Hepatitis C:
Short duration DAA therapy, DAA resistance

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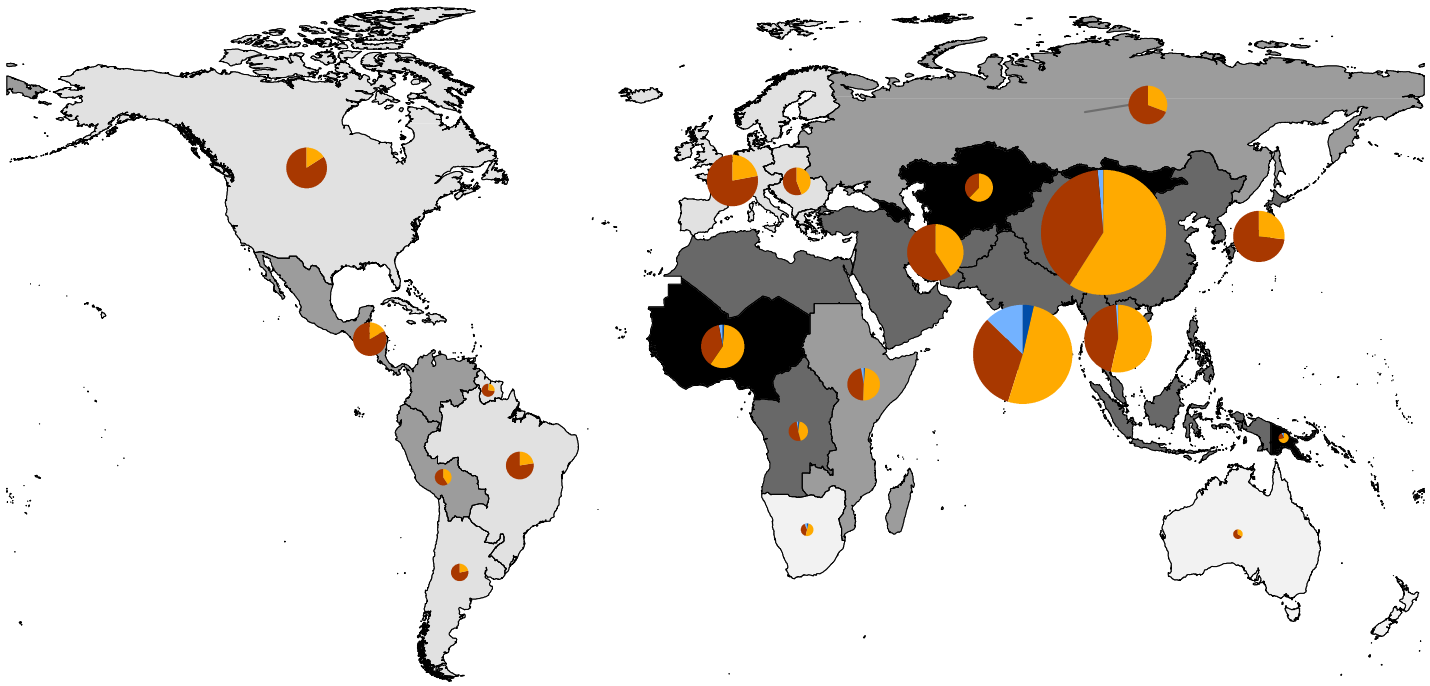
14th June, 2016

@grahamscooke

Hepatology Highlights

Speaker Name	Statement
Graham Cooke	Consultancy for Gilead, MSD, BI, BMS, Janssen, WHO Investigator on studies sponsored by Gilead, Janssen, BMS
Date	June 2016

Viral Hepatitis 7th leading cause of death



Mortality rate (per 100,000 py)

- <10
- 10 - 14.9
- 15 - 22.49
- 22.5 - 33.49
- 33.5 +

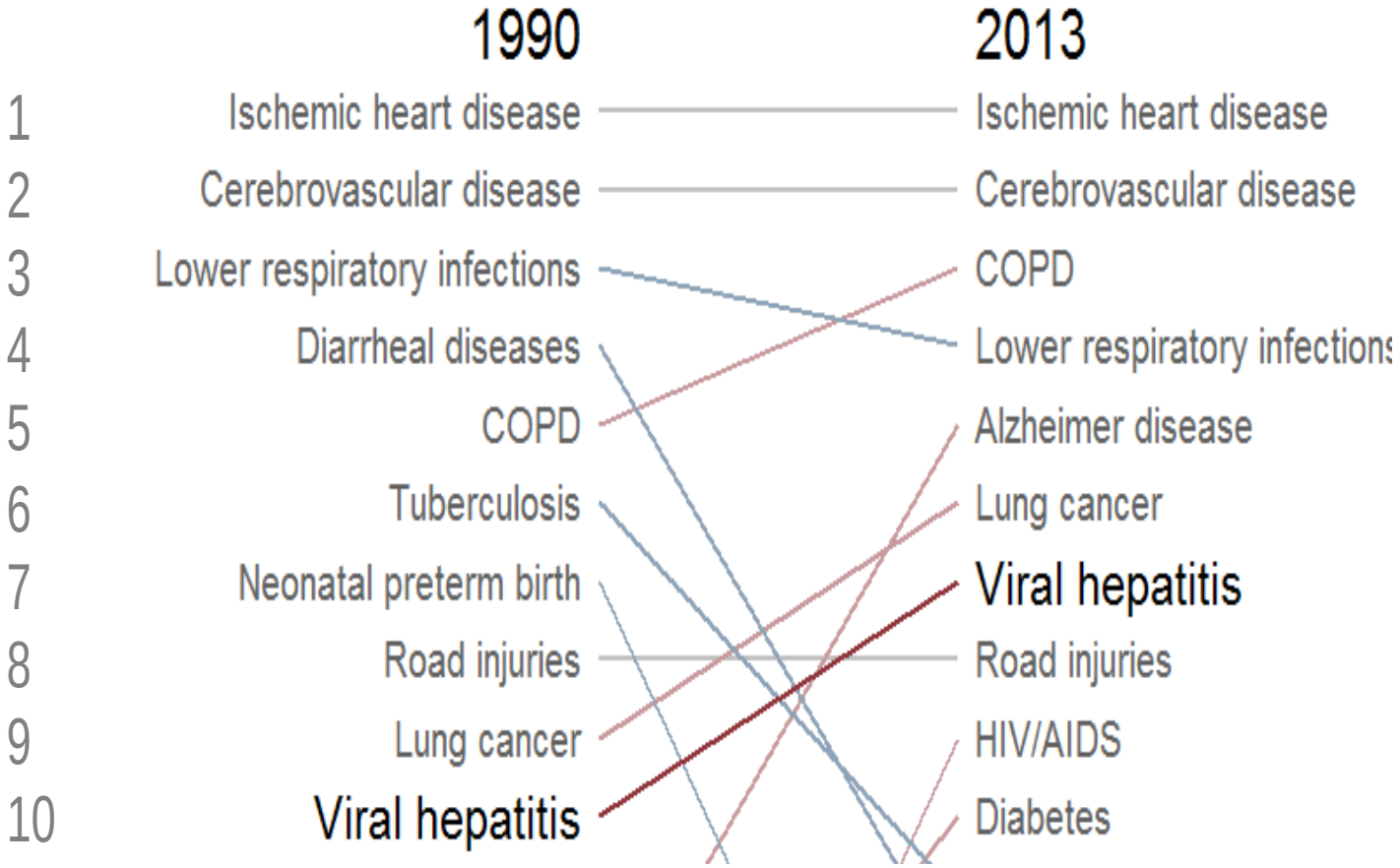
Proportion attributable to each virus

The area of each pie is proportional to that region's hepatitis-attributable mortality rate. The size of each wedge represents the proportion of that moratlity attributable to a given virus

- hepatitis_a_pr
- hepatitis_b_pr
- hepatitis_c_pr
- hepatitis_e_pr

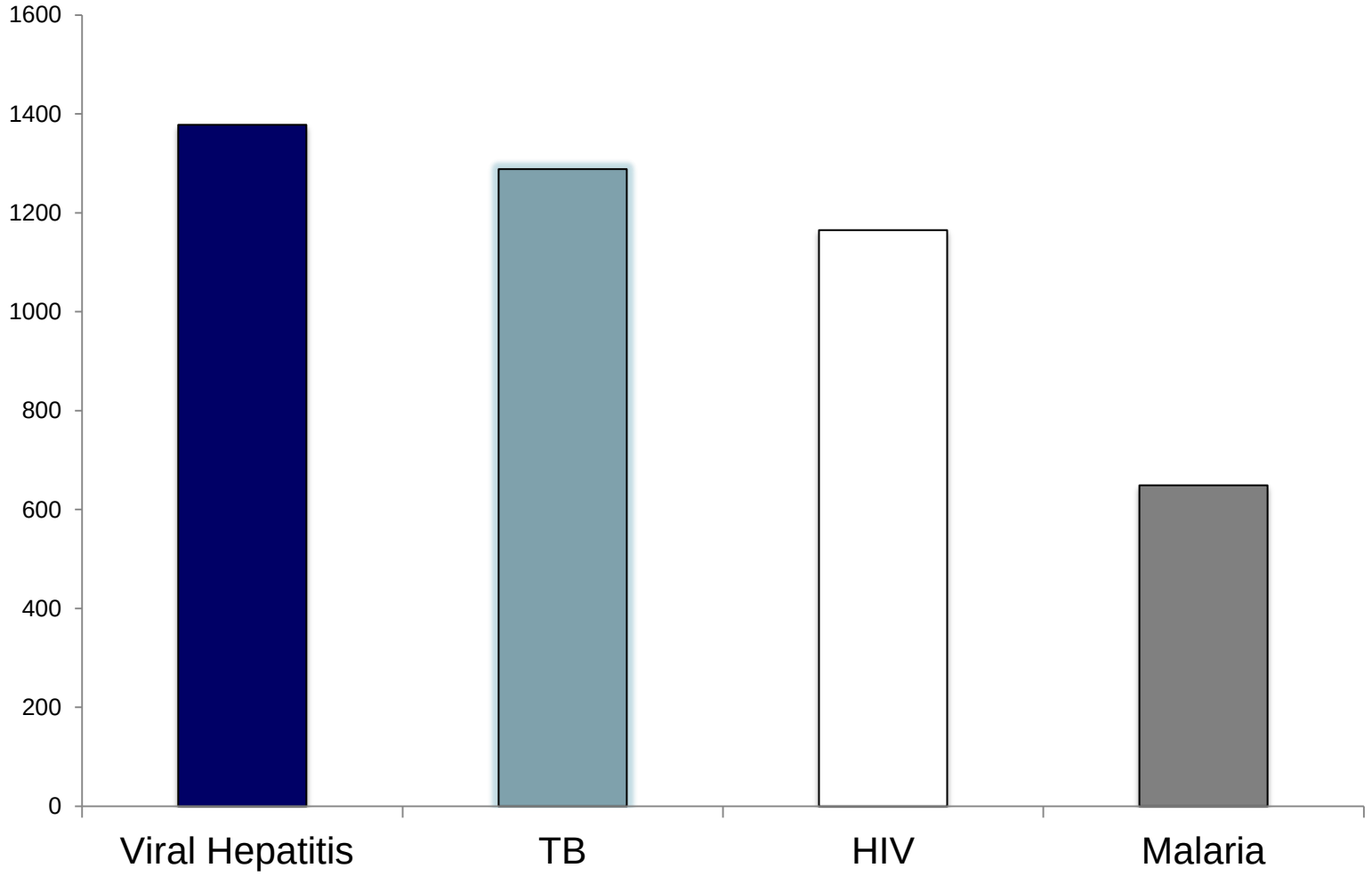
(Stanaway et al Lancet in press)

Bucking the trend of infectious diseases



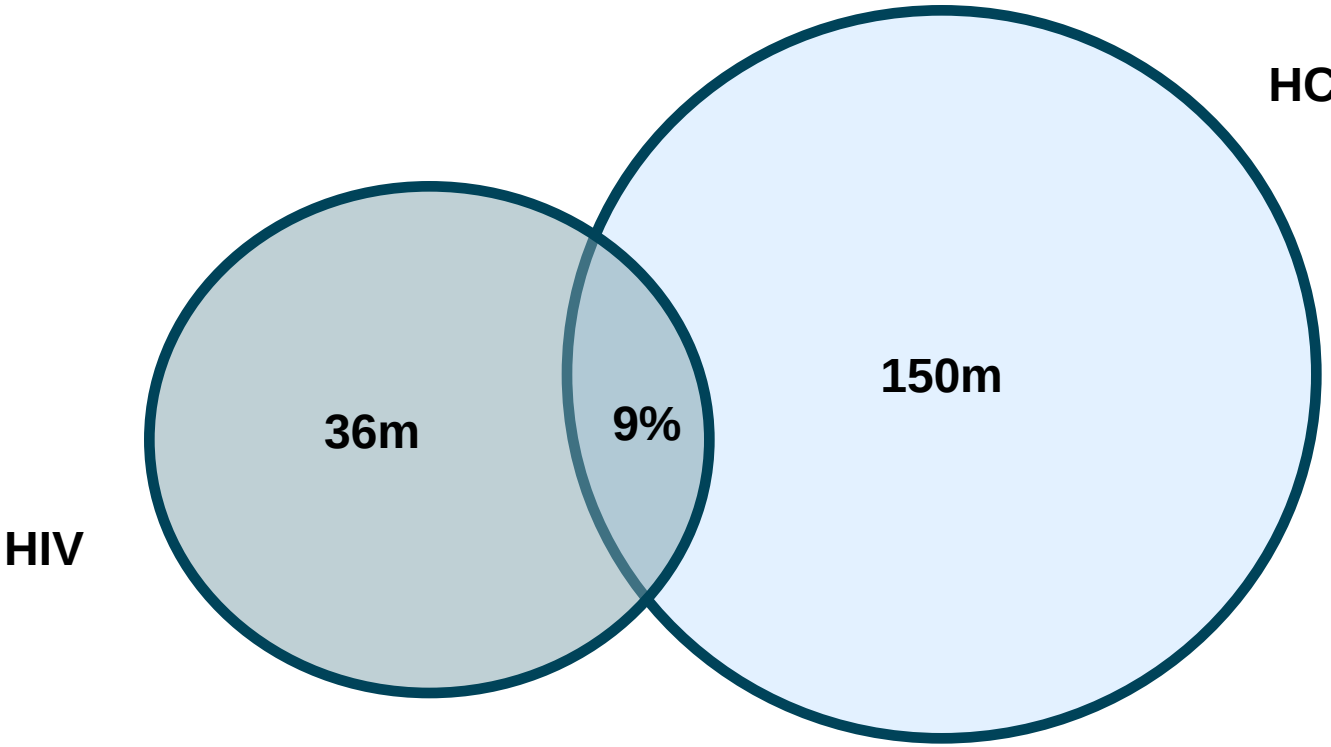
Stanaway et al (2015)

Hepatitis has overtaken other major infectious diseases



(GBD 2015 in preparation)

Co-infection in the World



~3m HCV/HIV co-infected

Platt et al 2016 LID

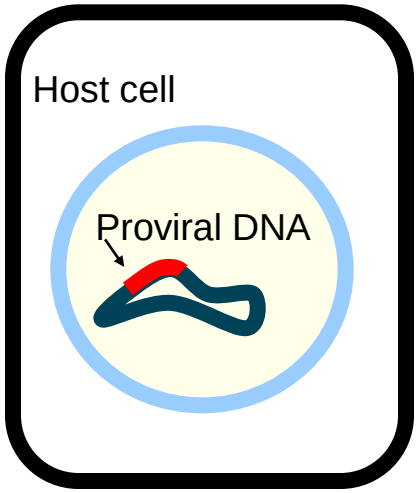
So what does it tell us about viral hepatitis?

