
(>4 fold increase in EC50)

Terms used to guide treatment response in HCV infection

- **HCV RNA undetectable**: HCV RNA level below the limit of detection of a particular assay (not necessarily to be interpreted as HCV RNA "negative" or having cleared HCV for patients on treatment)

- **RVR** (**Rapid virologic response**): Undetectable HCV RNA at week 4 of therapy
- **eRVR** (**Extended RVR**): Undetectable HCV RNA at weeks 4 and 12 of therapy

- **EVR** (**Early virologic response**): >2$\log_{10}$ decline in HCV RNA at week 12 of therapy (also known as partial EVR, pEVR)
- **cEVR** (**Complete EVR**): Undetectable HCV RNA at week 12 of therapy

- **SVR** (**Sustained virologic response**): Undetectable HCV RNA 24 weeks after treatment cessation

- **Null responder**: < 2$\log_{10}$ IU/mL decline in HCV RNA at week 12 of therapy

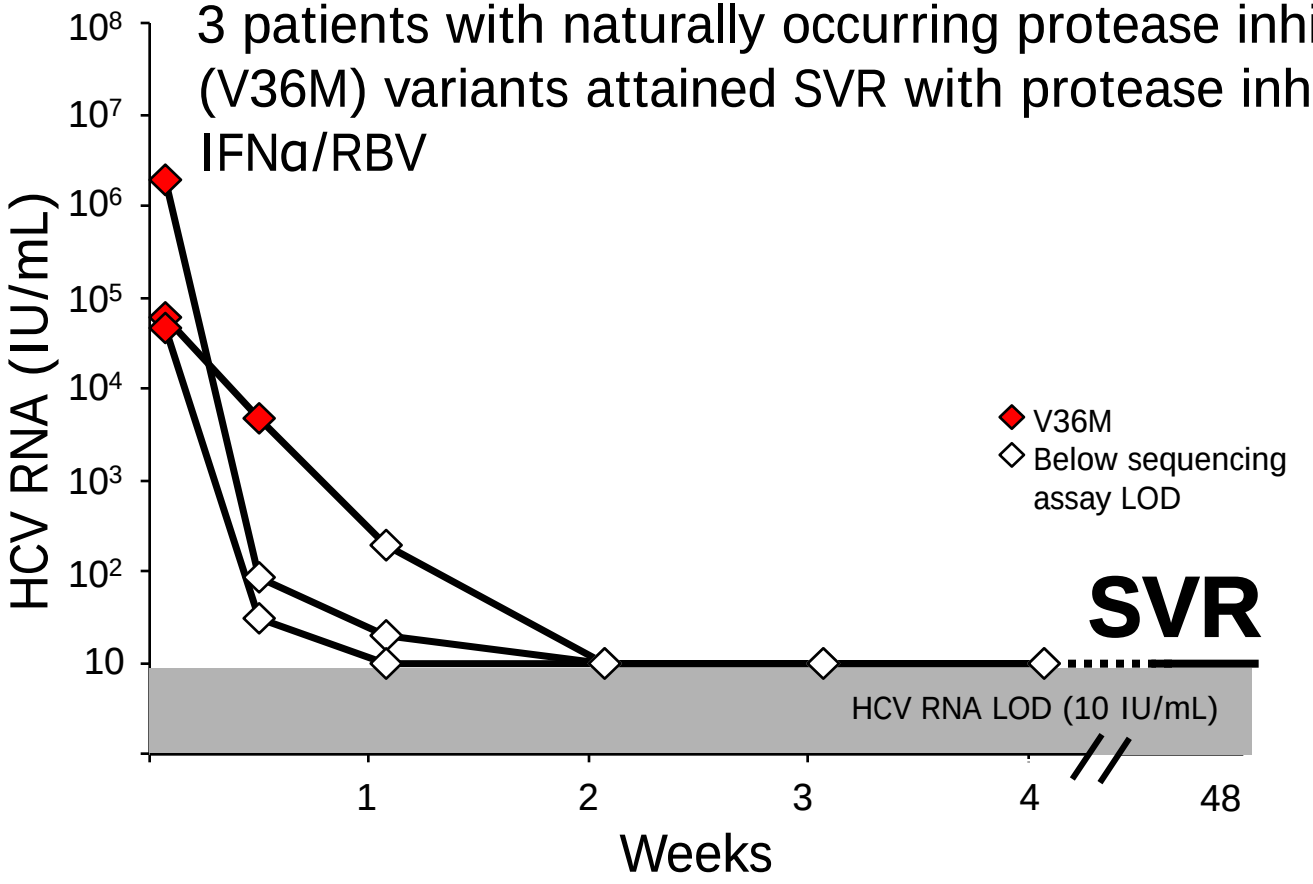
- **Failure of HCV therapy**: Persistence of HCV RNA in serum after therapy

Ghany, M.G., *et al.* *Hepatology* , 2009; 49:1335-74
Shiffman M.L. *Curr Gastro Reports* , 2006; 8:46-52

Resistant variants can be eliminated with a combination drug regimen

Target	Variant	NS3 Covalent: Slow Reversible	NS3 Non-covalent: Linear and Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb 1	NS5B Thumb 2	Peg-IFN	RBV
NS3	V36M	R	S	S	S	S	S	S	S	S

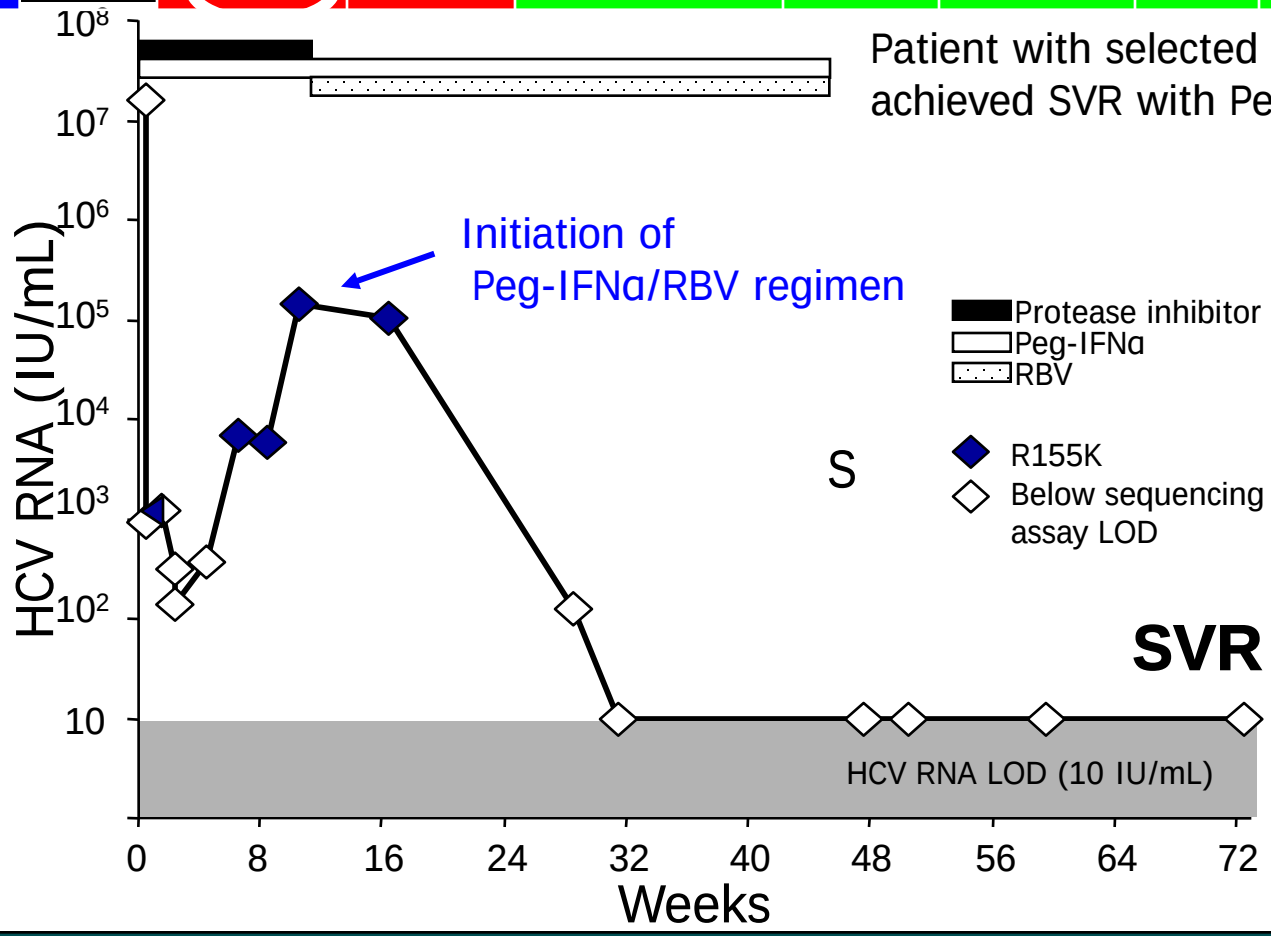
3 patients with naturally occurring protease inhibitor-resistant (V36M) variants attained SVR with protease inhibitor + Peg-IFNα/RBV