	Vaccine	Treatment
Hepatitis A	Yes	No
Hepatitis E	Yes	(Yes)
Hepatitis B	Yes	Yes
Hepatitis C	No	Yes

- Treatment is particularly important as a tool to control HCV

It's about cure = SVR

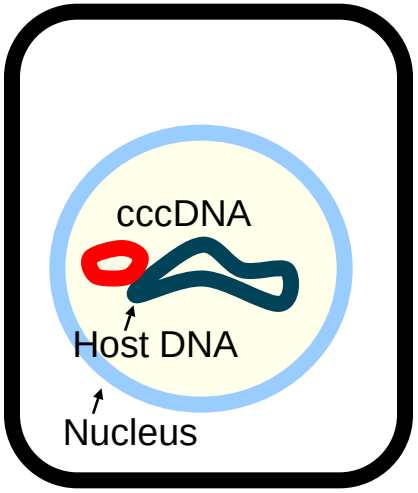
HIV



TREATMENT

Long-term suppression of viral replication[2,3]

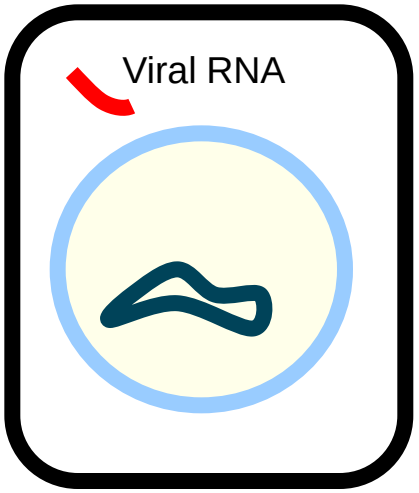
HBV



TREATMENT

Long-term suppression of viral replication

HCV



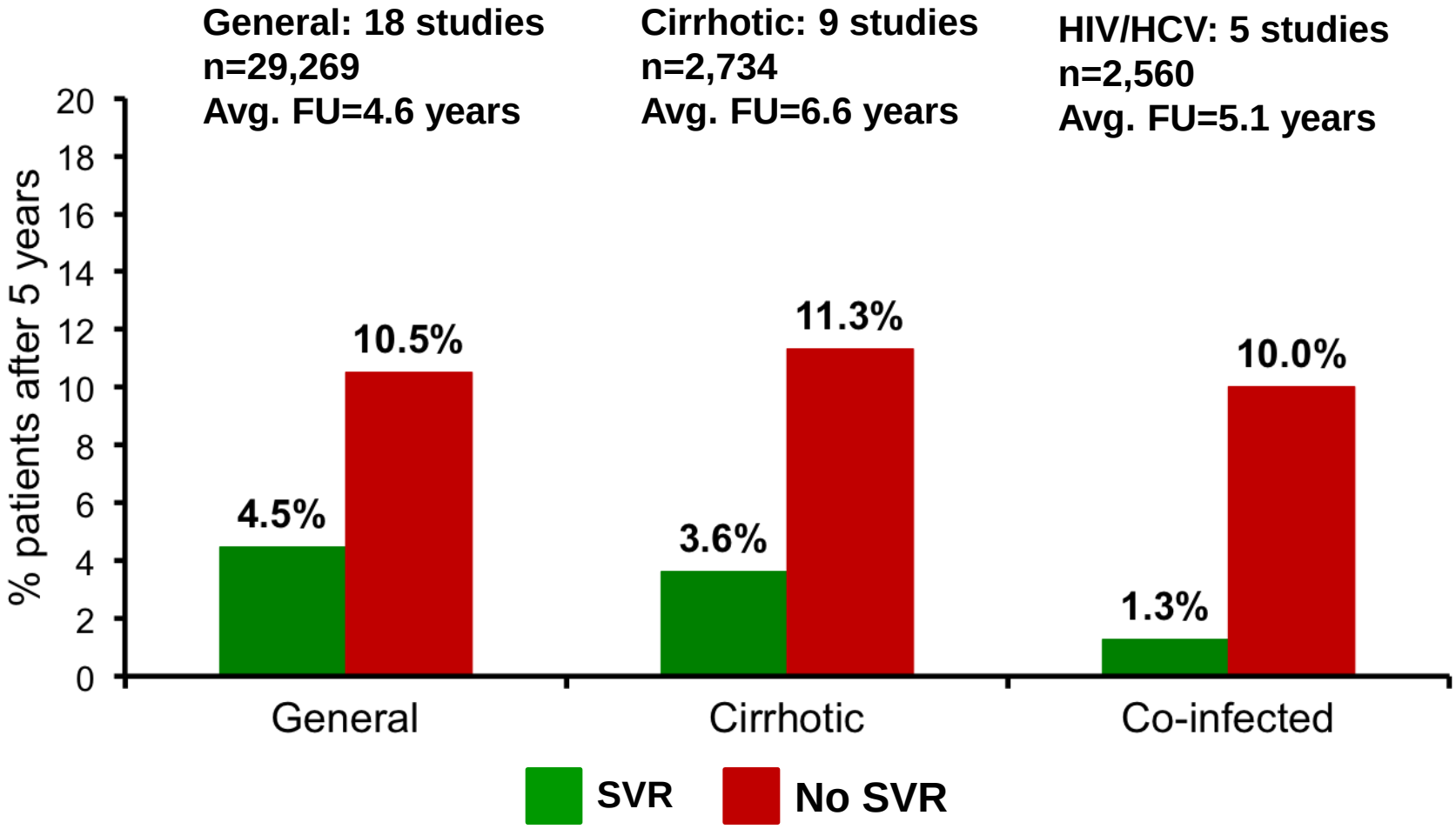
TREATMENT

Viral Eradication = Cure Genotypes important

cccDNA = covalently closed circular DNA

1. Pawlotsky JM. *J Hepatol* 2006;44:S10-S13; 2. Siliciano JD, Siliciano RF. *J Antimicrob Chemother* 2004;54:6-9;
3. Lucas GM. *J Antimicrob Chemother* 2005;55:413-416

Why do we want to achieve SVR? All-cause mortality

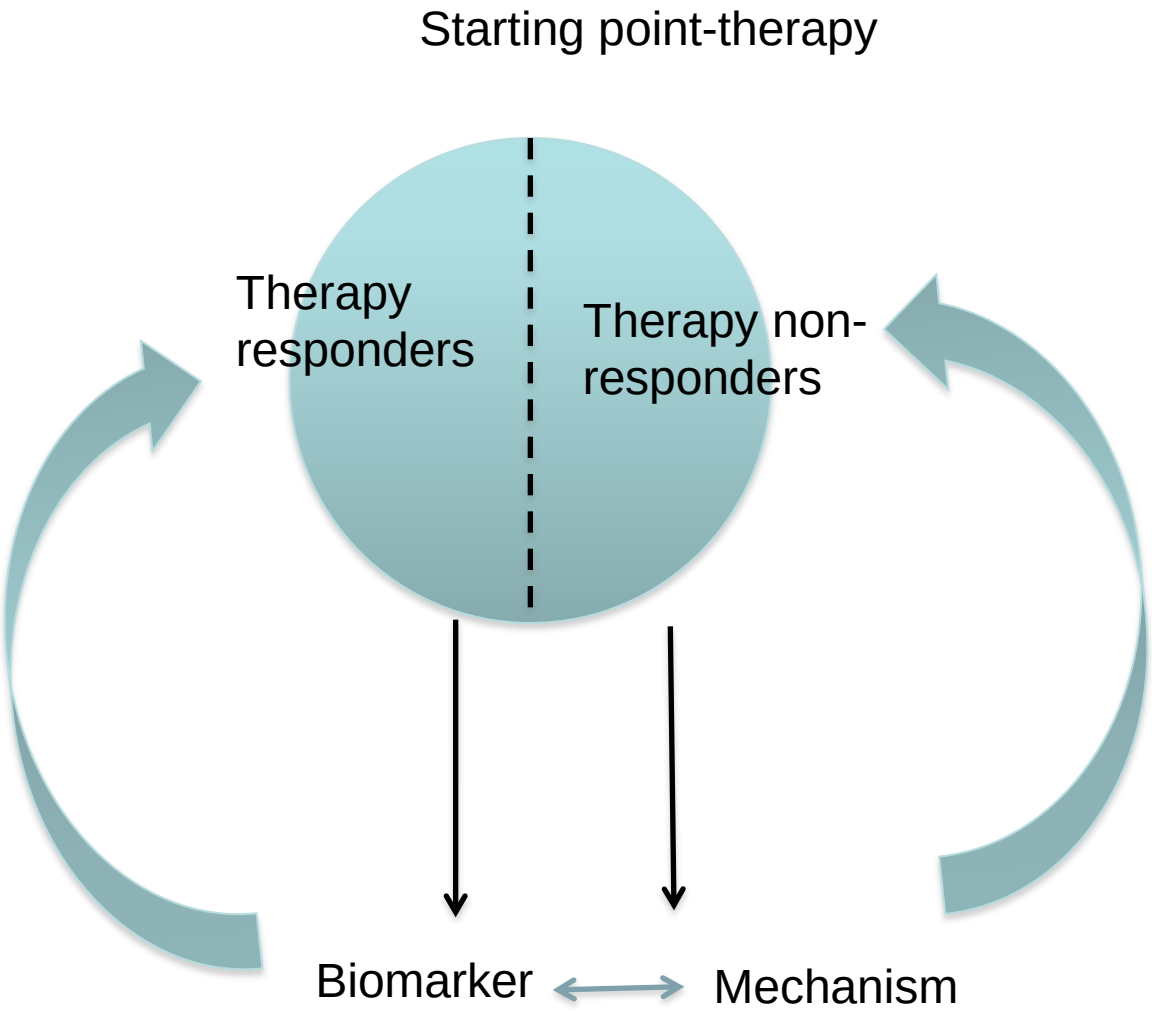


Simmons et al CID 2015

Precision HCV Medicine before "The Storm"

We already (variably) use precision/stratified medicine

Theragnostics and stratification



If get a biomarker:
•Right existing therapy to the right patients

If get mechanism:
•New therapies for existing non-responders e.g. IFN-lambda

•Attractive to industry

Anticipating the storm:
MRC funding stratified medicine consortia 2013

- Genuinely national consortia that could be outward facing to pharma
- Diseases with strong pipeline of high cost medication
- Required non-cancerous diseases with biological evidence for stratification

STOP-HCV
Stratified Medicine for HepC

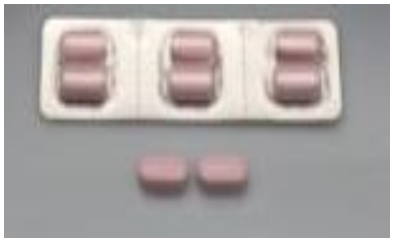
How did we achieve SVR back in June 2015 (UK)

Pegylated interferon

Once weekly subcutaneous
Immune activation

Ribavirin

Oral
Antiviral

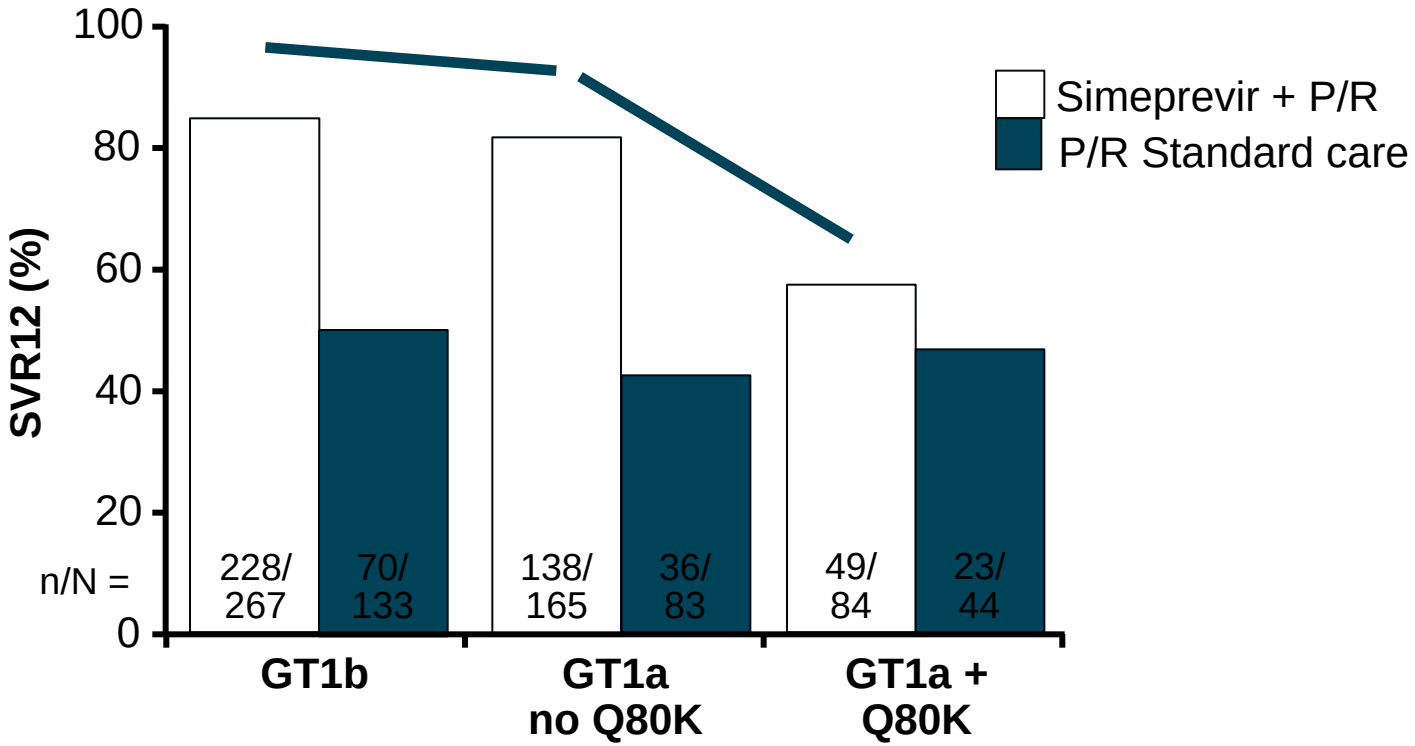


\+

G1 only
Boceprevir
Telaprevir

G1/4
Simeprevir

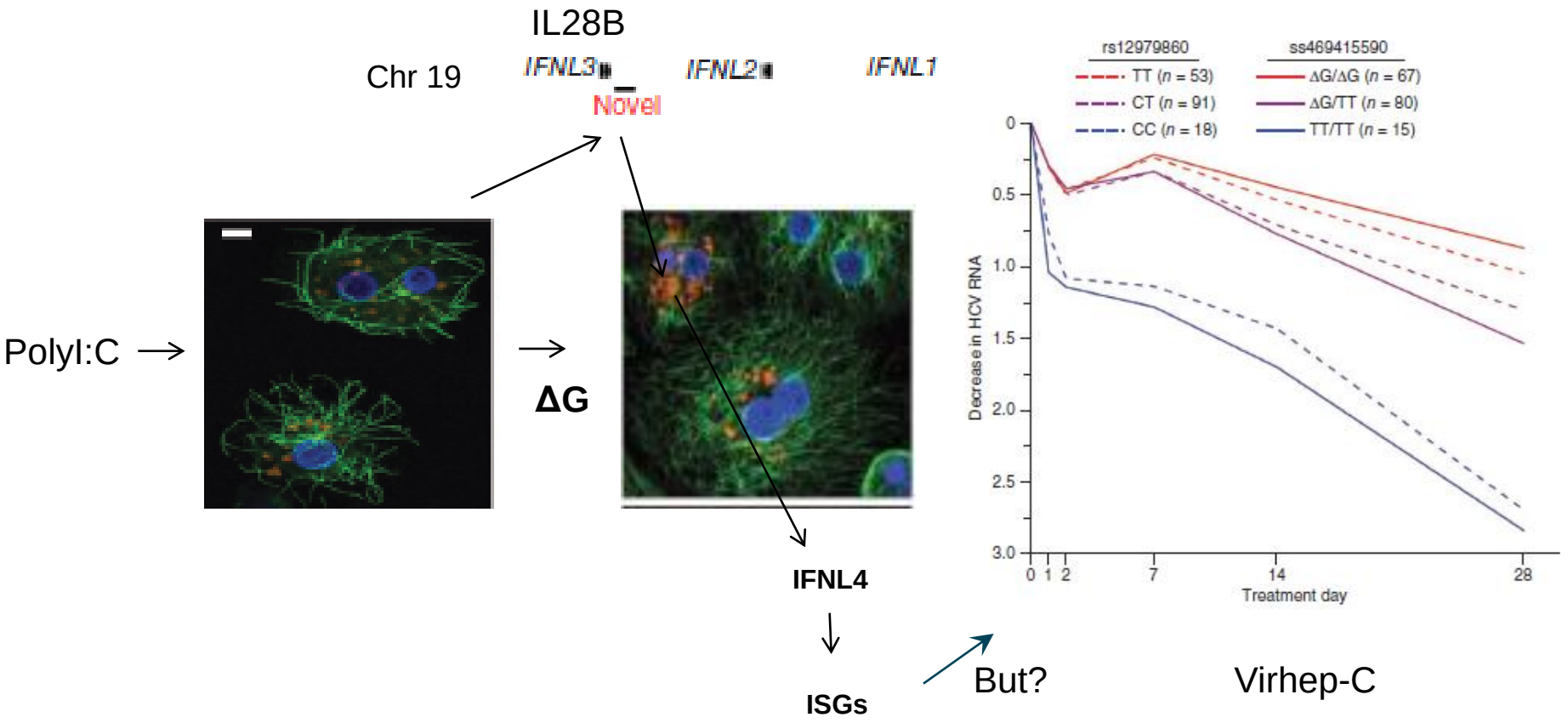
Back in 2015: Virus? Q80K and simeprevir



Q80K present in 34% of GT1a patients. No benefit of simeprevir if Q80K positive

Jacobson I, et al. AASLD 2013. Abstract 1122.