Adapted from Bartels DJ. , *et al. J Infec Dis,* 2008;198(6); 800-7

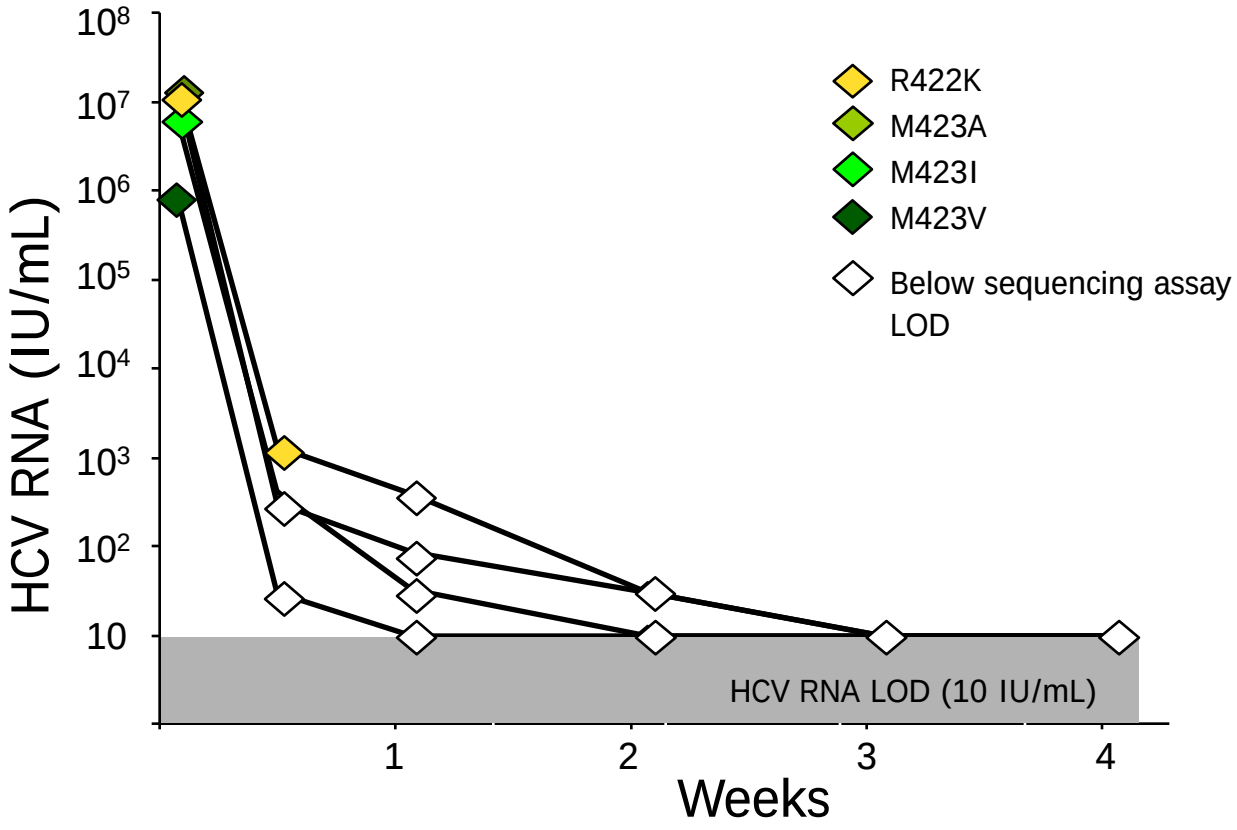
Patients with protease inhibitor-resistant variants can respond to Peg-IFNα/RBV

Target	Variant	NS3 Covalent Slow Reversible	NS3 Non-covalent: Linear	NS3 Non-covalent: Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb 1	NS5B Thumb 2	Peg-IFN	RBV
NS3	R155K	R	R	S	S	S	S	S	S	S	S



Patients with naturally occurring polymerase inhibitor-resistant variants can respond to protease inhibitor + Peg-IFNα/RBV

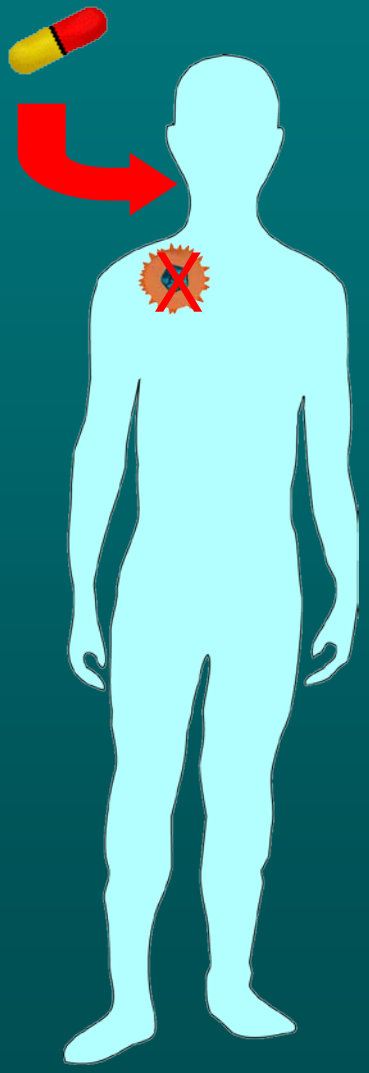
Target	Variant	NS3 Covalent: Slow Reversible	NS3 Non-covalent: Linear and Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb 1	NS5B Thumb 2	Peg-IFN	RBV
NS5B	R422K	S	S	S	S	S	S	R	S	S
	M423T	S	S	S	S	S	S	R	S	S



Unpublished data, examples from telaprevir PROVE1 study

Pharmacological barriers to resistance

Antiviral



Higher potency

- Create/use drugs with stronger binding affinity

Higher drug levels

- Create/use drugs with longer half-life
- Increase target organ exposure
- Take recommended dosage at recommended dosing intervals
- Follow recommended food intake requirements

Improved tolerability and adherence

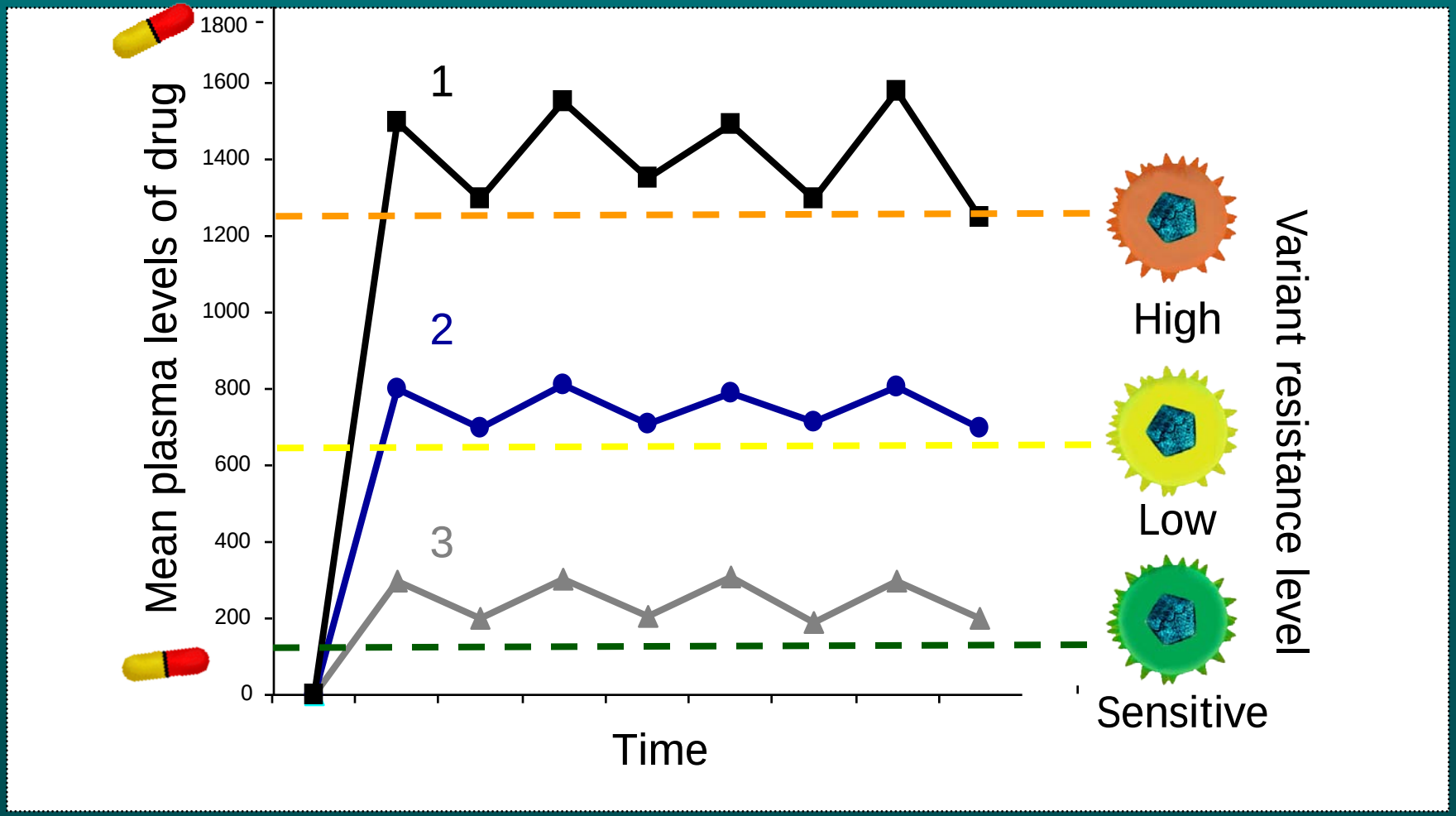
- Create/use drugs with minimal drug/drug interactions
- Create drugs with favorable safety profiles and convenient dosing schedules
- Develop better side effect management protocols

Combination drug regimens

- Develop potent regimen of direct-acting antiviral drugs with or without Peg-IFNα/RBV

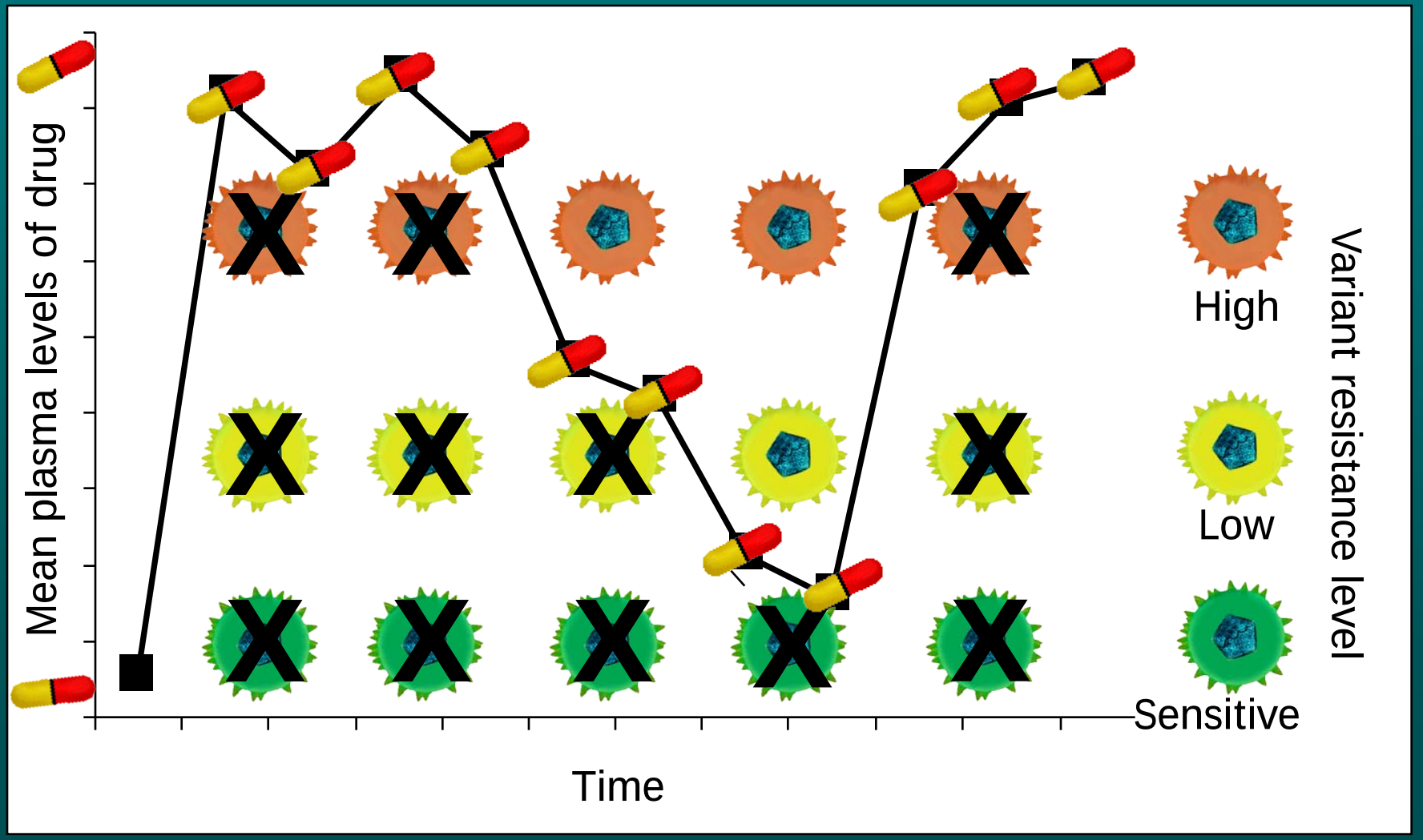
Resistance is not an all or none phenomenon

- Clinical resistance occurs if drug levels are not sufficient to inhibit viral replication
- Highly resistant viruses need very high drug levels (may not be achievable) to inhibit their replication

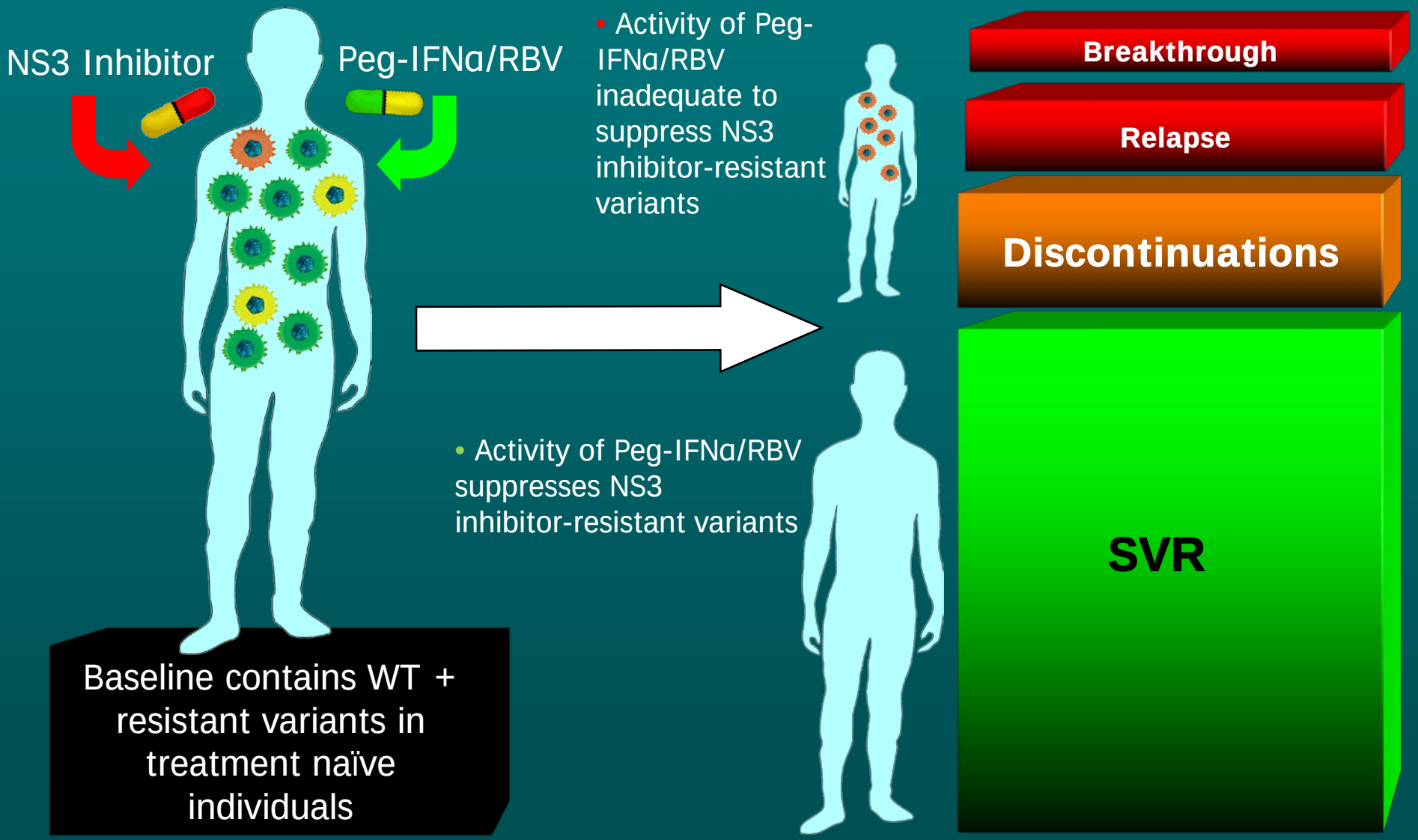


Importance of drug levels over time

Drug trough levels must be sufficient to suppress viral replication

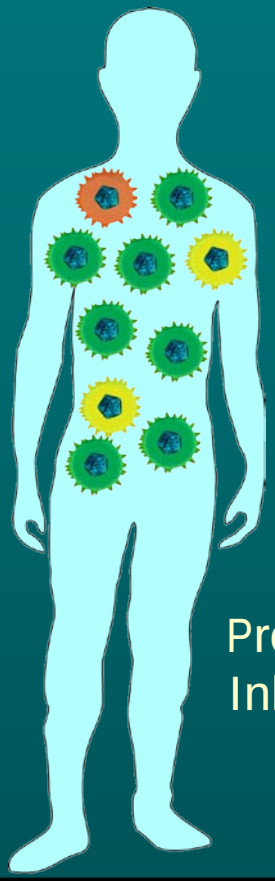


Resistance emerges as a result of treatment failure

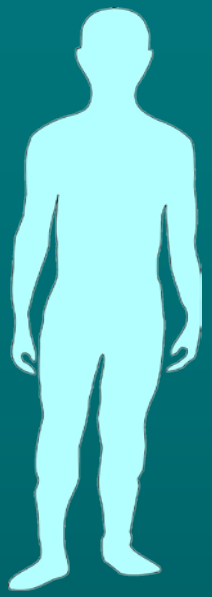


McHutchison JG. , *et al. N Engl J Med,* 2009; 360(18): 1827-183
Sarrazin, C. & Zeuzem, S. *Gastro,* 2010;138:447-62
Hezode C. , *et al. N Engl J Med,* 2009; 360(18): 1839-1850 Kwo PY., et al *Hepatology,* 2008;48:1027A