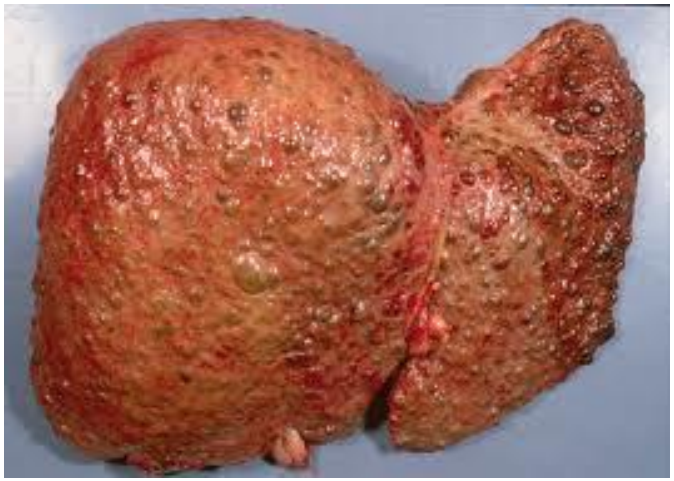
Back in 2015: Host genetics? IFNλ3 (IL28) and IFNλ4



Prokunina-Olsson NG (2013)

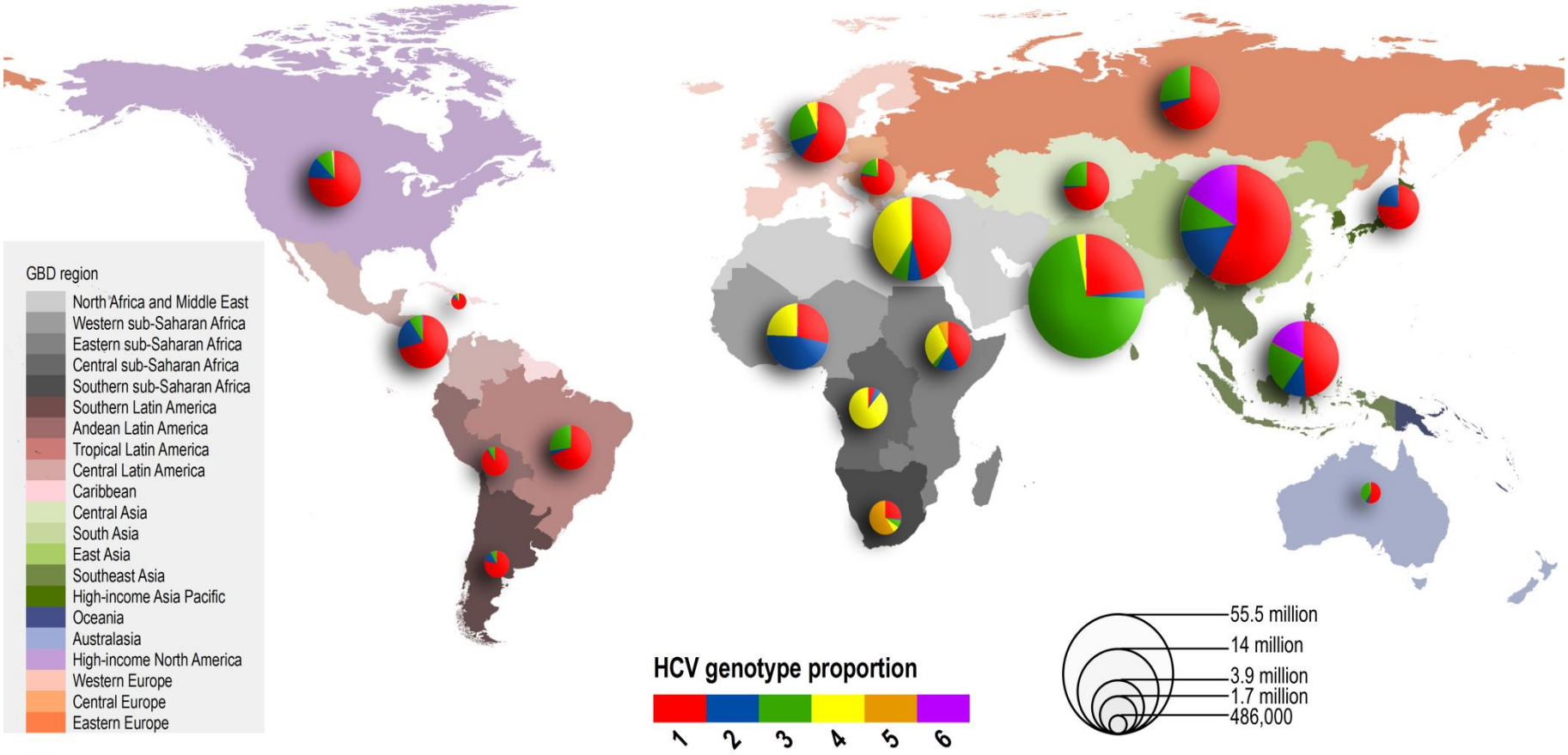
Hepatitis C: stratification in interferon era

- **Demographic**
  - Age
  - Male gender
  - Ethnicity
- **Clinical**
  - Fibrosis
  - BMI
  - HIV
- **Host genetic**
  - IL28B/ IFNL4
- **Viral**
  - Viral resistance mutations
  - **Genotype**



- **Response guided approaches**

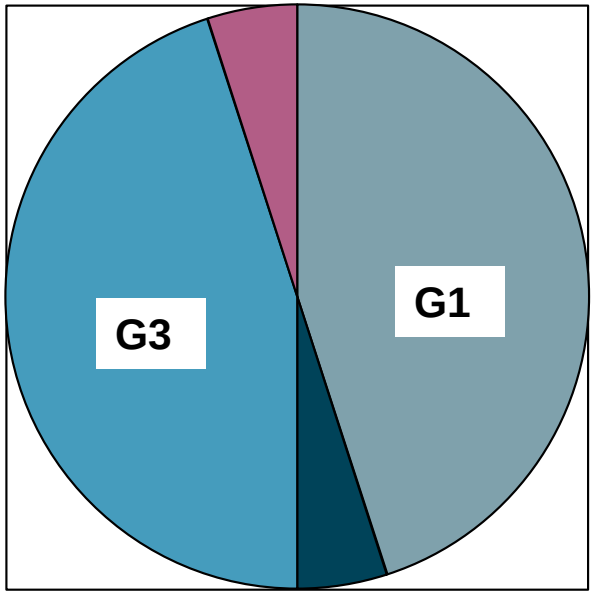
HCV genotypes still matter for now

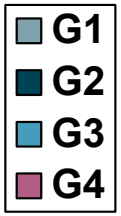


Messina et al Hepatology (2015)

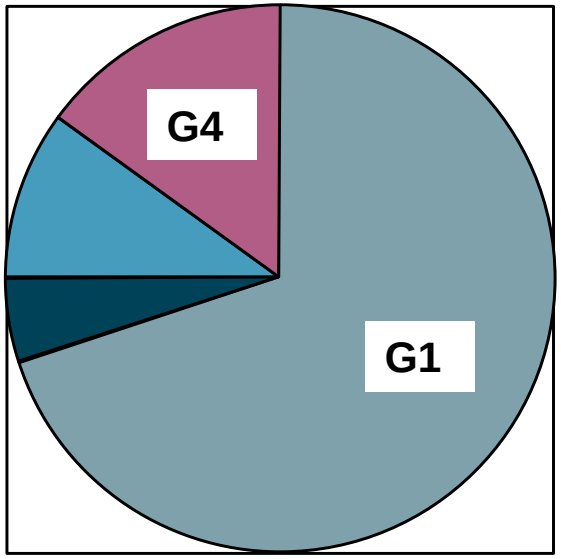
HCV Genotypes in the UK

General UK population





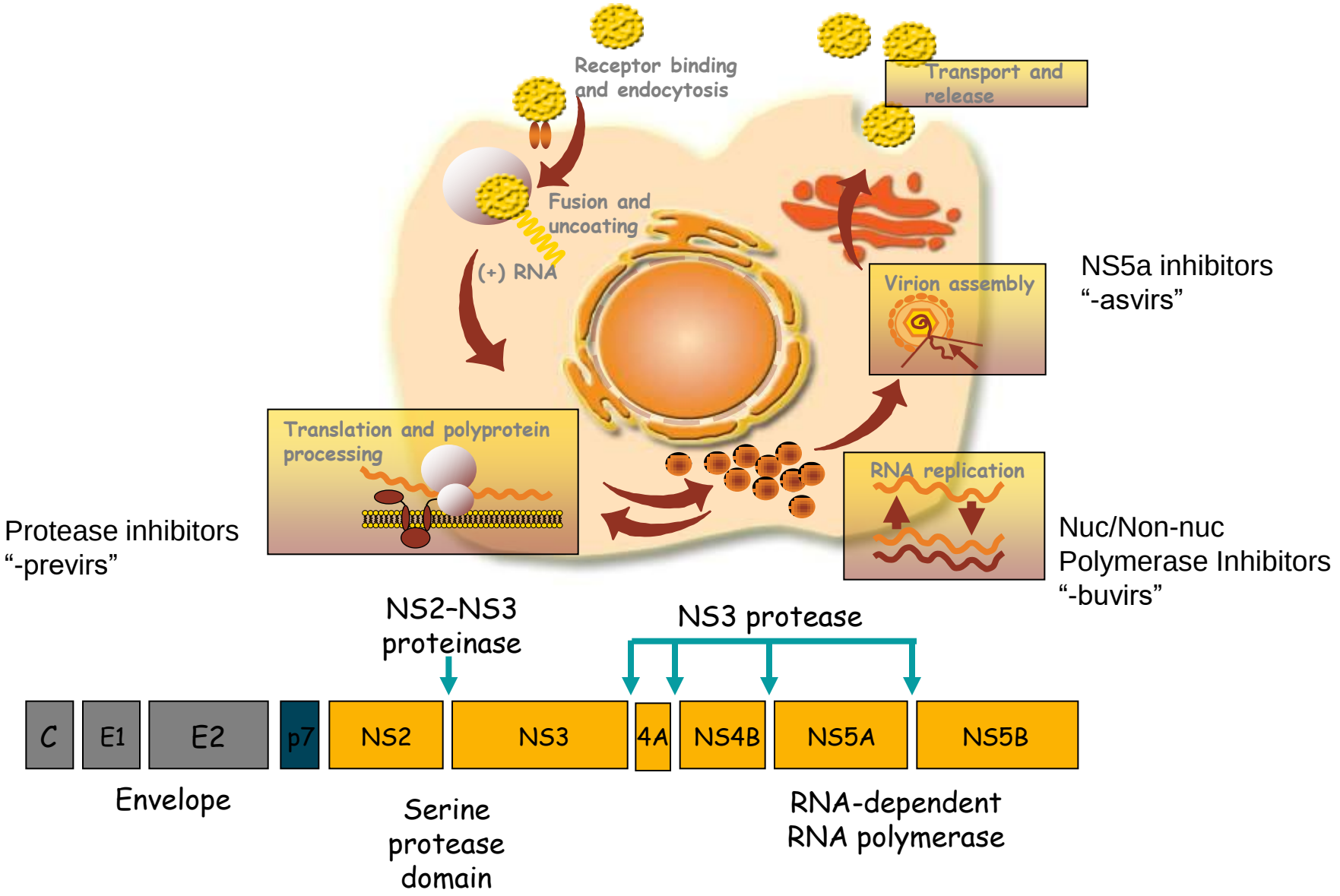
HIV positive population



Source: PHE, HCV UK

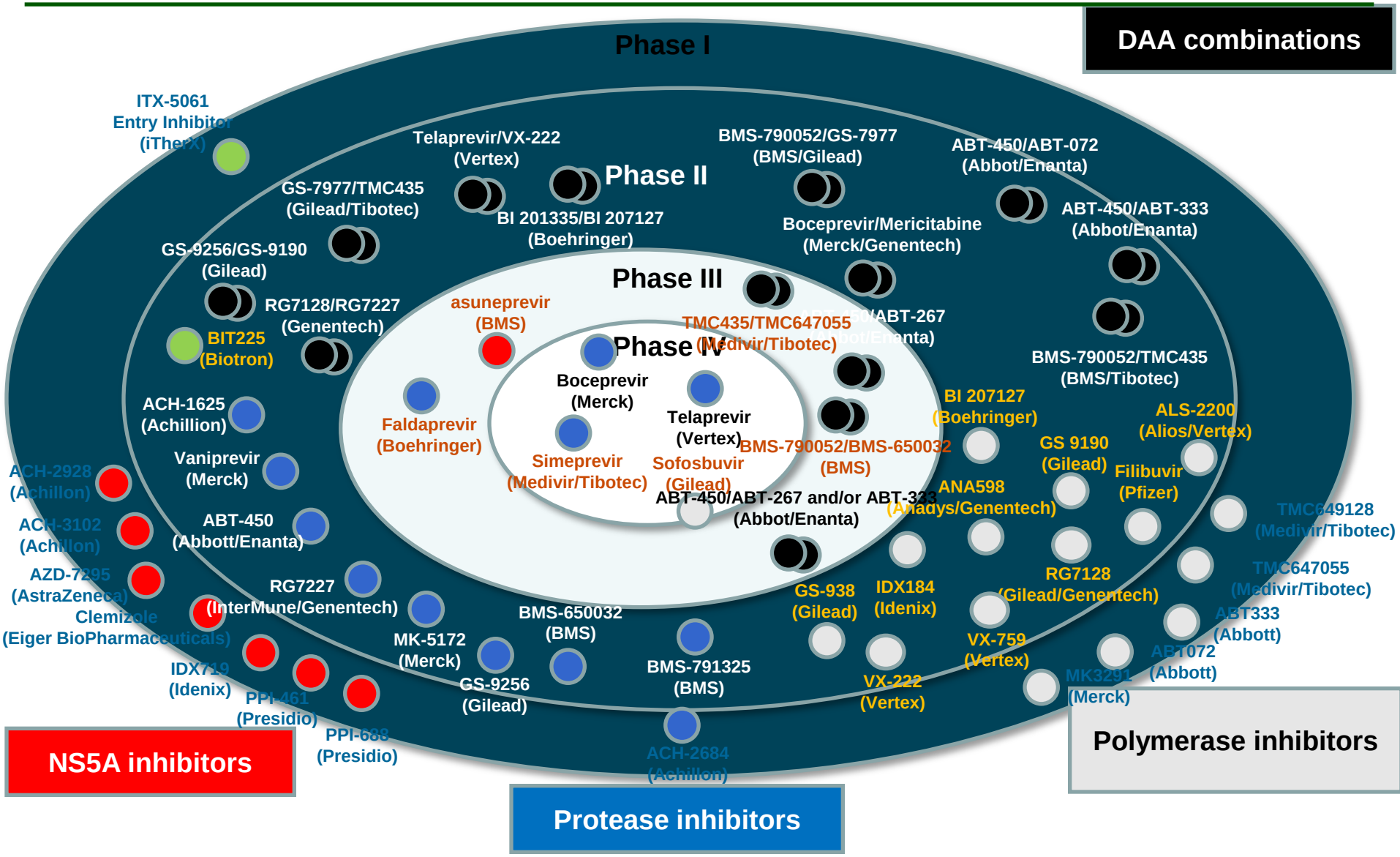
How relevant is this with new treatments?