Contribution of Peg-IFNα/RBV to SVR



Protease Inhibitor + Peg-IFNα+RBV



SVR~70%

Peg-IFNα+ RBV

SVR~46%

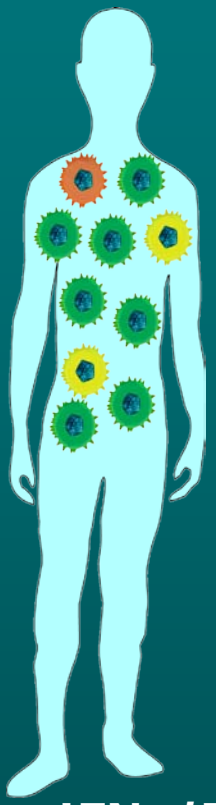
Protease Inhibitor + Peg-IFNα

SVR~36%

Baseline contains WT + resistant variants in treatment naïve individuals

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
Kwo PY., *et al. Hepatology* , 2008;48:1027A

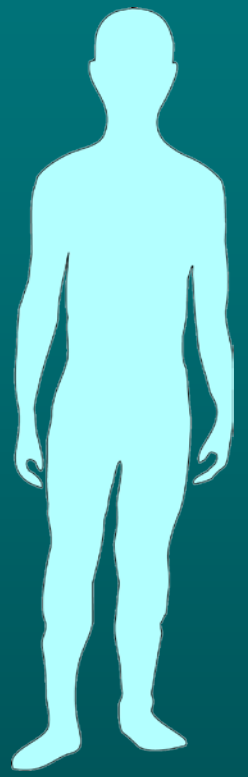
Peg-IFNα/RBV (PR) treatment experienced patients can be re-treated



Peg-IFNα/RBV treatment experienced

Prior PR response	Retreatment SVR rate (approximate)	
	PR	PR + Protease Inhibitor
Relapse	22%	86%
Partial	15%	60%
Null	5%	32%

New regimen: Protease Inhibitor + Peg-IFNα+RBV



SVR

Definitions

Prior relapser: Achieved undetectable HCV RNA at end of treatment, but failed to achieve SVR

Prior partial responder: Achieved ≥2 log drop in HCV RNA at week 12 of prior therapy, but never became undetectable while on treatment

Prior null responder: Achieved <2log drop in HCV RNA at week 12 of prior therapy

See prescribing information of approved therapies for treatment recommendations and available data supporting re-treatment of specific patient populations

IL28B genotype: Is there a role in the era of direct acting antivirals (DAAs)?

- Certain single nucleotide polymorphisms (SNPs) upstream of *IL28B* gene are associated with the rate of SVR in patients treated with **Peg-IFNα/RBV**:
  - SNP rs12979860: favorable allele=C, unfavorable allele=T
  - SNP rs8099917: favorable allele=T, unfavorable allele=G
- IL28B genotype can have an impact on the efficacy of a Peg-IFNα/RBV/DAA regimen
- IL28B genotype has also recently been shown to affect the activity of an interferon-free IFN-free, combination DAA regimen, although its impact is likely dependent on the anti-HCV potency and durability of the regimen

Ge D., *et al.*, *Nature* , 2009; 461:399-401
Tanaka Y., *et al. Nature Genetics* , 2009; 41:1105-1109
Suppiah V., *et al. Nature Genetics* , 2009; 41: 1100-1104

IL28B genotype effect on SVR in genotype-1 treatment-naïve patients

- Certain single nucleotide polymorphisms (SNPs) upstream of *IL28B* gene are associated with SVR in patients treated with Peg-IFNα/RBV (PR)[1-3]:
  - SNP rs12979860: favorable allele=C, unfavorable allele=T

IL28B SNP rs12979860	PR (Ideal)		Telaprevir[5] (ADVANCE)		Boceprevir[6] (SPRINT-2)	
	ITT[4] Population	Adherent[3] Population	TVR/PR	PR control	BOC/PR*	PR control
CC	69%	~79%	90%	64%	80-82%	78%
CT	33%	~38%	71%	25%	65-71%	28%
TT	27%	~26%	73%	23%	55-59%	27%

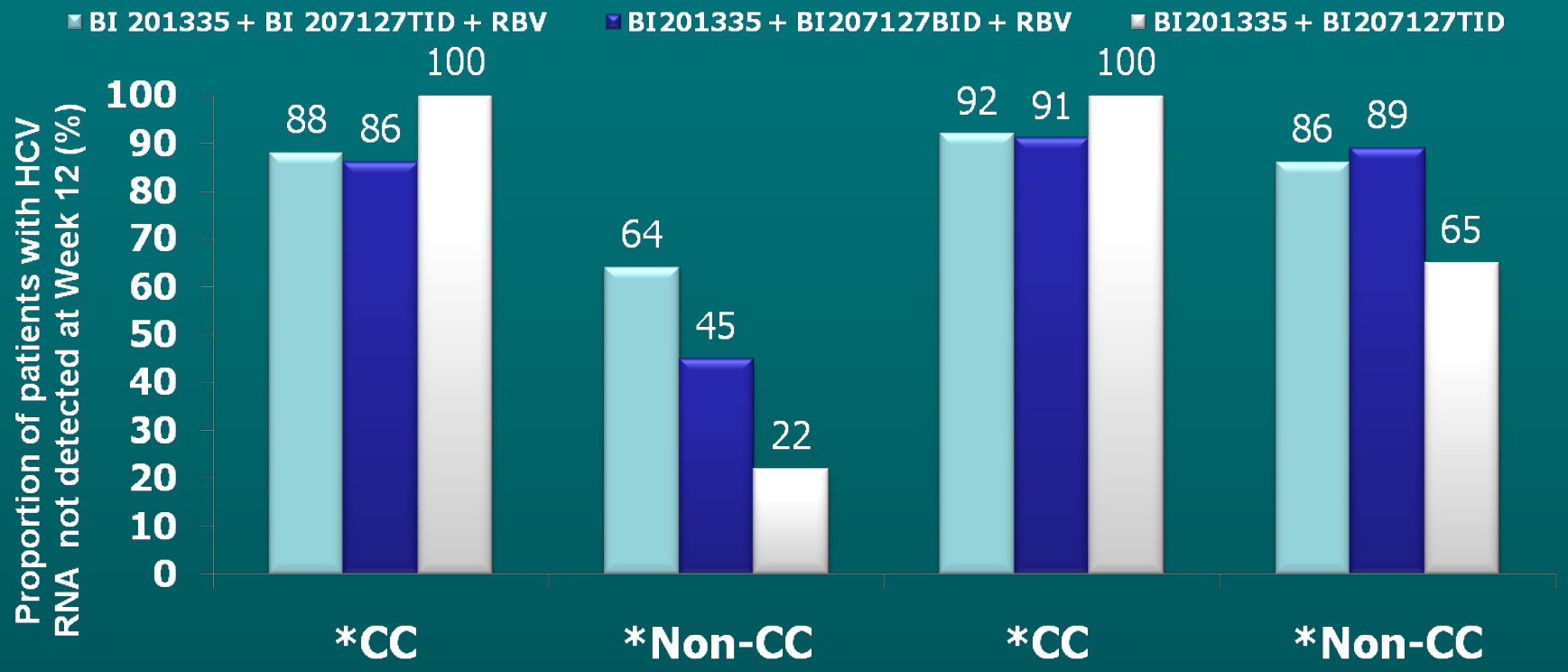
*** Includes BOC/RGT and BOC/PR48 arms, mITT**

1 Tanaka Y., *et al. Nature Genetics* , 2009; 41:1105-1109
2 Suppiah V., *et al. Nature Genetics* , 2009; 41: 1100-1104
3 Ge D., *et al. Nature* , 2009; 461:399-401
4 Thompson A.J., *et al. Gastro , 2010; 139: 120-129*
5 INCIVEK™ [package insert]. Cambridge, Mass: Vertex Pharmaceuticals Inc; 2011
6 VICTRELIS™ [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2011

Footnotes: 1) Data from ADVANCE and SPRINT-2 based only on subjects who consented to IL28B genotype analysis; 2) Results are confounded by variable treatment durations in active and control arms

IL28B Genotype Can Influence Activity of an IFN-free Regimen:

Proportion of GT1 patients with HCV RNA Not Detected at Treatment week 12 by IL28B Genotype and Subtype (per protocol analysis)



*IL28B SNP rs12979860

	GT-1a		GT-1b	
BI201335 + BI207127$_{TID}$ +RBV	22/25	39/61	24/26	79/92
BI201335 + BI207127$_{BID}$ + RBV	6/7	10/22	10/11	32/36
BI201335 + BI207127$_{TID}$, no RBV	3/3	2/9	7/7	13/20

BI 201335: Protease Inhibitor BI 207127: Polymerase Inhibitor

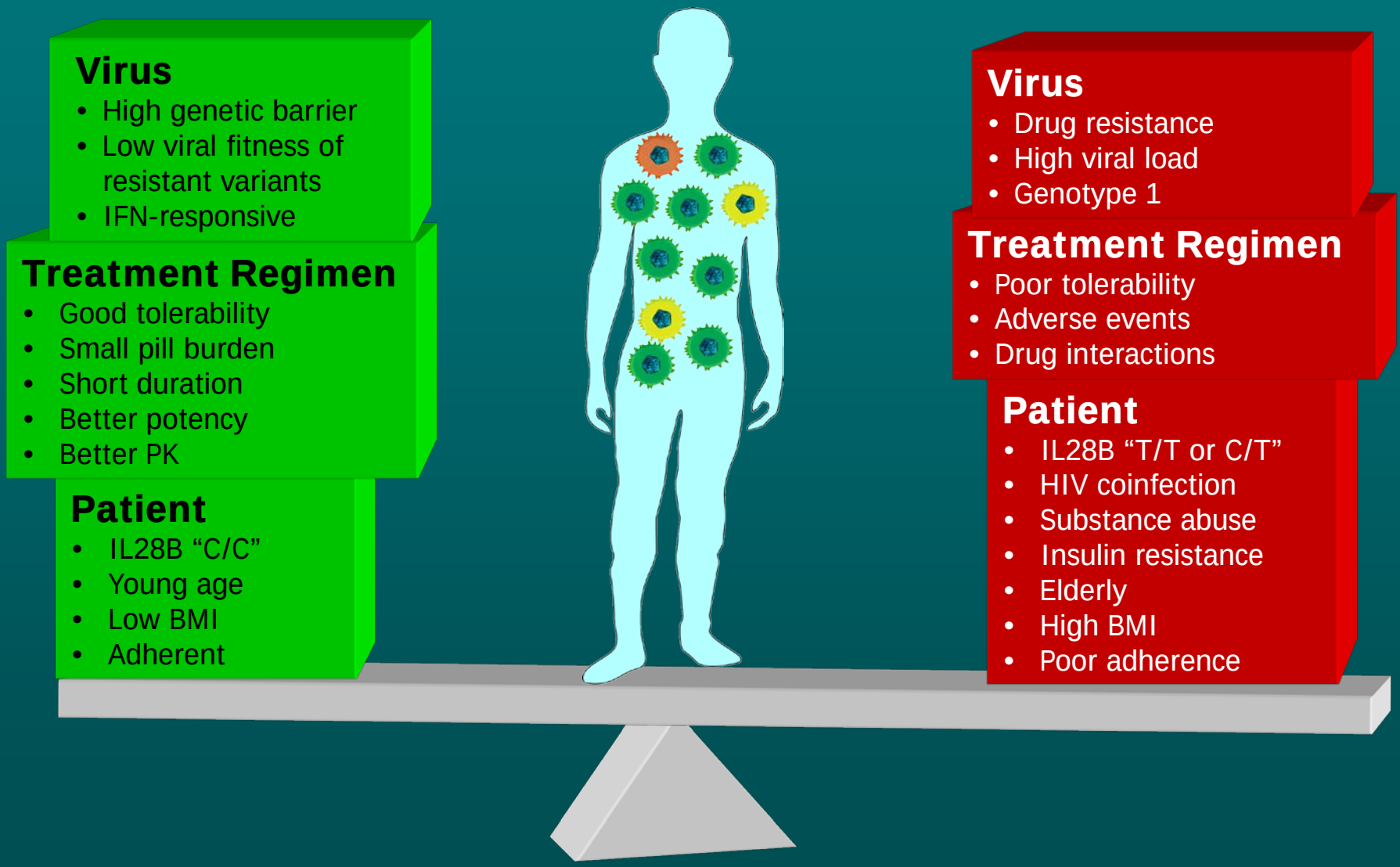
Zeuzem et al, 2011 AASLD Annual Meeting Boston, USA. Late-breaker#15

Interferon-free, combination direct acting antiviral (DAA) regimens: Progress and challenges

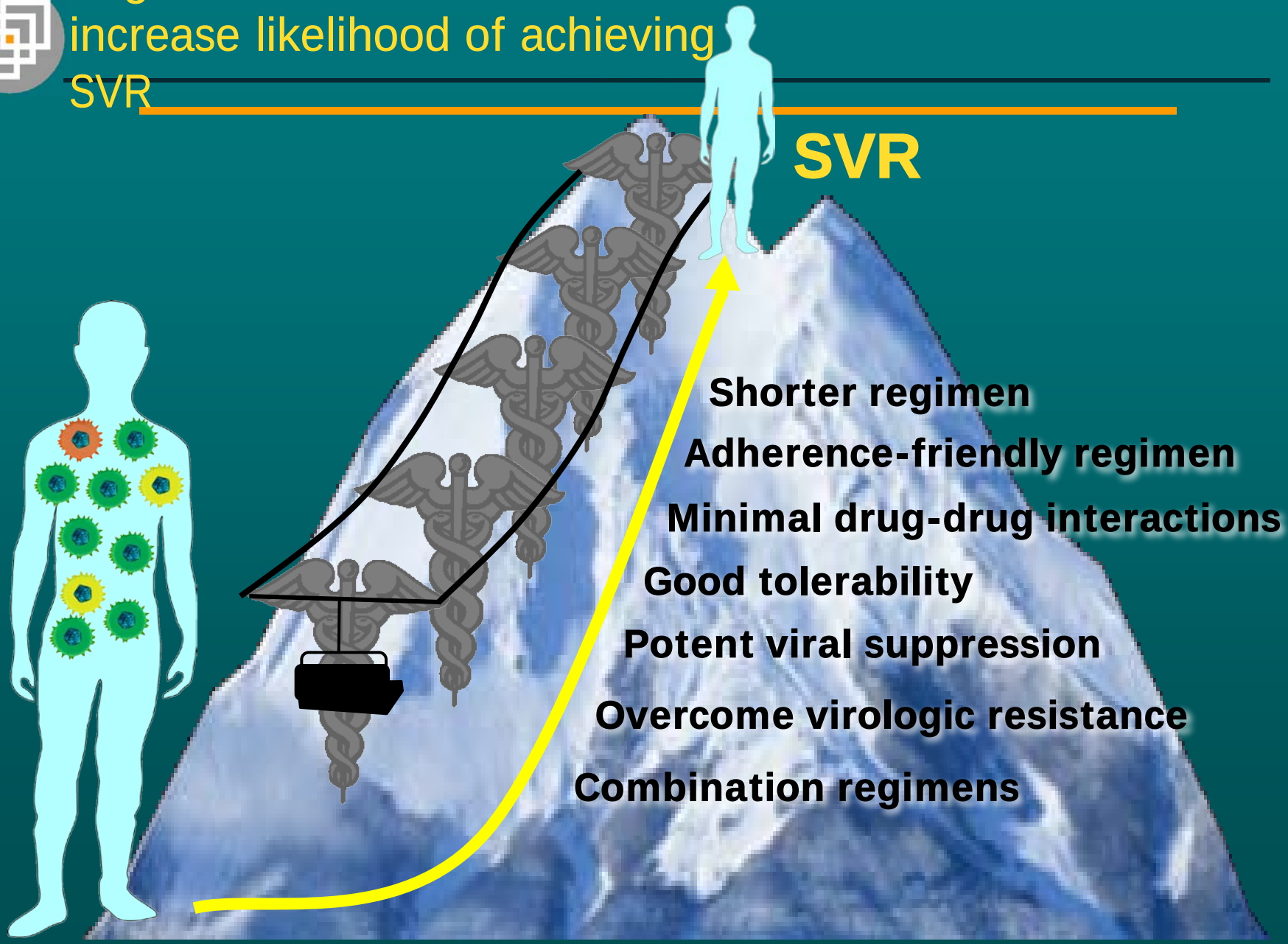
- There is an urgent need for safe and effective treatment regimens that do not include Peg-IFNα and/or RBV.
- In a Peg-IFNα/RBV/DAA regimen, Peg-IFNα/RBV enhance DAA antiviral durability by suppressing DAA-resistant variants
- Numerous clinical trials investigating the efficacy of combination DAA regimens to replace Peg-IFNα and/or RBV have been conducted or are in progress.
- Challenge: **Anti-HCV potency without durability ≠ SVR**
- Lessons learned from trials conducted to date:
  - Two potent, low resistance barrier DAAs are most likely not adequate to achieve SVR for a majority of patients
  - Virologic breakthrough with a combination DAA regimen can occur early (few days) or late (2-3 months); only SVR proves efficacy
  - HCV genotype/subtype can have a major impact
  - Inclusion of RBV may have a role in combination DAA therapy