HCV lifecycle provides multiple targets for new drugs

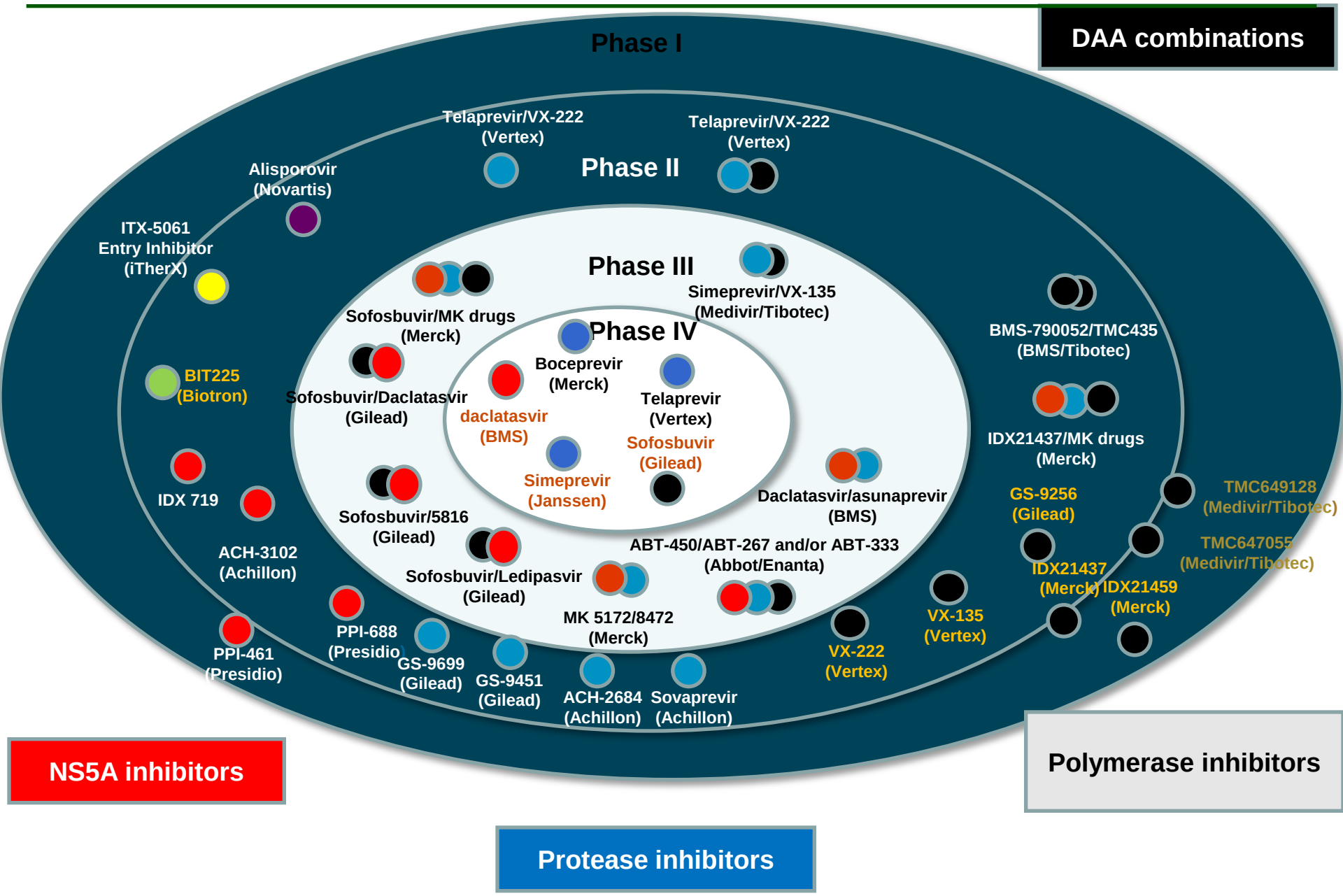


1. Lindenbach BD & Rice CM. Unravelling hepatitis C virus replication from genome to function. *Nature* 2005;436:933-938

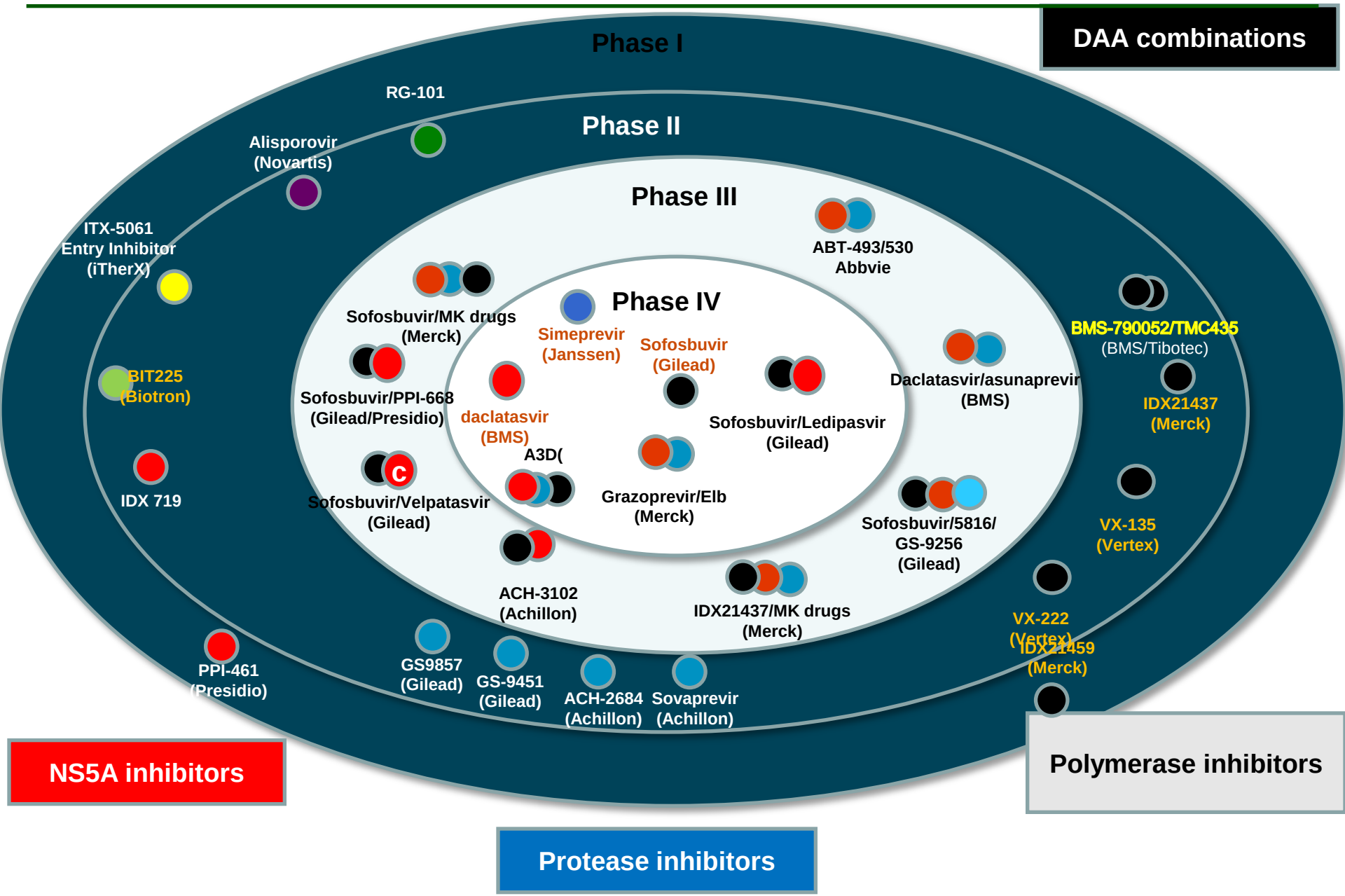
Hepatitis C pipeline has been very busy: 2013



Drug development end 2014



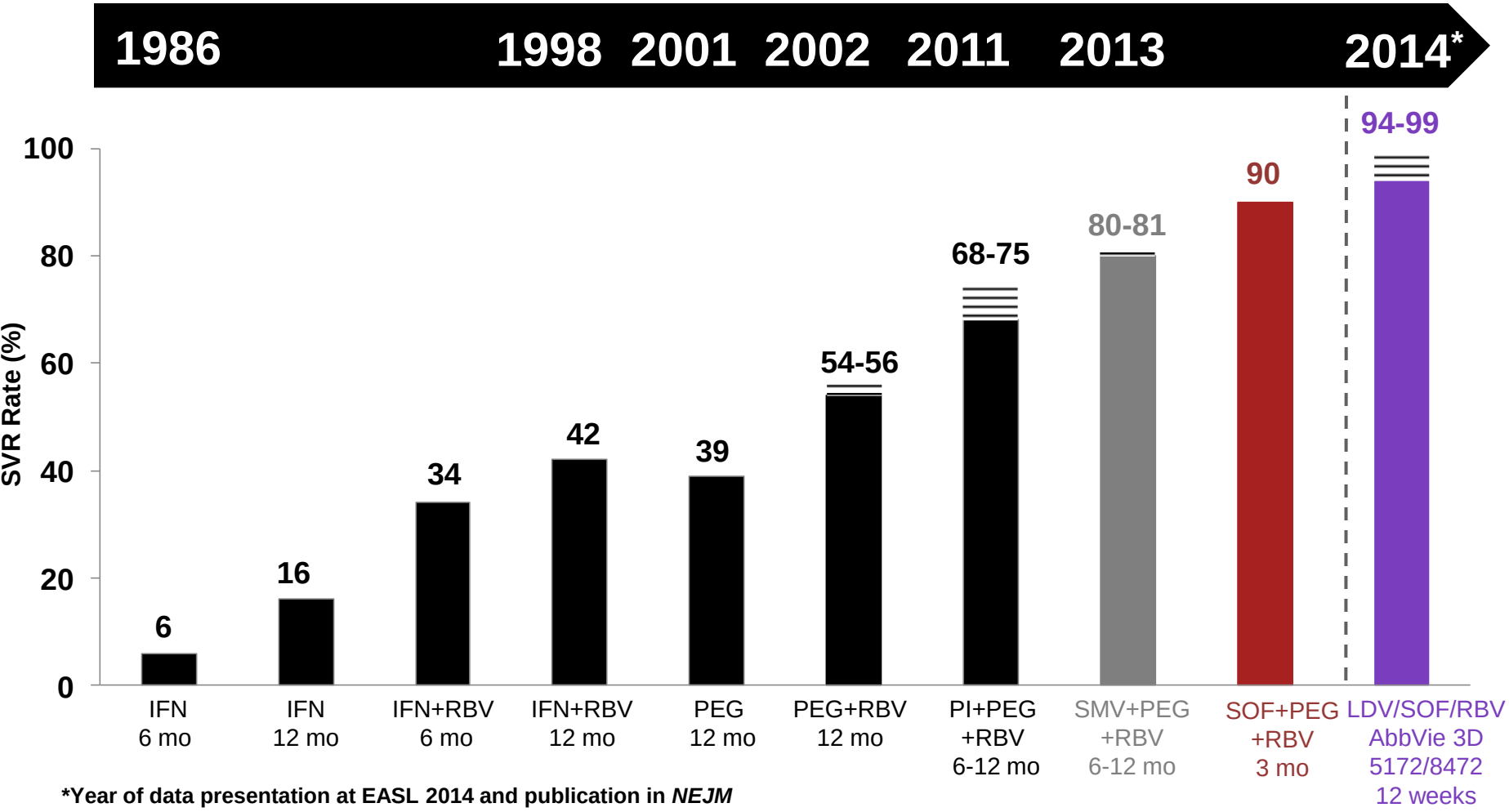
Field is consolidating



Selected DAA Combinations in Late Development/ Approval

Nucleotide/ nucleoside	**Non-nucleoside**	**Protease Inh**	**NS5a**
Sofosbuvir			
Sofosbuvir			Ledipasvir
Sofosbuvir		(GS-9857)	Velpatasvir
	Dasabuvir	Paritaprevir/R	Ombitasvir
		ABT-493	ABT-530
(MK-3682)		Grazoprevir	Elbasvir
(MK-3682)		Grazoprevir	MK8408

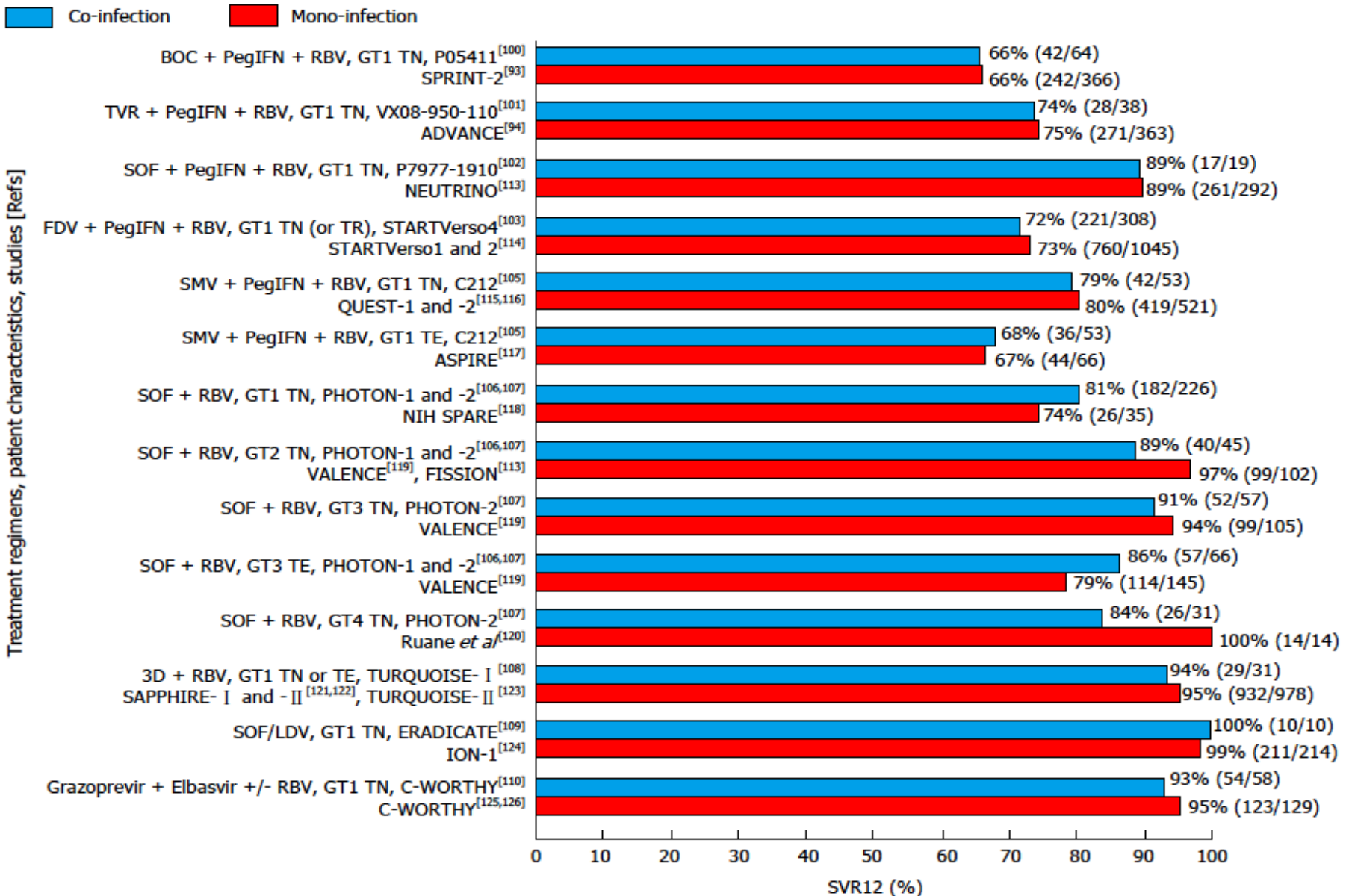
HCV Genotype 1 Treatment-Naïve Patients – improving SVRs



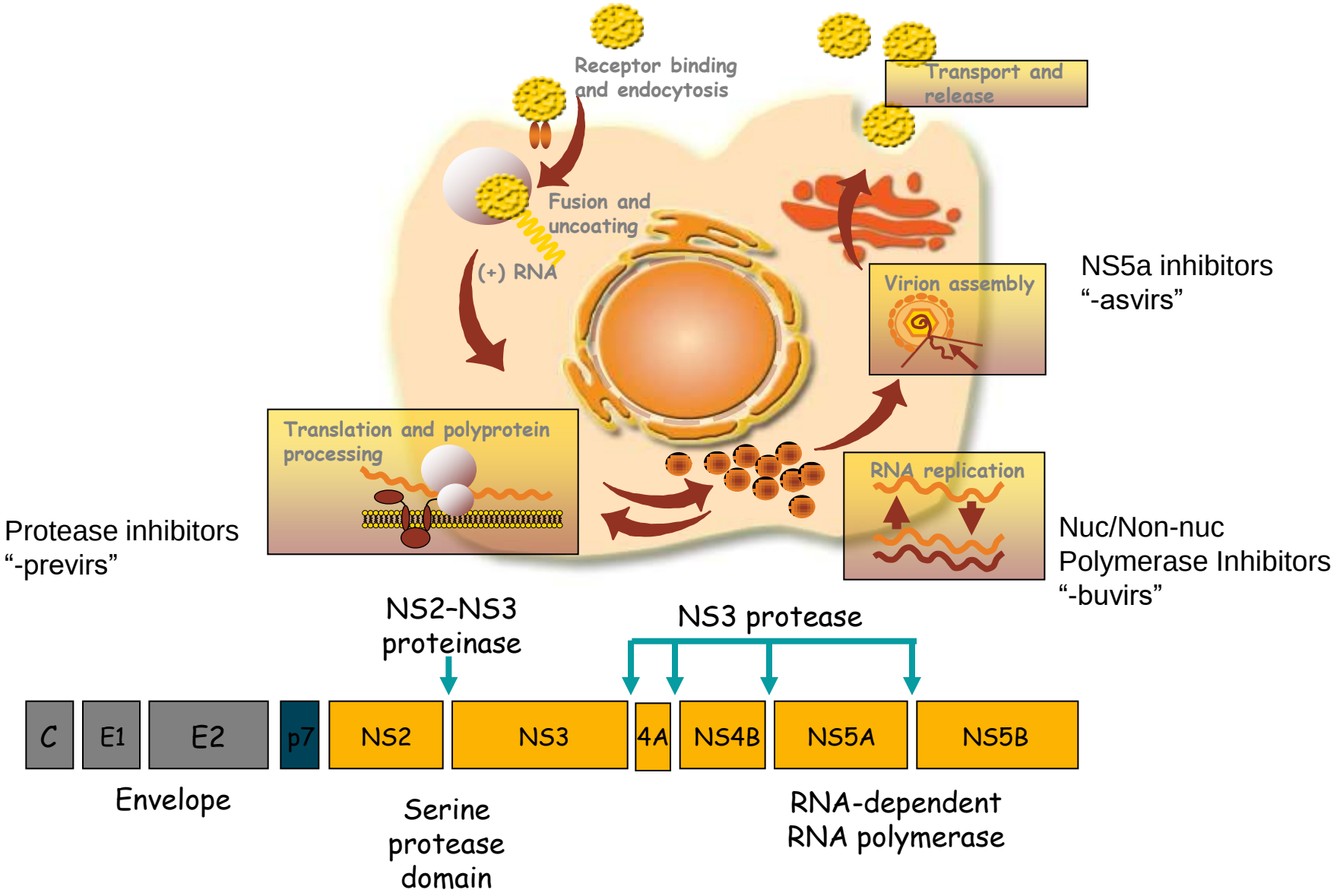
Year of data presentation at EASL 2014 and publication in *NEJM

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02; Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 ; Kowdley K, et al. *N Engl J Med* 2014; 2014 Apr 11

Outcomes in HIV very similar to monoinfection



Resistance



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Baseline RAVs (sic) are relatively common