Maximize Response, Minimize Resistance

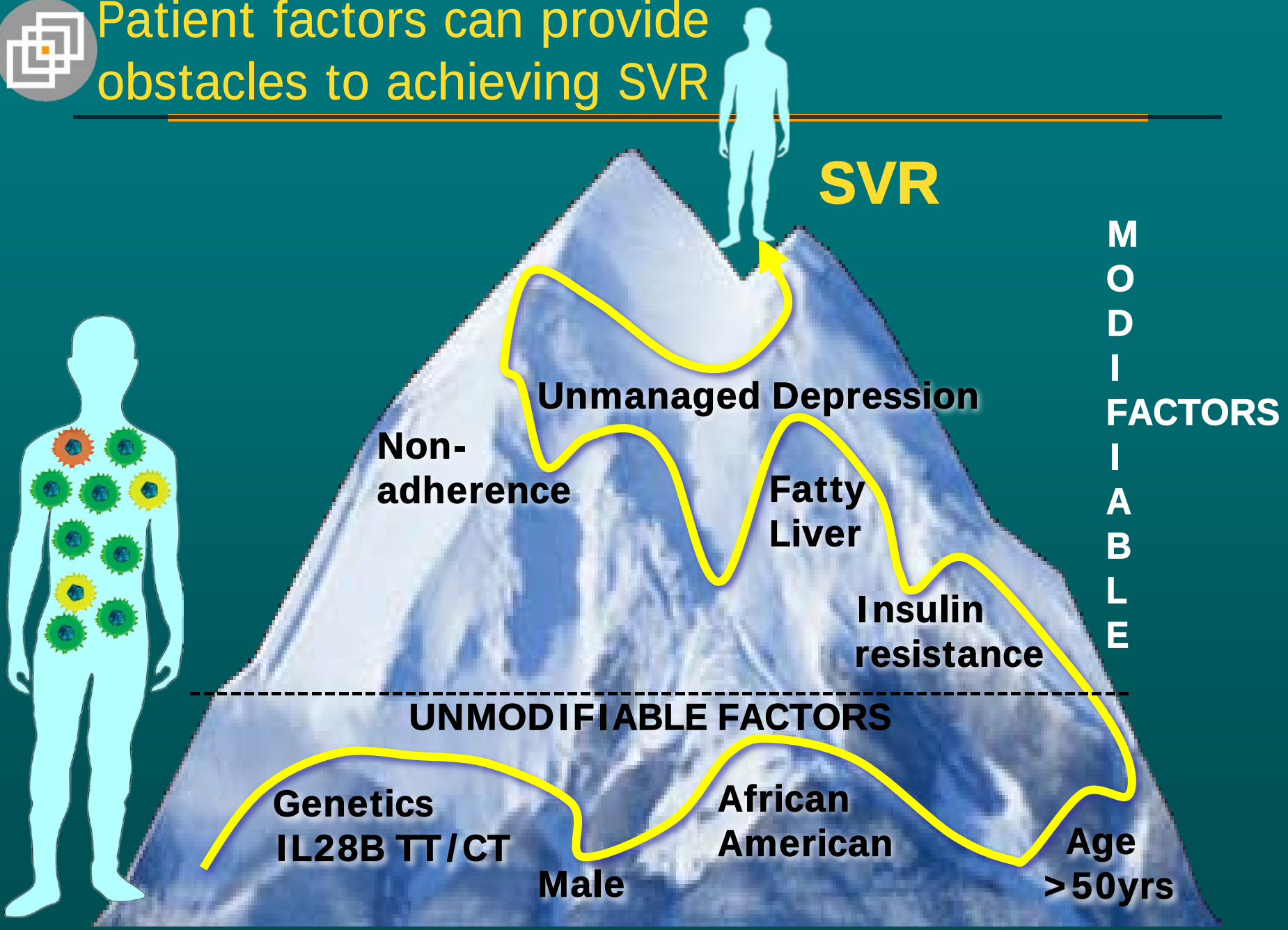
A balance of multiple factors contribute to SVR



Regimen characteristics that increase likelihood of achieving SVR



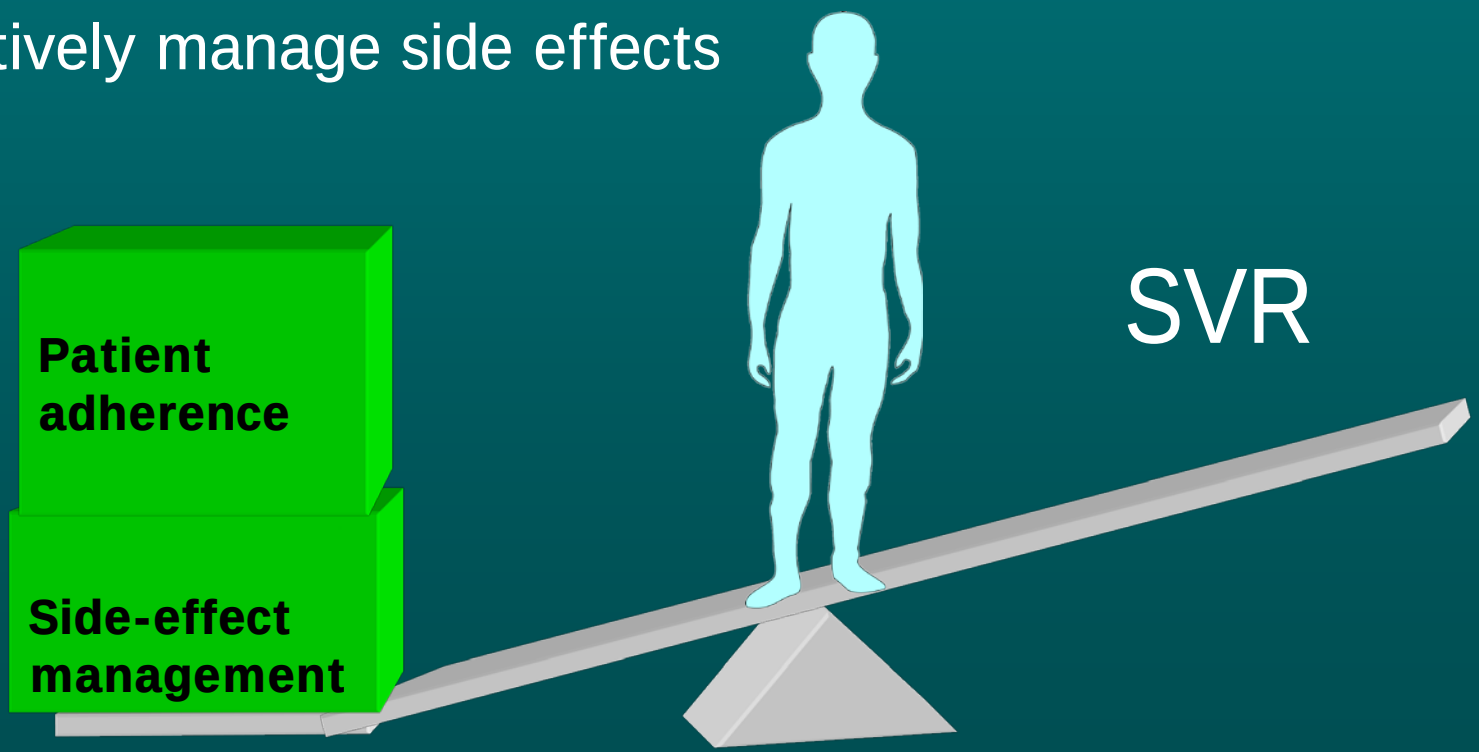
Patient factors can provide obstacles to achieving SVR



Adherence shifts the balance for SVR

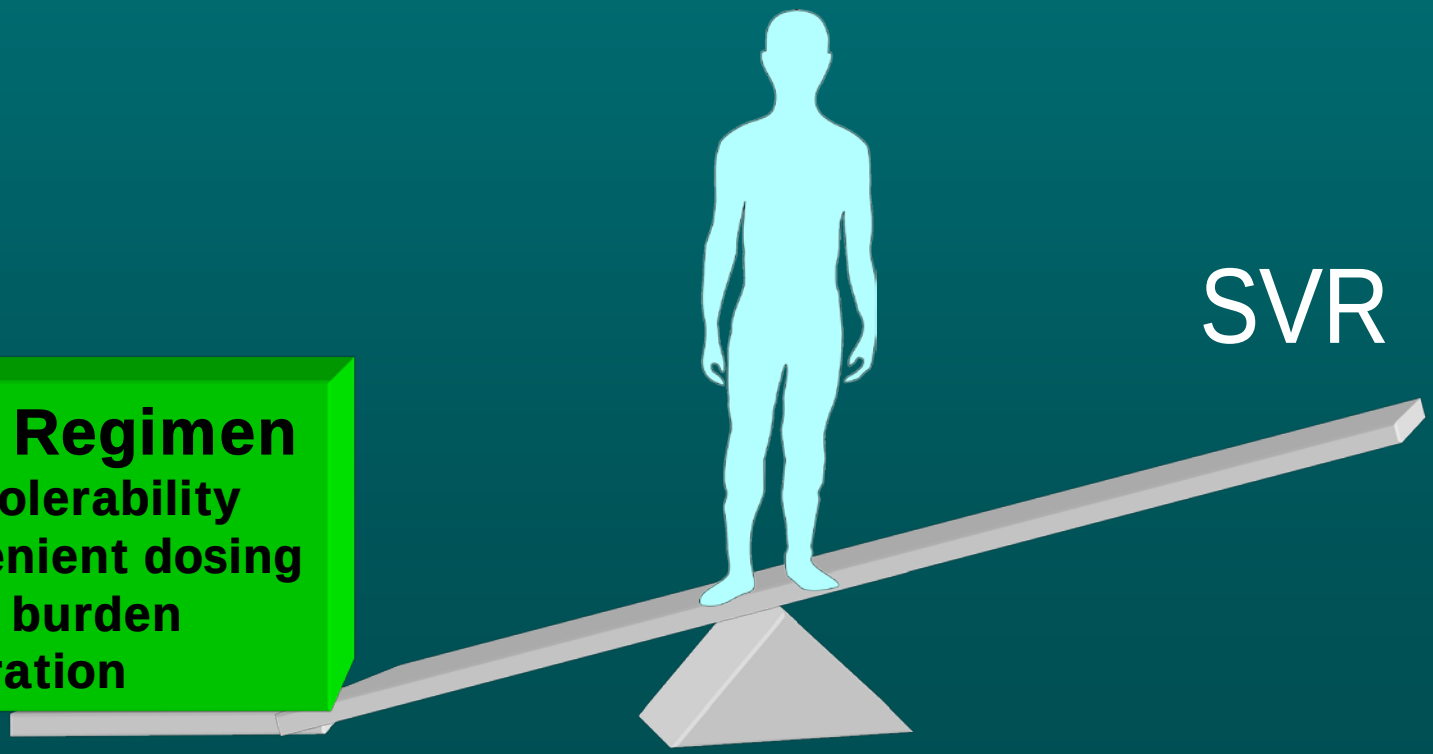
Doctors and patients can maximize response:

- ✓ Right dose of drug
- ✓ At the right time
- ✓ Follow dietary recommendations
- ✓ Actively manage side effects



Future drug regimens could improve SVR rates

Industry, academia, regulators and community can work together to improve the quality of drugs available for HCV infected patients



Improved Regimen

- **Improved tolerability**
- **More convenient dosing**
- **Smaller pill burden**
- **Shorter duration**

Acknowledgements

Nathalie Adda
Bambang Adiwajaya
James Appleman
Doug Bartels
Connie Benson
Michelle Berrey
Mari Brill
Abby Carney
Sarah Cowherd
Sandra De Meyer
Shelley George
Donna Goolkasian
Cami Graham
Patrick Harrington
Ira Jacobson
Dale Kempf
Tara Kieffer
George Kukolj
Ann Kwong
Jules Levin
Kai Lin
Nina Mani
Fiona Mcphee
John McHutchison
Veronica Miller
Hongmei Mo
Steven Mousterakis
Isabel Najera
Jules O'Rear
Michael Otto
Jean-Michel Pawlotsky
Alan Perelson
Diana Picariello
Gaston Picchio
Stuart Ray
Doug Richman
Christoph Sarrazin
Chip Schooley
Scott Seiwert
Debra Sieminski
Mark Sulkowski
Tracy Swan
Theresa Turcotte
David Wyles

Selected Bibliography

Berman K. & Kwo P. Y. Boceprevir, an NS3 Protease Inhibitor of HCV. *Clin Liver Dis* 2009; 13:429–439

Ghany M. G. Diagnosis, Management, and Treatment of Hepatitis C: An Update. *Hepatology* 2009; 49:1335-1374

Hezode, C. Telaprevir and Peginterferon with or without Ribavirin for Chronic HCV Infection. *N Engl J Med* 2009;360:1839-50

Kieffer T. L. Viral resistance to specifically targeted antiviral therapies for hepatitis C (STAT-Cs). *J Antimicro. Chemother* 2010; 65: 202-212

Kwong A. et al. Sequence and phenotypic analysis for resistance monitoring in hepatitis C virus drug development: Recommendations from the HCV DRAG. (in press) *Gastroenterology* 2011. DOI:10.1053/j.gastro.2011.01.029

McHutchison J. G. Telaprevir with Peginterferon and Ribavirin for Chronic HCV Genotype 1 Infection. *N Engl J Med* 2009;360:1827-38

McHutchison J. G. Telaprevir for Previously Treated Chronic HCV Infection. *N Engl J Med* 2010;362:1292-303

Selected Bibliography contd.

Rong L. Rapid Emergence of Protease Inhibitor Resistance in Hepatitis C Virus. *Sci Transl Med* 2010; 2:30ra32

Ralston R. et al. Long-term Follow-up of Patients Treated with Boceprevir in Combination with PEG-Intron/Ribavirin (P/R): Durability of Responses and Rates of Reversion of Resistance Mutations. *International HIV and Hepatitis Drug Resistance Workshop*, 2010

Sarrazin C. & Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. *Gastroenterology*. 2010 138:447-62

Susser S. et al. Characterization of Resistance to the Protease Inhibitor Boceprevir in Hepatitis C Virus–Infected Patients. *Hepatology* 2009; 50:1709-1718

Zeuzem S. et al. Long-Term Follow-up of Patients with Chronic Hepatitis C Treated with Telaprevir in Combination with Peginterferon Alfa-2a and Ribavirin: Interim Analysis from the EXTEND Study. *AASLD* 2010

Please send comments to:

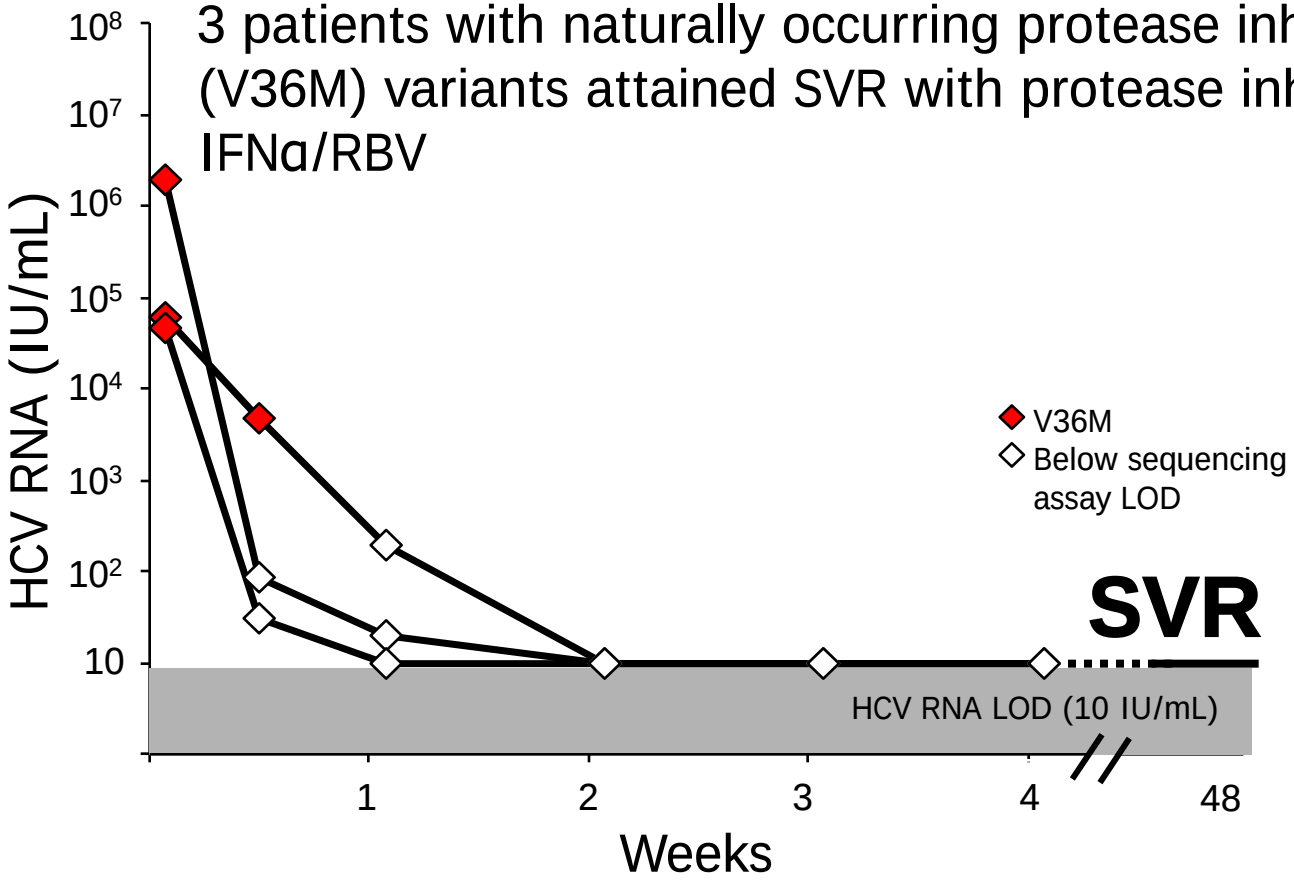
Nina Mani, FCHR

nmani@hivforum.org

Resistant variants can be eliminated with a combination drug regimen

Target	Variant	NS3 Covalent: Slow Reversible	NS3 Non-covalent: Linear and Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb 1	NS5B Thumb 2	Peg-IFN	RBV
NS3	V36M	R	S	S	S	S	S	S	S	S