Frequency at baseline

NS5A > NS3 protease > NS5B

Persistence

NS5A > (NS5B) > NS3 protease

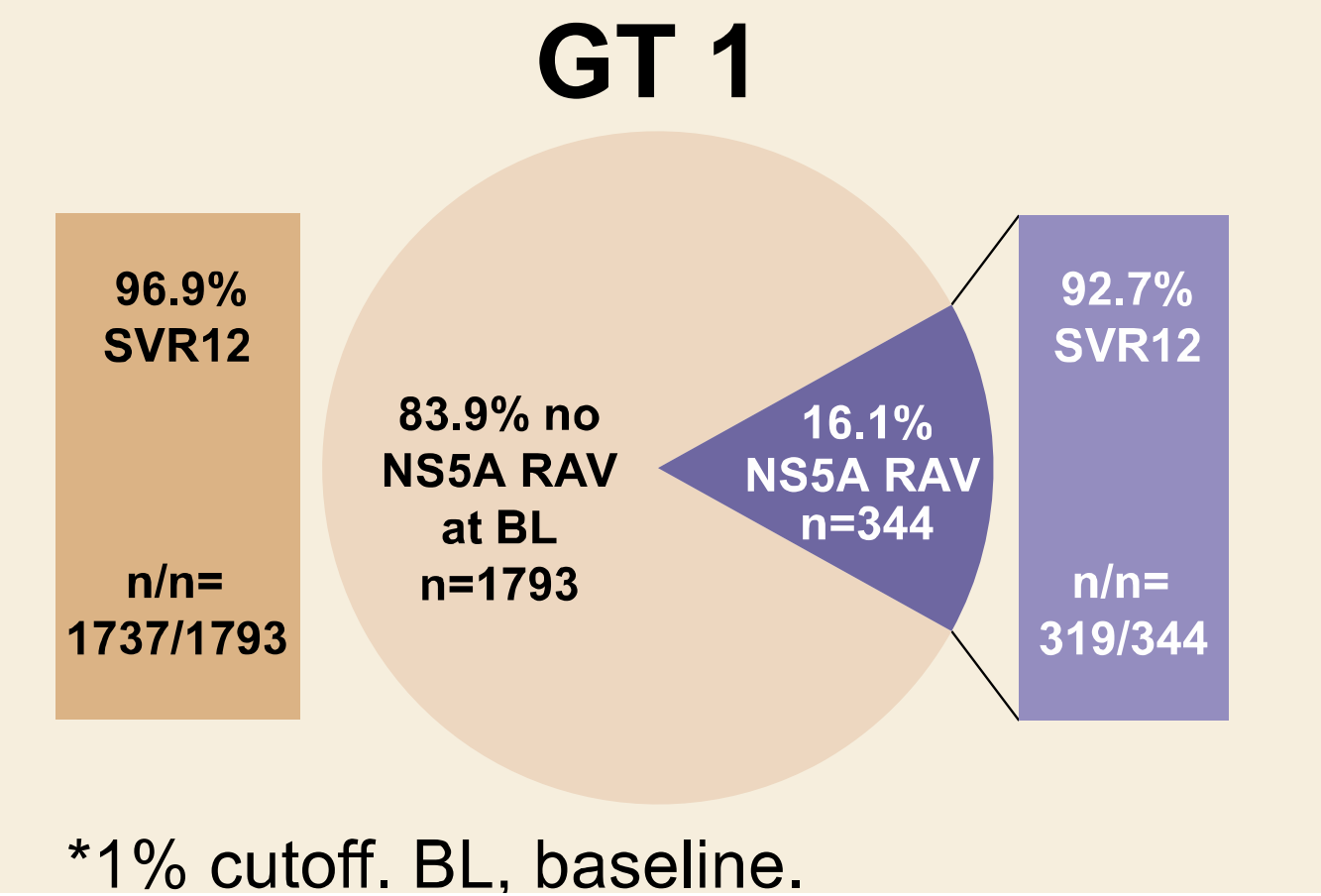
Sarrazin et al (2016)

RAVs differ in frequency across genotype

Variant	Gene	1a	1b	2	3	4
Q30H/R/E/L/T	NS5a	0.3%-1.3%	-	-	90.4-100% (Q30A)	50-100% (Q30R)
L31M	NS5a	0.9-1.8%	2.1-6.3%	74-85%	1%	92.5-100%
Y93H	NS5a	<1.5%	3.8-14.1%	-	1.3-8.3%	5-13%
Q80K	NS3	4.8-75%	0.5-1.2%	-	-	-
S282T	NS5B	-	-	-	-	-

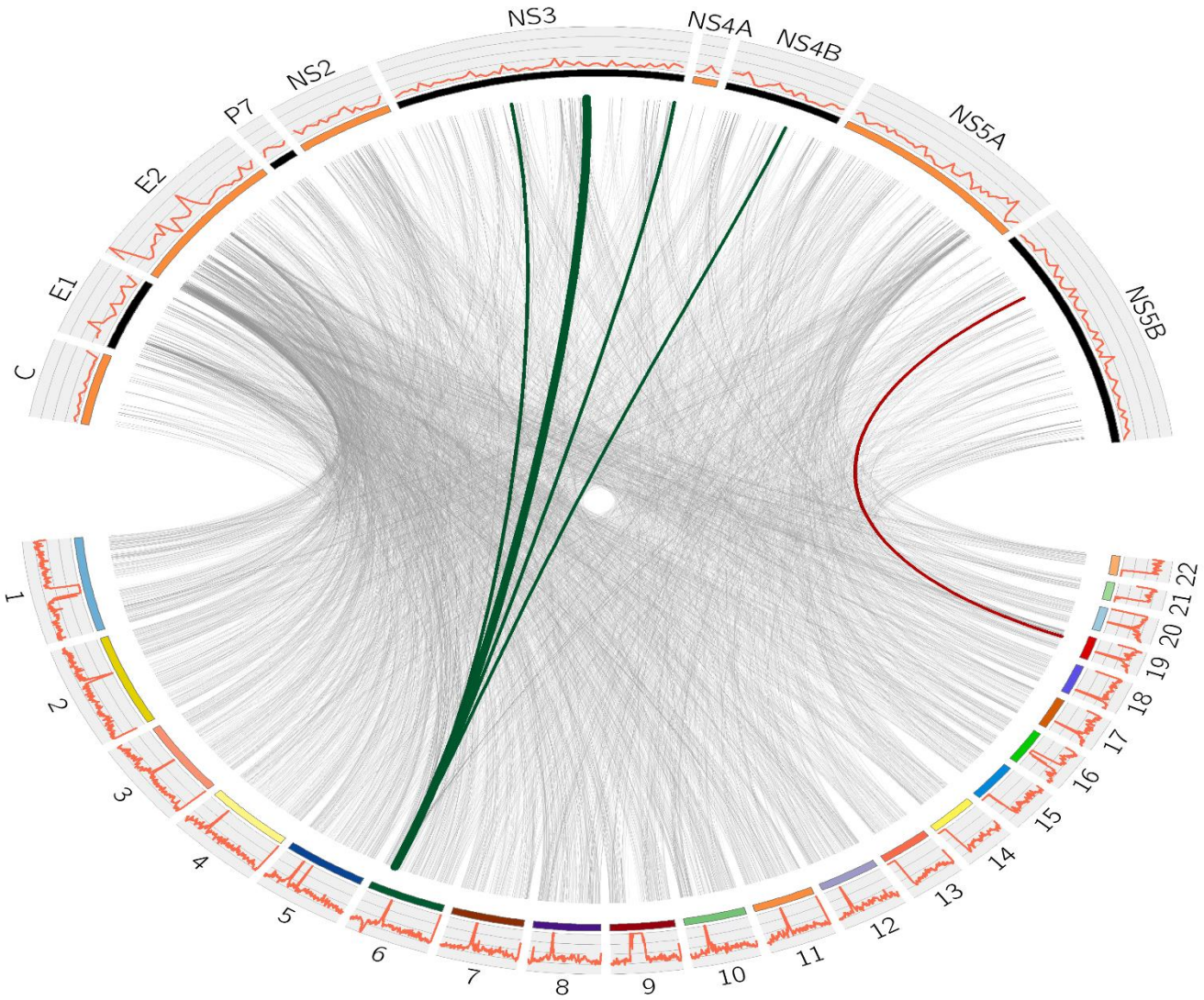
Sarrazin et al (2016)

But have relatively limited impact on SVR12



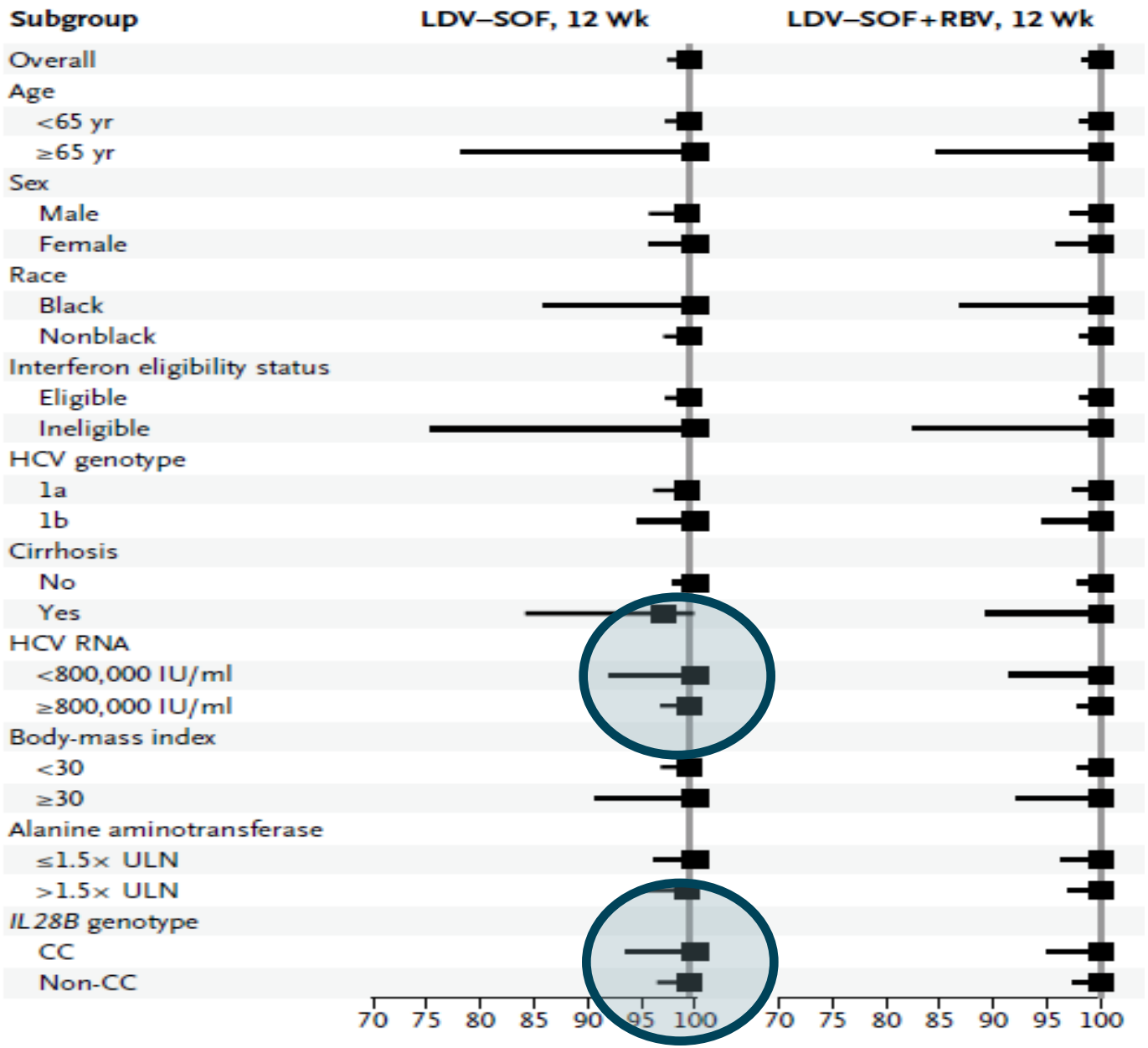
Sarrazin et al (2014)

Genomics giving us greater understanding of host and virus



Pedergnana et al EASL 2016

Role for precision medicine if very good outcomes?



Afdhal NEJM 2014

Why not give everyone 12 weeks of next generation therapy?

Two big challenges

- **Money**
- **Nature of the therapy (adherence)**

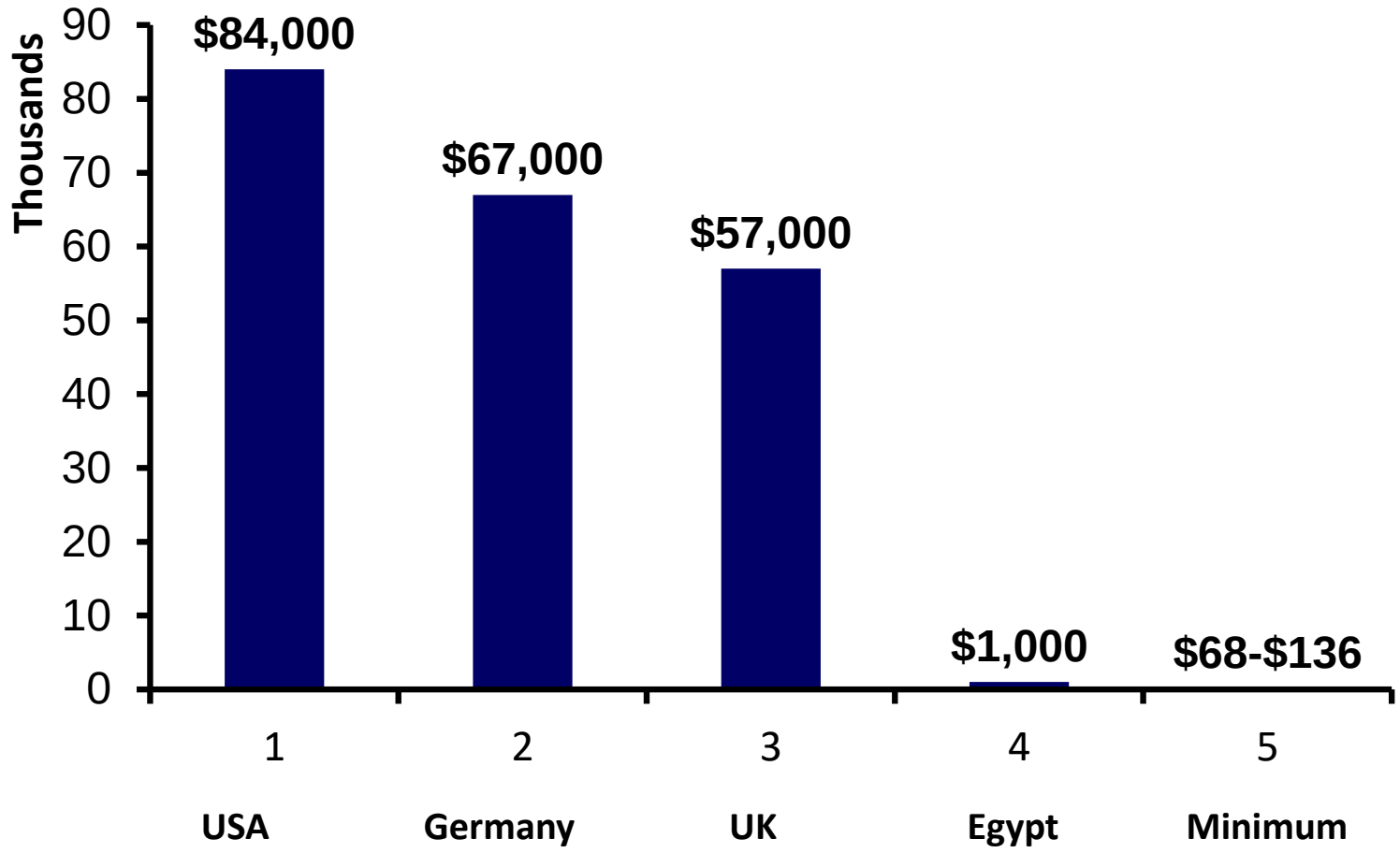
Recent case

- 45 year old male ex- IDU
- Chronic HCV (mild disease)
- Pre-existing paranoid ideation
- Baseline HCV VL 6000000 IU/l, genotype 1a
- Started OMB/PAR/DAS/RIT/RBV
- Stopped treatment early at 3/52
- Achieved SVR12

Could we have known before treatment started that 3/52 would be enough?