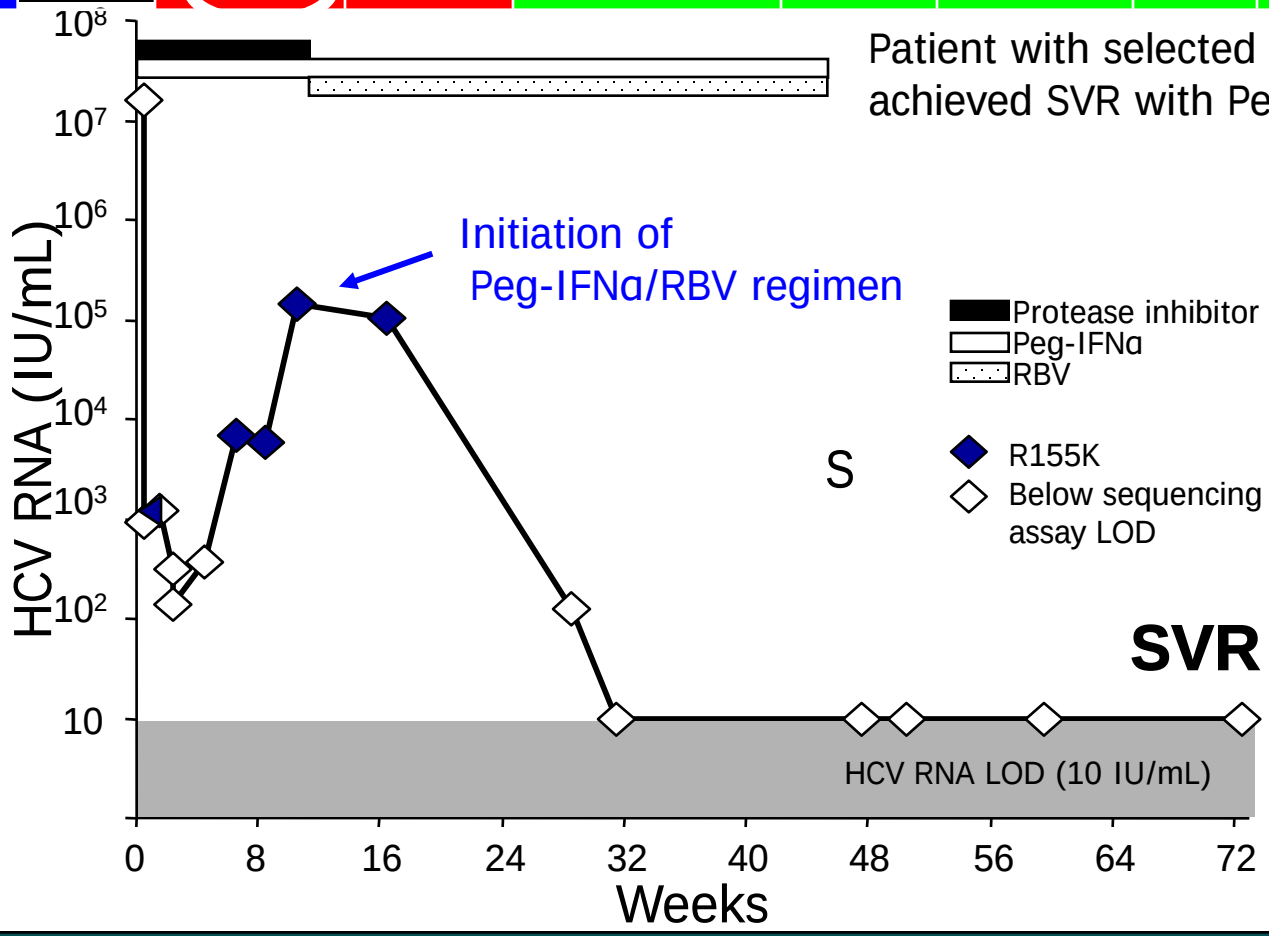
3 patients with naturally occurring protease inhibitor-resistant (V36M) variants attained SVR with protease inhibitor + Peg-IFNα/RBV



Adapted from Bartels DJ. , *et al. J Infec Dis,* 2008;198(6); 800-7

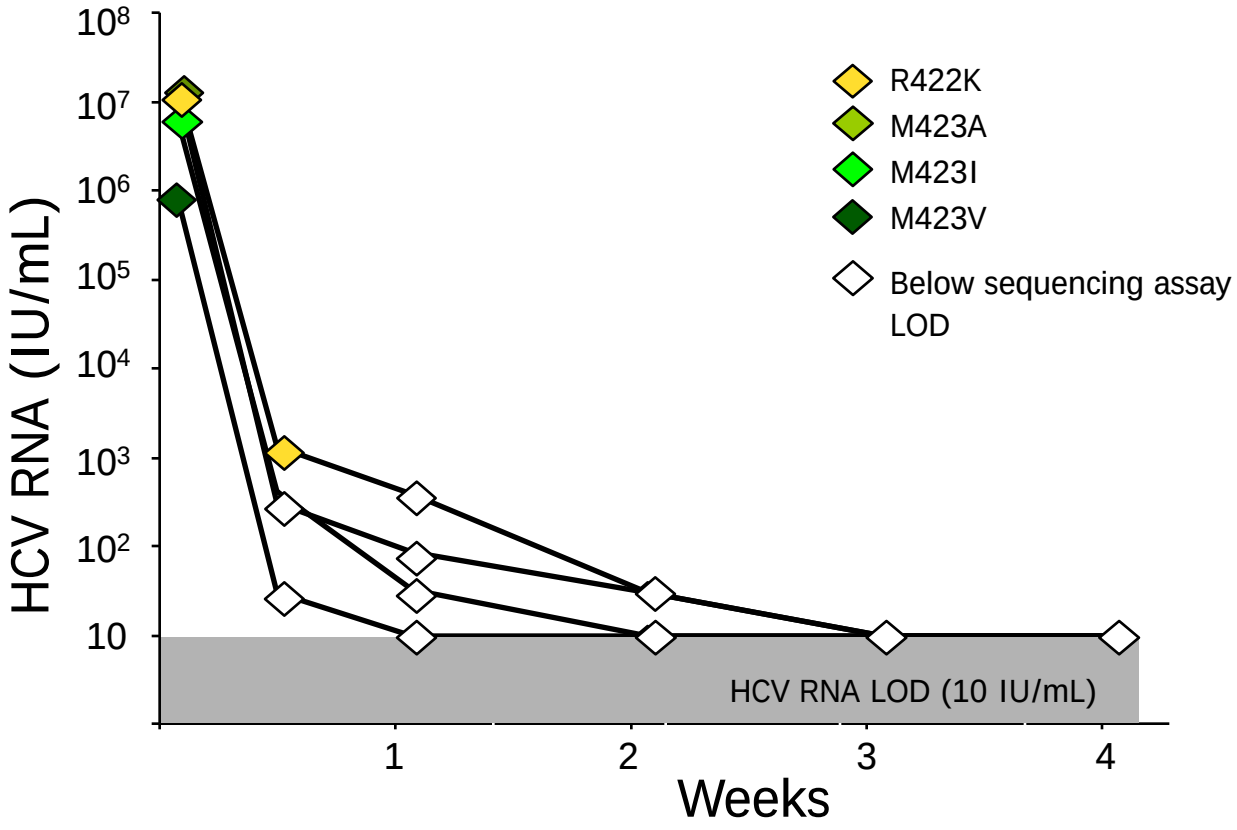
Patients with protease inhibitor-resistant variants can respond to Peg-IFNα/RBV

Target	Variant	NS3 Covalent Slow Reversible	NS3 Non-covalent: Linear	NS3 Non-covalent: Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb 1	NS5B Thumb 2	Peg-IFN	RBV
NS3	R155K	R	R	S	S	S	S	S	S	S	S



Patients with naturally occurring polymerase inhibitor-resistant variants can respond to protease inhibitor + Peg-IFNα/RBV

Target	Variant	NS3 Covalent: Slow Reversible	NS3 Non-covalent: Linear and Macrocyclic	NS5A inhibitor	NS5B nucleoside	NS5B Palm	NS5B Thumb 1	NS5B Thumb 2	Peg-IFN	RBV
NS5B	R422K	S	S	S	S	S	S	R	S	S
	M423T	S	S	S	S	S	S	R	S	S



Unpublished data, examples from telaprevir PROVE1 study