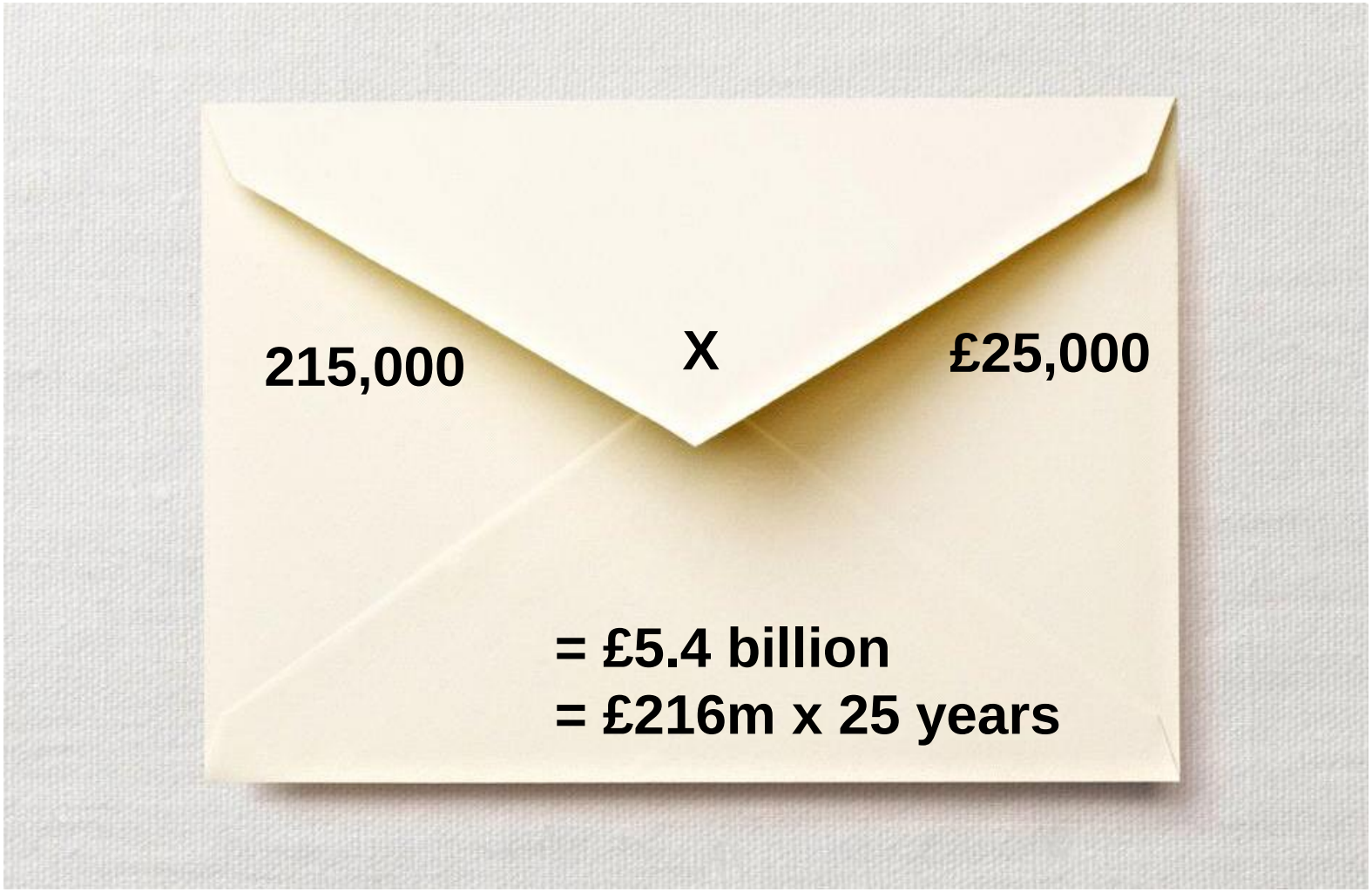
Money:
Not just a UK problem

The cost of sofosbuvir for Hepatitis C per person, 12 weeks treatment

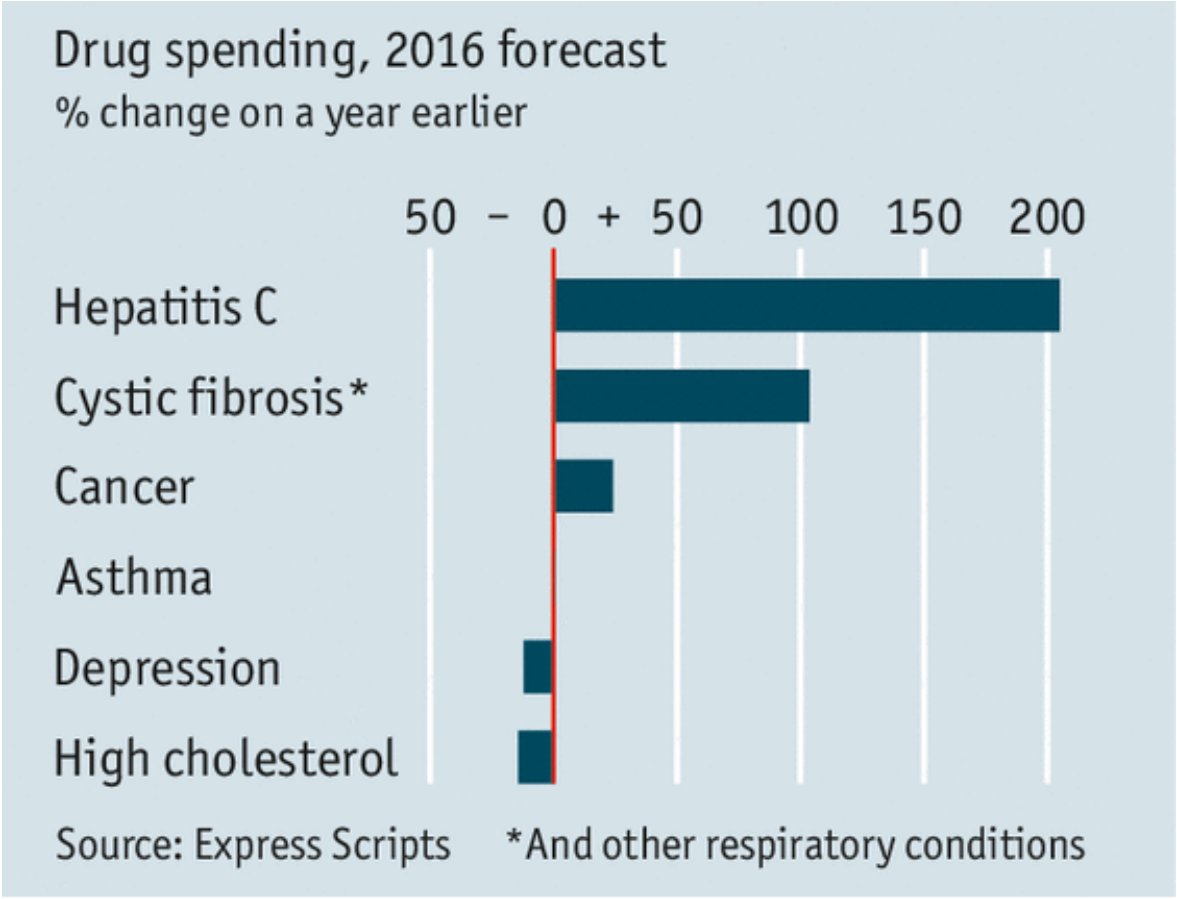


Hill & Cooke (Science 2014)

UK



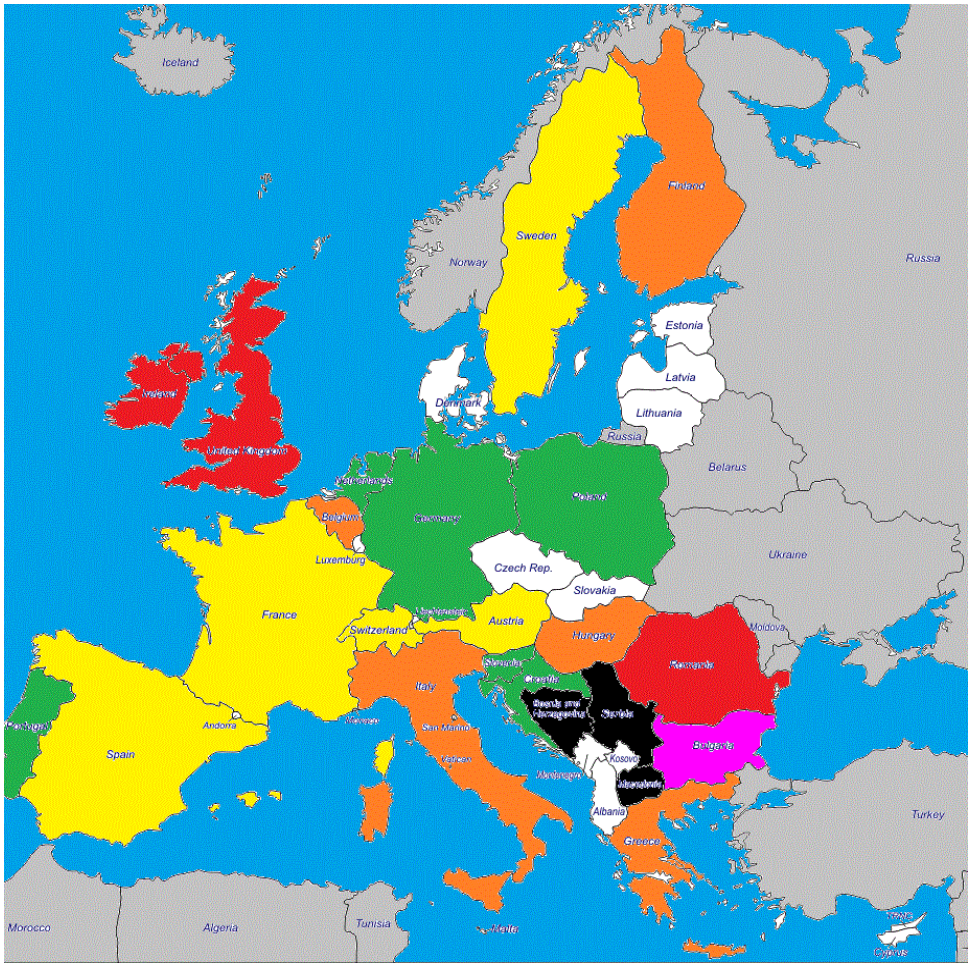
Cost and convenience



Economist 2014

Restrictions for access to HCV innovative drugs 2° generation*

Europe, Balkans, Switzerland



	No restricions
	F2-F4
	F3-F4
	F4
	In discussion
	No drugs avaiable
	No informations available

Other main details/restrictions

Germany	*Drug users and prisoners are still excluded in real life. Some complexity with insurances*
Portugal	*Some drugs need special authorization*
Poland	*Some limitations for F0 patients*
France	*All HIV/HCV coinfected + symptmatic cryoglobulimeia + Lymphoma can be treated w/o restrictions*
Croatia	*Naive and G3 patients it is still P/R first line . F3 and F4 patients has priority*
Greece	*F3 patients can be treated only if failed in the past*
Hungary	*Naive pt treated with PEG+RBV, tx and pt with IFN-contraindication treated with IFN-free independently*
UK	*From Beginning of March all G1s will get Harvoni or AbbVie 3D. Other GT waiting for Velpatasvir*
Bulgaria	*Some drugs approved, Defining the access criteria*
Spain	*Extrahepatic manifestations and/ or high risk of infectivity with F0-F1*
Italy	*Tx and pt with severe extra hepatic diseases can be treated independently fibrosis stage. F0-F2 can be treated with INF, RIBA and SIMPEREVIR*
Finland	*All naïve pt. GT1,2,3 start with INF+RIBA. If negative w/e 4 continue.F3-F4 if not EVR continue with DAAs. F0-F2 Stop*

I. Gardini, on behalf of ELPA.
Jenuary 2016

***Informations given by ELPA members, and taken from presentations and internet research**

England : Run rates

Monthly Patient numbers rising each quarter			Confirmed			Provisional			Provisional			Provisional			
ODN	Region	Prevalence[1]	Q1 2000			Q2 2500			Q3 2650			Q4 2850			Annual Total
			Apr	May	Jun	Jly	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	
1. North East & Cumbria	North	4.4%	29	29	29	37	37	37	39	39	39	42	42	42	441
2. Greater Manchester & Eastern Cheshire	North	7.5%	50	50	50	62	62	62	66	66	66	71	71	71	747
3. Cheshire & Merseyside	North	4.5%	30	30	30	38	38	38	40	40	40	43	43	43	453
4. South Yorkshire	North	4.1%	27	27	27	34	34	34	36	36	36	39	39	39	408
5. Humberside and North Yorkshire	North	4.1%	27	27	27	34	34	34	36	36	36	39	39	39	408
6. West Yorkshire	North	7.0%	47	47	47	59	59	59	62	62	62	67	67	67	705
7. Lancashire and South Cumbria	North	4.3%	29	29	29	36	36	36	38	38	38	41	41	41	432
8. Leicester	Midlands	2.7%	18	18	18	22	22	22	24	24	24	26	26	26	270
9. Birmingham	Midlands	8.7%	58	58	58	73	73	73	77	77	77	83	83	83	873
10. Nottingham	Midlands	3.8%	26	26	26	32	32	32	34	34	34	36	36	36	384
11. Eastern Hepatitis Network	Midlands	6.0%	40	40	40	50	50	50	53	53	53	57	57	57	600
12. West London	London	4.8%	32	32	32	40	40	40	43	43	43	46	46	46	483
13. North Central London	London	7.5%	50	50	50	63	63	63	67	67	67	72	72	72	756
14. Barts	London	5.0%	33	33	33	42	42	42	44	44	44	48	48	48	501
15. South Thames Hepatitis Network (STHepNet) Kings & St George's	London	9.5%	63	63	63	79	79	79	84	84	84	90	90	90	948
16. Surrey Hepatitis Services	South	1.6%	11	11	11	13	13	13	14	14	14	15	15	15	159
17. Sussex Hepatology Network	South	1.8%	12	12	12	15	15	15	16	16	16	17	17	17	180
18. Oxford University Hospitals NHS Trust - Thames Valley	South	3.6%	24	24	24	30	30	30	32	32	32	34	34	34	360
19. Wessex Hep C ODN	South	3.2%	22	22	22	27	27	27	29	29	29	31	31	31	327
20. Bristol and Severn Hep C ODN	South	1.7%	11	11	11	14	14	14	15	15	15	16	16	16	168
21. South West Peninsula Hepatitis C ODN	South	2.3%	15	15	15	19	19	19	20	20	20	22	22	22	228
22. Kent Network via Kings	South	1.8%	12	12	12	15	15	15	16	16	16	17	17	17	180
Goal			666	666	666	834	834	834	885	885	885	952	952	952	10,011

Overcoming the cost barriers to improve access

- More competition from manufacturers
- Value based pricing and other funding structures (“Australia model”), France, Ireland
- NGO activity (activism)
- Access to generic treatments from outside EU (gathering momentum)
- Making smarter use of the treatments we have

We will be overtreating most patients despite the costs

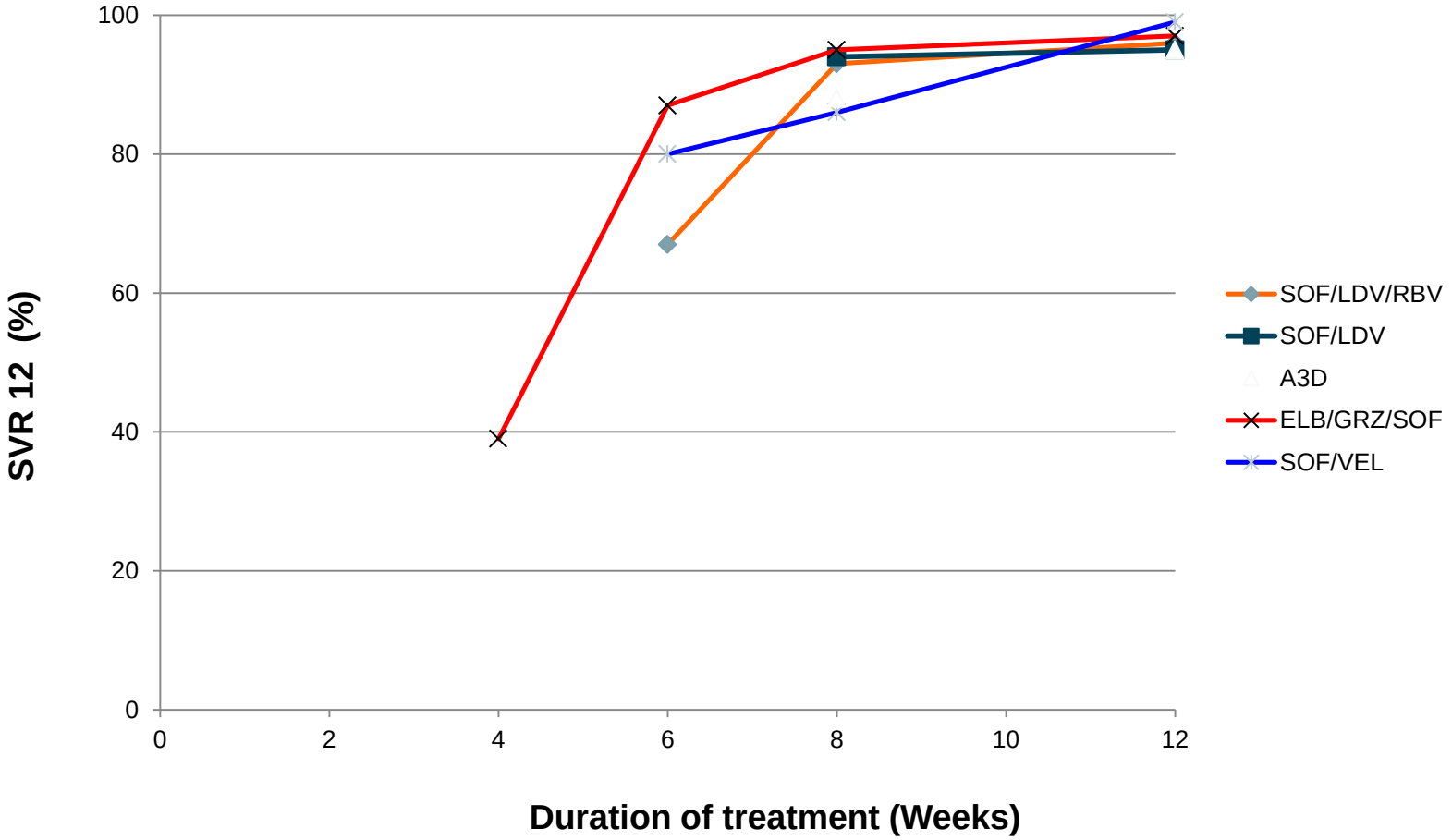
A challenge common to many infectious diseases

This is true in

TB	(6-24/12)
Sepsis and bacterial infection	(7-21d)
Hepatitis C	(8-12/52)

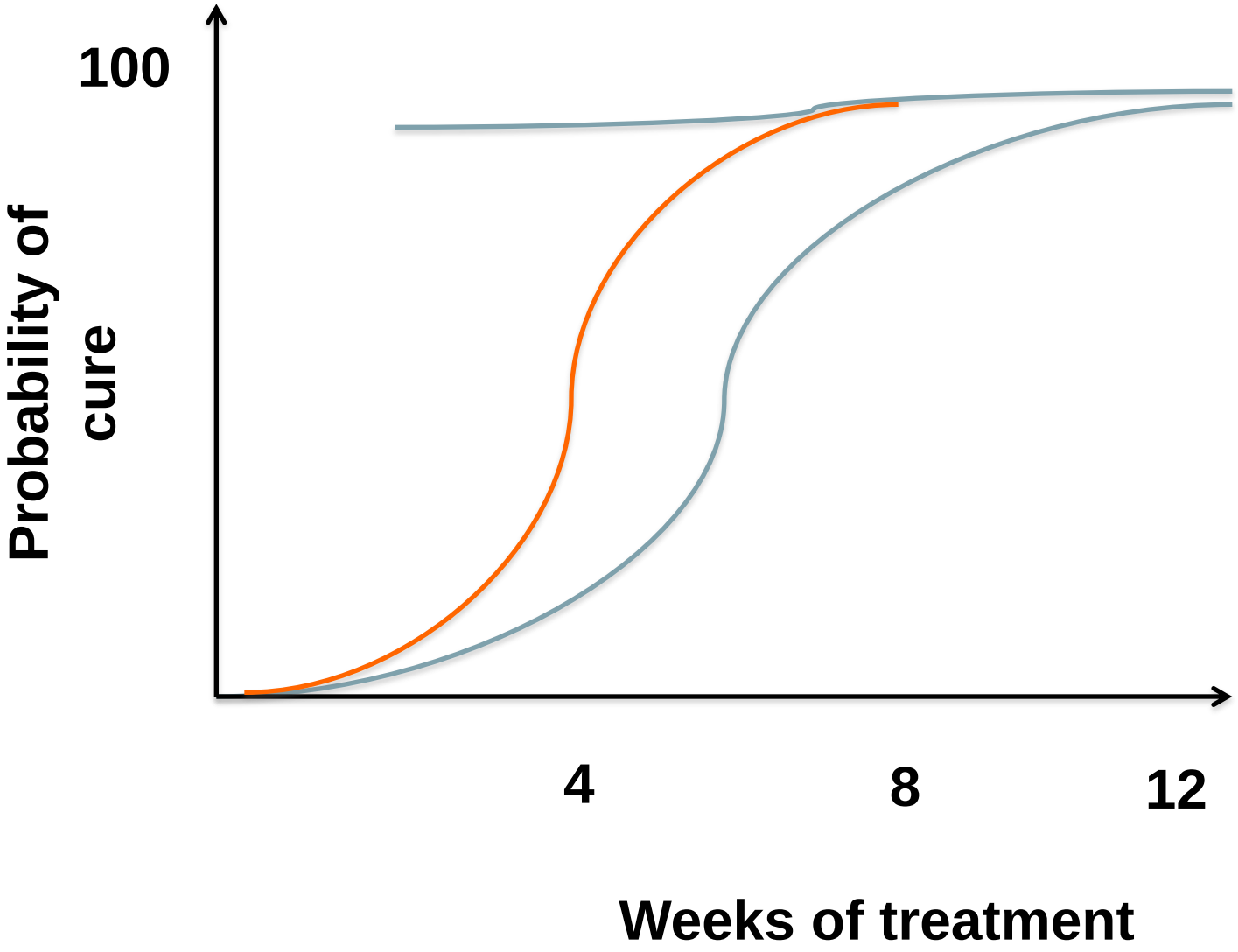
Our evidence base for predicting who will be cured with shorter duration of therapy is not often good enough to change practice

Most patients will get too much HCV treatment



G1

What is the relationship between duration and cure?



Selected studies on shortened DAA therapy

Acute HCV (small studies)

SLAM-C
Gilead 6/52 study

Recent HCV

TARGET 3D

Chronic HCV / HIV

STOP HCV-1

SLAM-C : Pilot short course in IDU

Inclusion

Largely non-Caucasian males

HIV negative, acute HCV active IDU

Baseline VL mean 1.2/1.6 million

Intervention

A) 4/52 SOF/LDV

B) 8/52 SOF/SIM

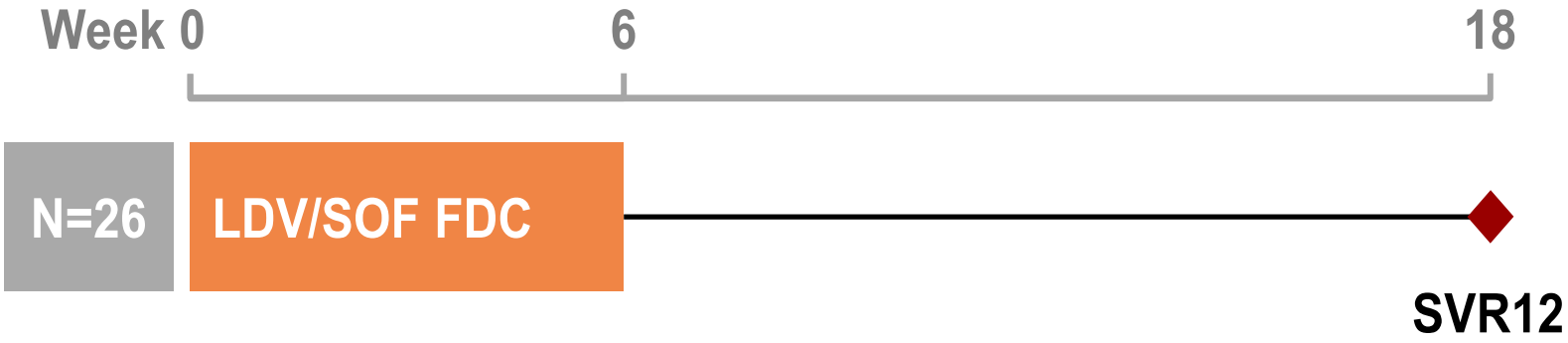
Basu et al APASL 2016

SLAM-C

Undetectable	Group A SOF/LDV 4/52 N=14	Group B SOF/SIM 8/52 N=15
Day 7	13/14 (92.9%)	13/15 (86.7%)
EOT	14/14 (100%)	14/15 (93.3%)
SVR12	14/14 (100%)	13/13 (100%)
Retention	13/14 (92.9%)	13/15 (86.7%)

Basu et al APASL 2016

Gilead 6/52 pilot in acute HCV/HIV



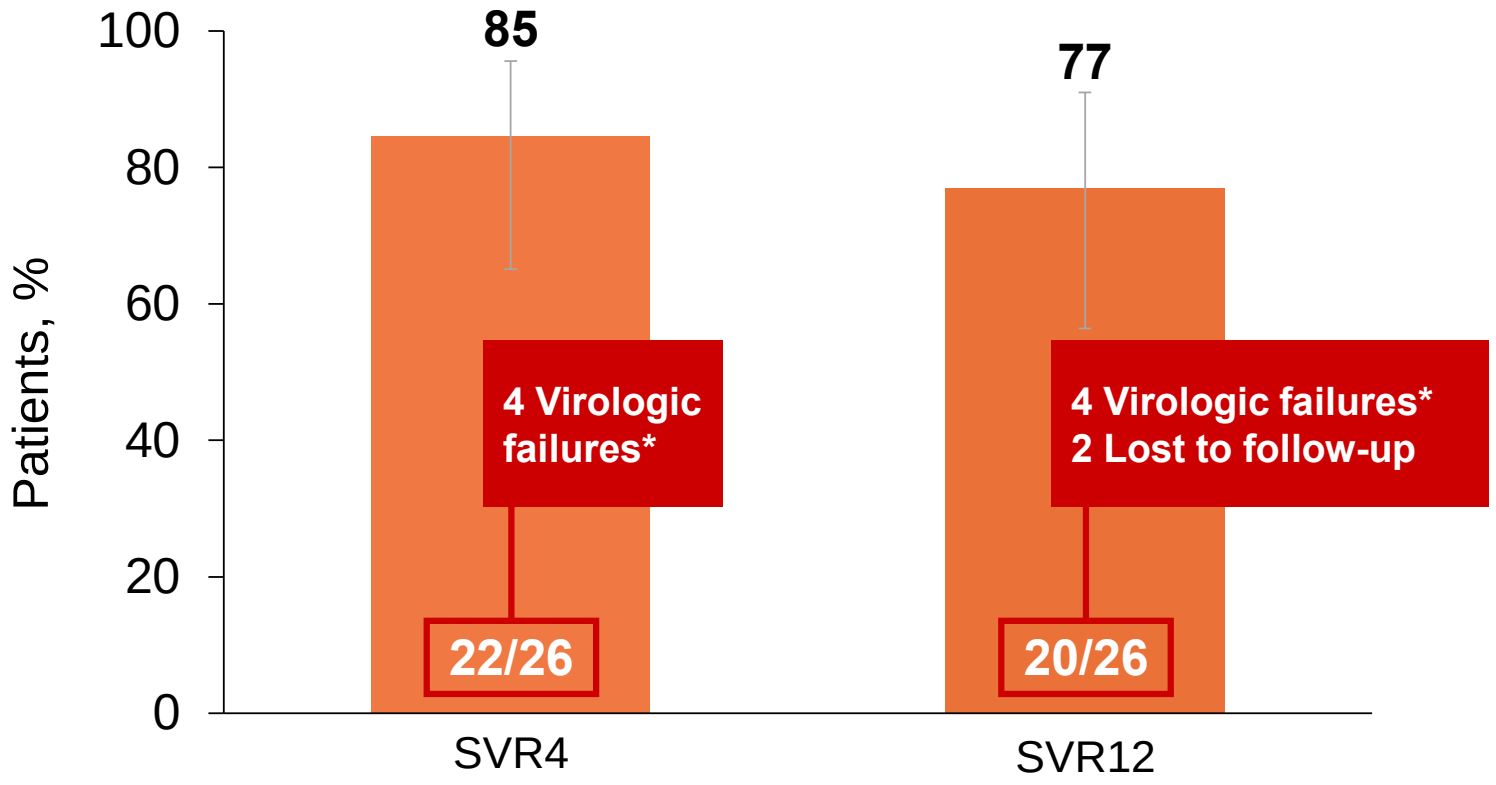
Inclusion

Male, mostly caucasian

Median baseline VL <1 million

Nelson et al BHIVA Thurs

Gilead 6/52



Nelson et al BHIVA Thurs

Points worth noting

No resistance identified

SVR 77% reduced by LFTU and reinfection

Lower SVR that SLAM-C, possibly reflecting VL

All relapsers have baseline VL >10 million

Nelson et al BHIVA (Thurs)

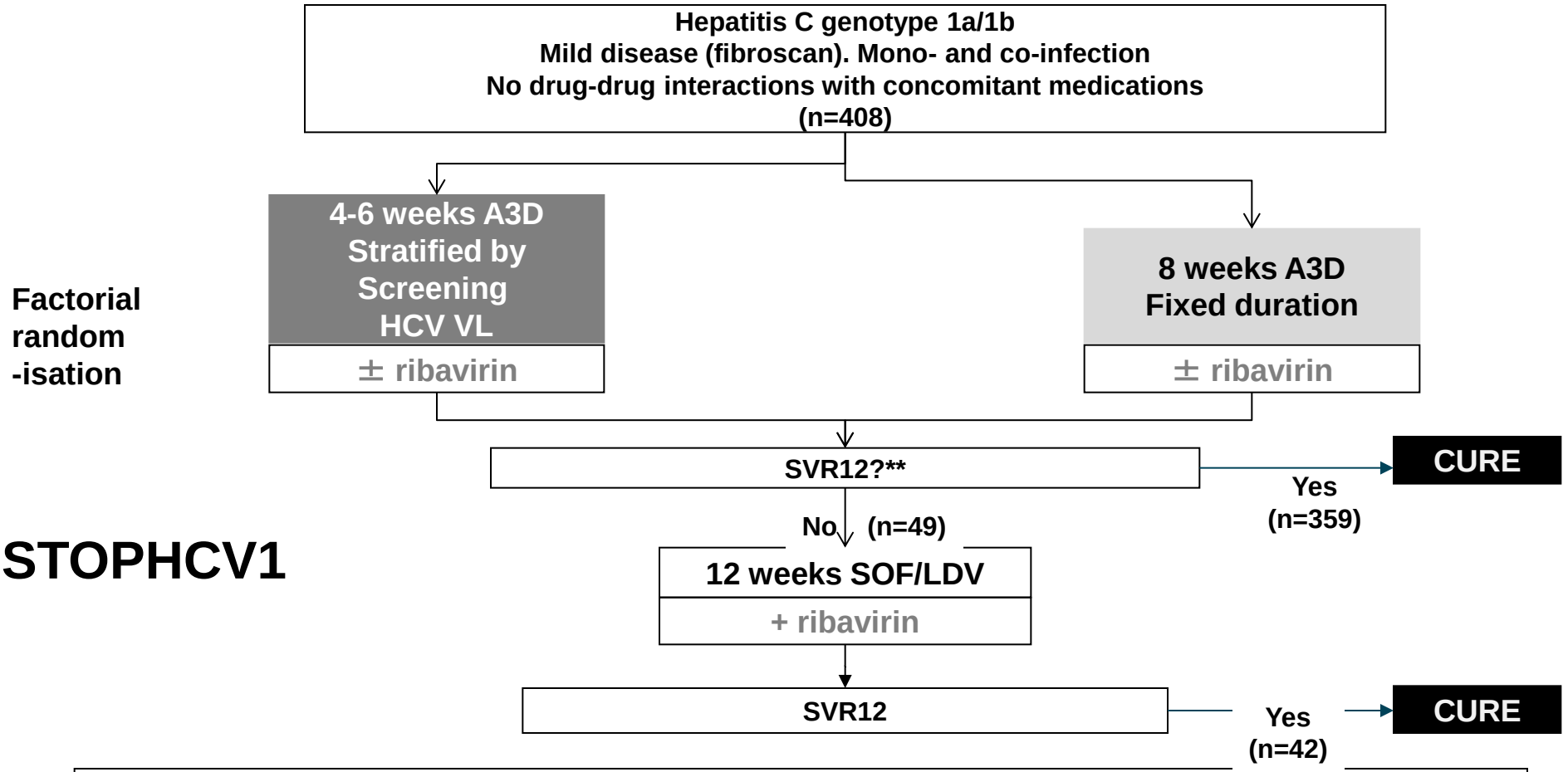
We can do better: redefining stratification in IFN free era

Baseline stratification ; Viral load thresholds for Harvoni
Viral resistance testing for Graz/Elb

On treatment responses; data emerging

Treatment/Retreatment ; SYNERGY, C-SWIFT

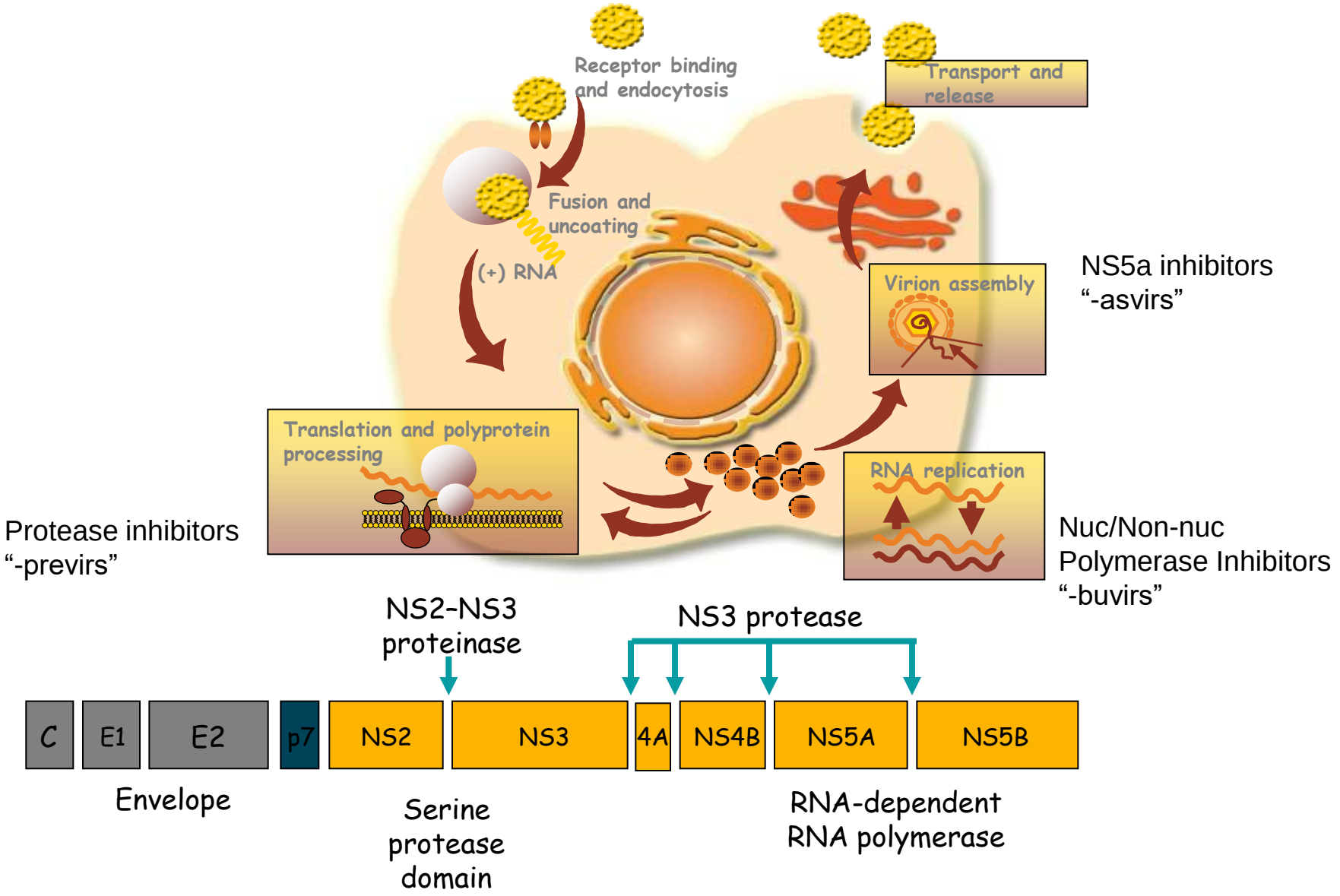
STOPHCV1



Follow-up:	day 3, 7, 14, 28: then every other week until 4 weeks post end of treatment; then 4-weekly until 12 weeks post end of treatment, then 24 weeks 24 post end of treatment.
Primary endpoint:	Overall SVR12 (ie cure) at the end of first-line and any re-treatment (stratified randomisation) SVR12 at the end of first-line (ribavirin comparison)
Secondary endpoints:	SVR24; lack of initial virological response; viral load rebound (relapse) after becoming undetectable; serious adverse events; grade 3 or 4 adverse events; adverse events of any grade judged definitely/ probably related to the intervention; treatment-modifying toxicity of any grade; grade 3 or 4 anaemia; emergence of resistance-associated Hepatitis C variants; cost.

**not achieving SVR12= failure to suppress virus during treatment; relapse after suppression either prior to or at week 12 after end of therapy.

Resistance



1. Lindenbach BD & Rice CM. Unravelling hepatitis C virus replication from genome to function. *Nature* 2005;436:933-938

Treatment/Retreatment and Resistance?

- Key difference from the same challenges posed in other infections (e.g. TB, sepsis)

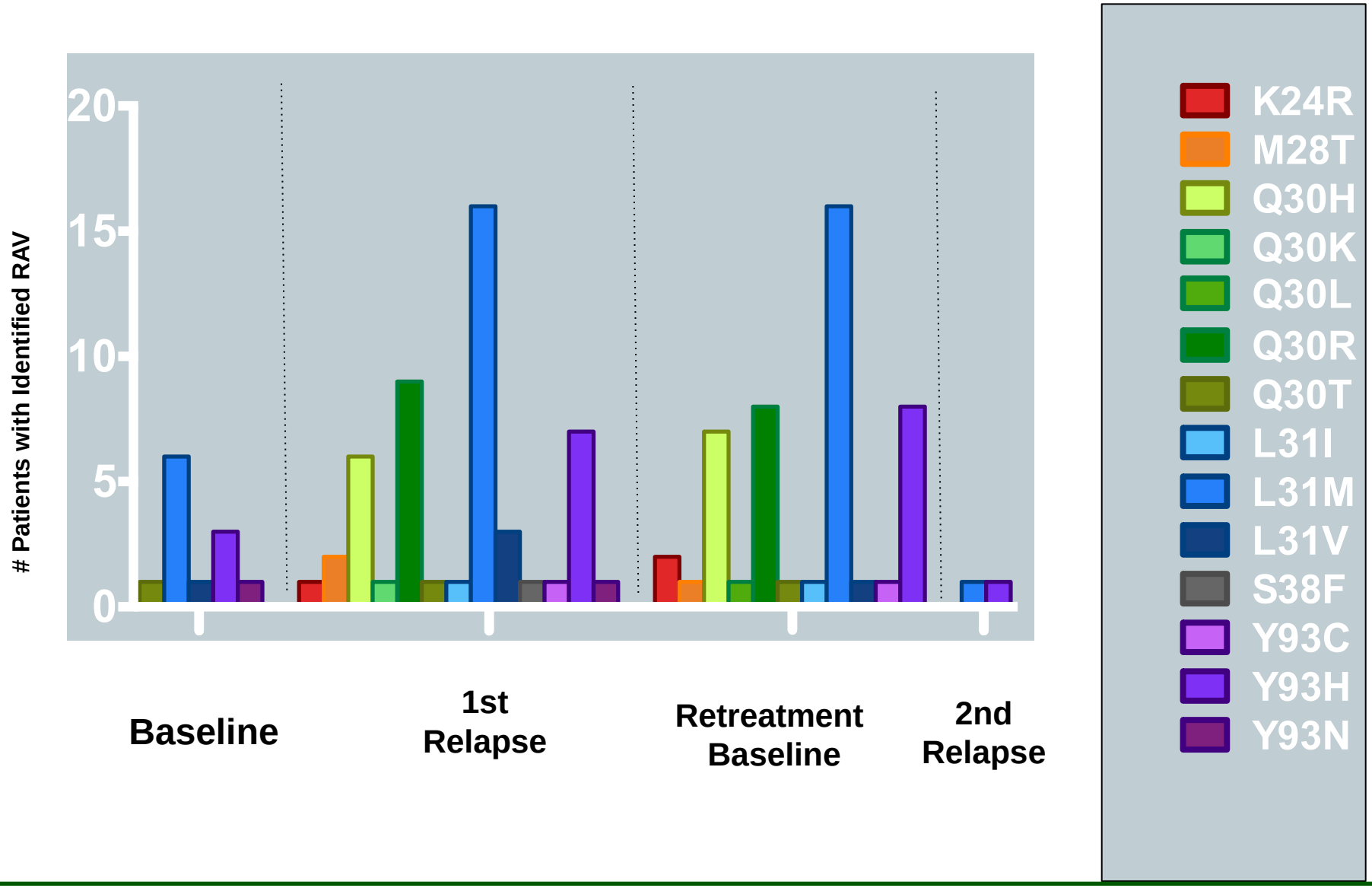
- Merck's C-SWIFT (ELB/GRAZ/SOF) studied durations down to 4/52

  Retreatment of failures presented in AASLD – 100% SVR

- NIH/Gilead Synergy Study also down to 4/52

  Retreatment success of over 90% despite high rates of NS5a emergence

Emergence of RAVs after short course Rx



Slide courtesy of Eleanor Wilson

STOP HCV-1

Open for recruitment at two sites, others in set-up

All but one of the ODN in England have expressed interest

Supported by MRC, NIHR and NHS England

Wales and Scotland too

Currently navigating recruitment within NHSE restrictions on treatment

Where do we want to get to?

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We want to be able to offer all patients >90% chance of cure with minimum duration of therapy

Leverage expertise in genetics (viral>host) and immunology to support this in routine practice

Achieve this through further studies

- To evaluate other genotypes
- To validate rules for shortened treatment with goal of >90%

Integrate with developments in informatics

UK system should be better placed than anyone to do this

Thank you

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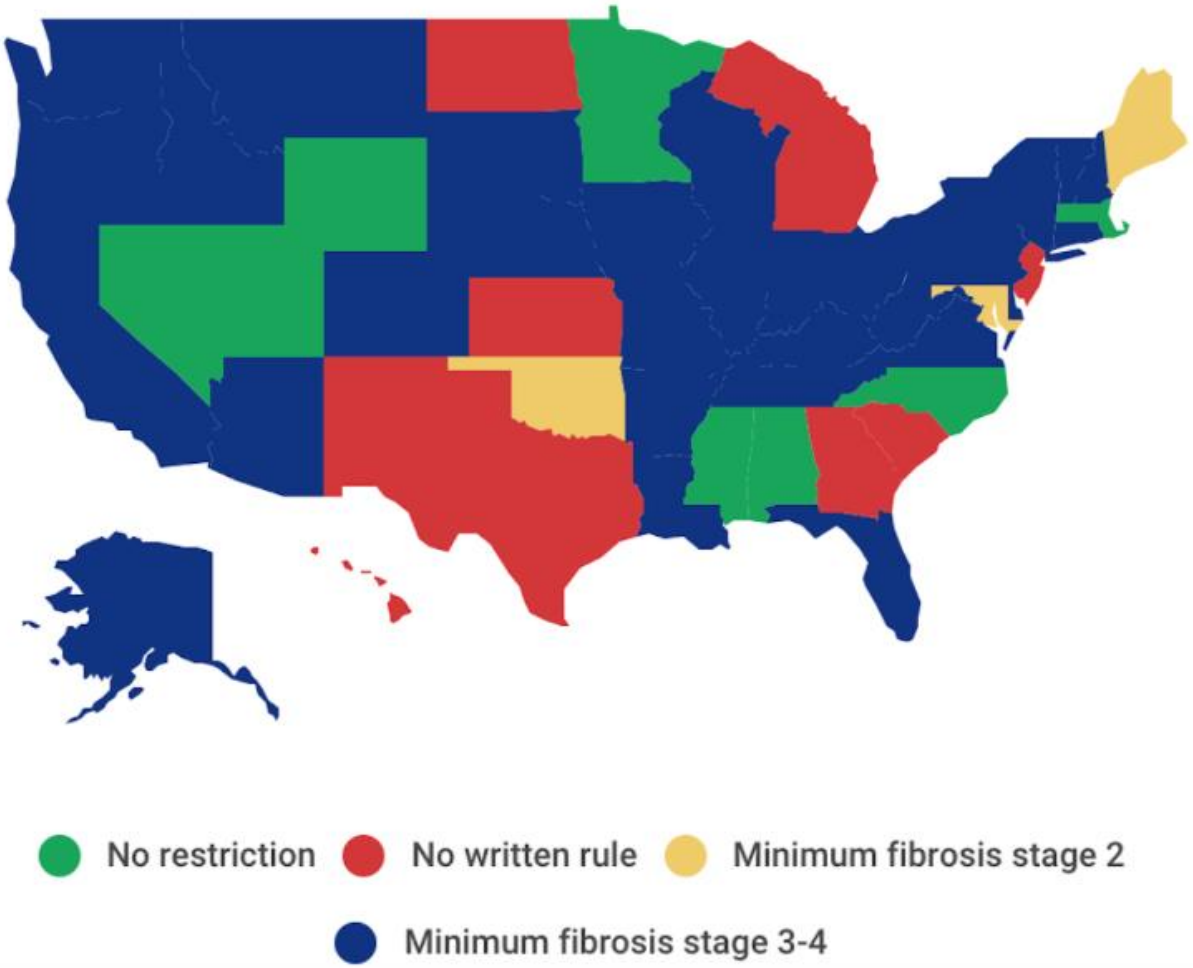
Janice Main
Mark Thursz
Ashley Brown
Simon Taylor-Robinson
Shahid Khan
Maud Lemoine

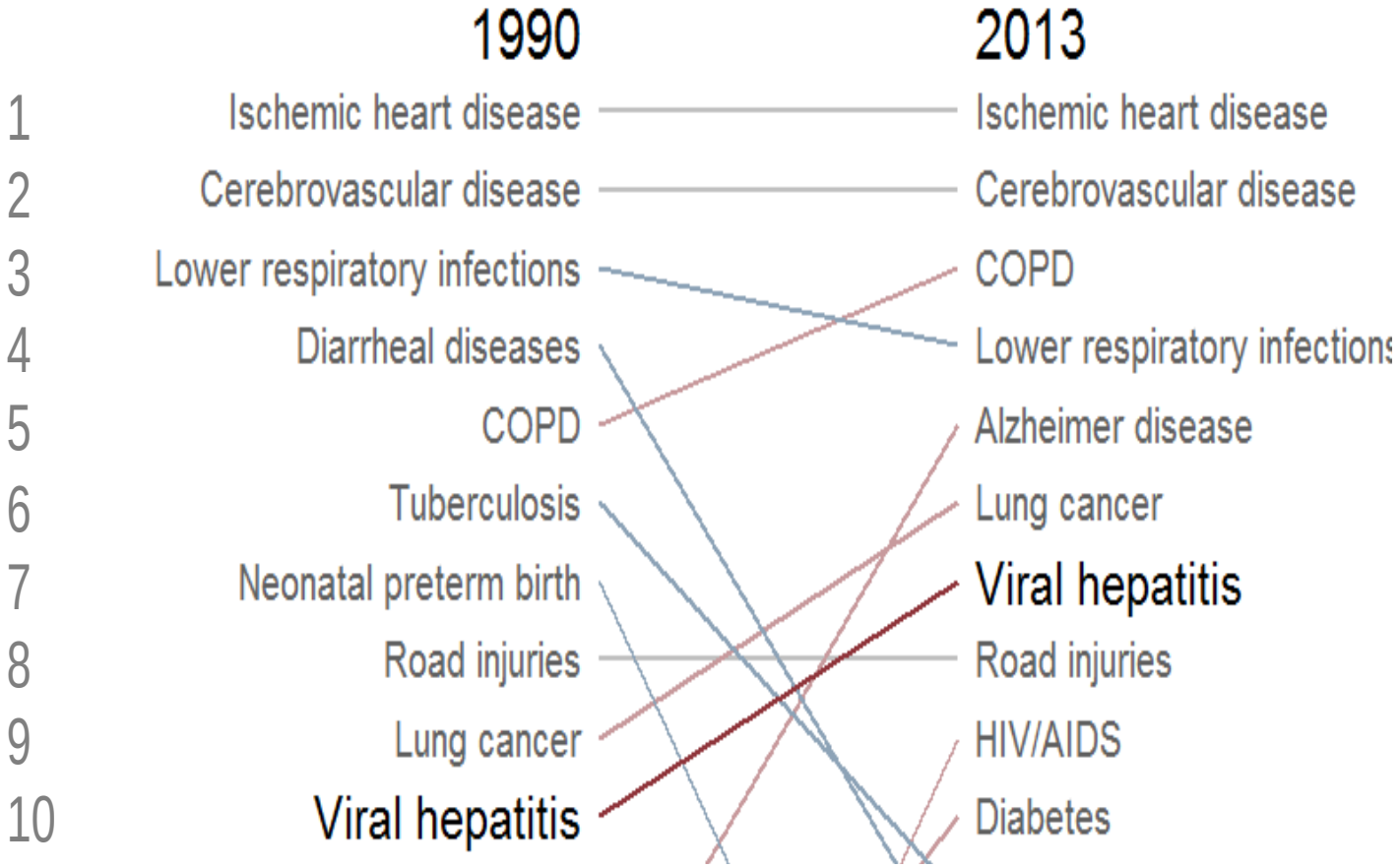
Q &A

Major impact on access in US systems



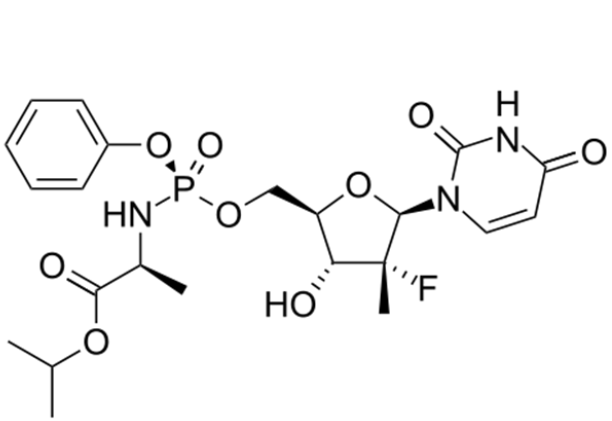
Barua et al JAMA 2015

Bucking the trend of infectious diseases



Stanaway et al (2015)

Costs



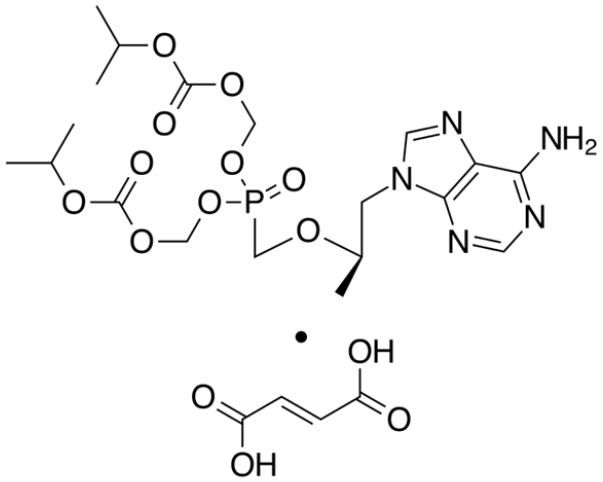
HCV: Sofosbuvir

$C_{22}H_{29}FN_3O_9P$

Molecular weight:

529 g/mol

34g per treatment course



HIV: Tenofovir disoproxil fumarate (TDF)

$C_{23}H_{34}N_5O_{14}P$

Molecular weight: 636 g/mol

$0.52 per gram

Hill et al CID 2014

HCV DAA	Daily dose	Total dose (12wk)	Predicted cost
Ribavirin	1000mg	84g	$21-63*
Daclatasvir	60mg	5g	$10-30
Sofosbuvir	400mg	34g	$68-136
Faldaprevir	120mg	10g	$100-210
Simeprevir	150mg	13g	$130-270

*$25-76 for 1200mg daily dose of ribavirin

Hill et al CID 2014

Factors considered in pricing of HCV drugs

GILEAD

Stakeholders	Wave 1 Regimen	$60,000	$70,000	$90,000	$105,000	$125,000
	Wave 1 SOF product (12 wks)	$50,000	$60,000	$80,000	$95,000	$115,000
	Wave 2 FDC (8 wks or 12 wks?)	$70,000	$80,000	$100,000	$115,000	$135,000
Payers	Likelihood of applying directly observed therapy due to high price	Unlikely	Possible	Possible	Likely	Likely
Physicians	Likelihood of delay treatment of GT-1 TN patients due to pricing	Unlikely	Possible	Possible	Likely	Likely
	Likelihood of losing some KOL endorsement/support as price too high	Very Unlikely	Unlikely	Possible	Likely	Likely
	Likelihood of getting rejection on TE patients and delay treatment for all due to misconception of restriction for SOF	Possible	Possible	Possible	Possible	Possible
Patients and Advocacy groups	Likelihood of AHF, FPC and other advocacy groups reacting negatively to price, and affecting public opinion	Likely	Likely	Very Likely	Very Likely	Very Likely
	Higher out-of-pocket costs (not offset by patient support) could drive patient choice away from SOF, especially AbbVie has great patient support programs	Very Unlikely	Very Unlikely	Unlikely	Unlikely	Possible
	Likelihood of AHF, FPC and other advocacy groups promote AbbVie products due to the relationship and lower price	Unlikely	Unlikely	Possible	Possible	Likely
Treatment Guidelines	Likelihood of AASLD develop treatment pathway to prioritize (staging) patients (per KOLs or/and professional community request)	Possible	Possible	Possible	Possible	Possible
	Likelihood of a "price mention or asterisk" in AASLD (per KOLs or/and professional community request)	Unlikely	Unlikely	Possible	Possible	Likely
Others	Likelihood of public outcry if SOF revenue exceed $2B as government trying to control healthcare cost	Possible	Possible	Possible	Likely	Very Likely
	Likelihood of a letter from congress on SOF price	Possible	Likely	Likely	Likely	Likely
	Likelihood of a congressional hearing if SOF revenue exceed $2B	Unlikely	Unlikely	Unlikely	Unlikely	Possible

Gilead Internal from Senate Report 2015