The role of resistance in HCV treatment in current practice

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BHIVA November 2017

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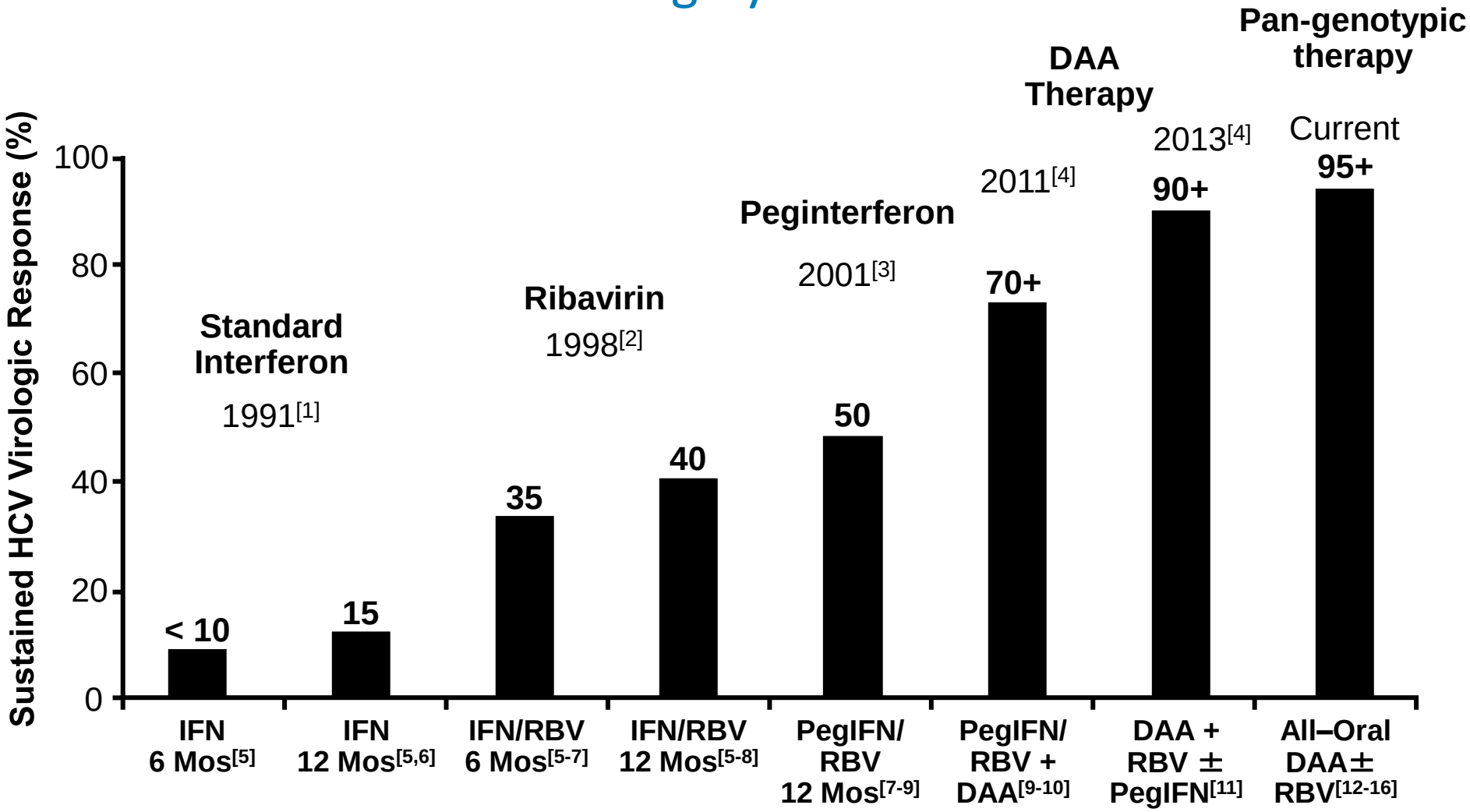
Outline

- HCV treatments – old and new
- Resistance mutations of note
- New pangenotypic regimens - current guidelines from BVHG/BASL/BSG/BHIVA/BIA/CVN
- “Rare” genotypes and potential impact on eradication of HCV

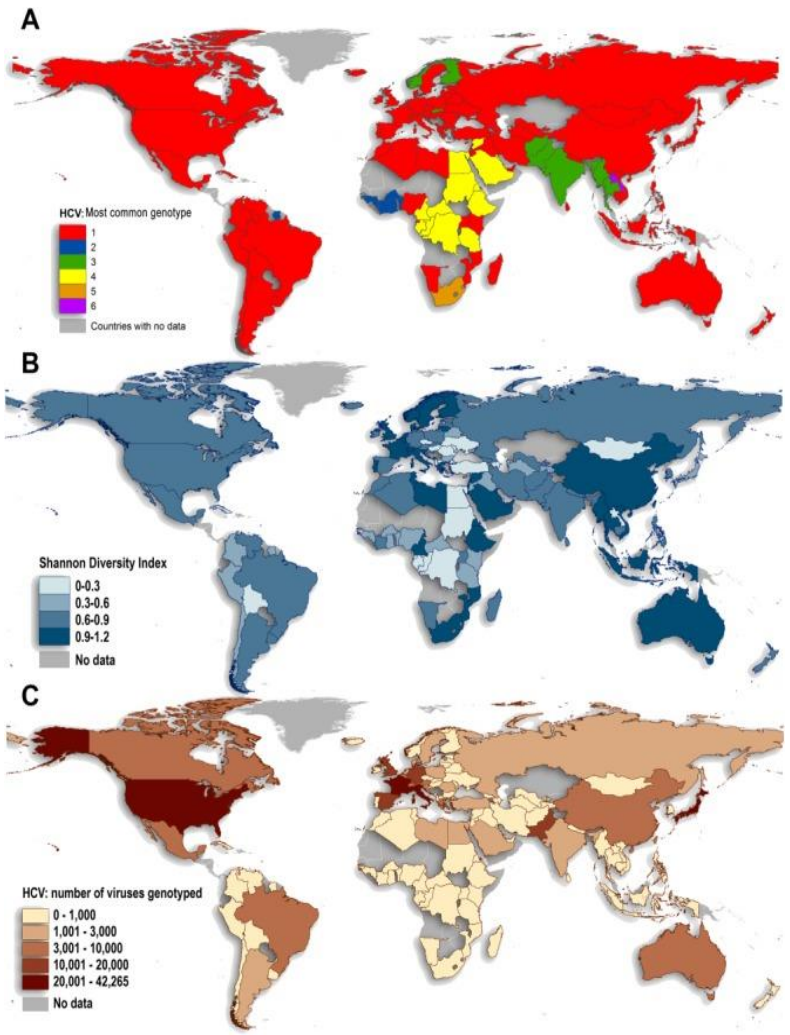
Treatment for HCV is now safe and highly effective



Where HCV Therapy Stands Now

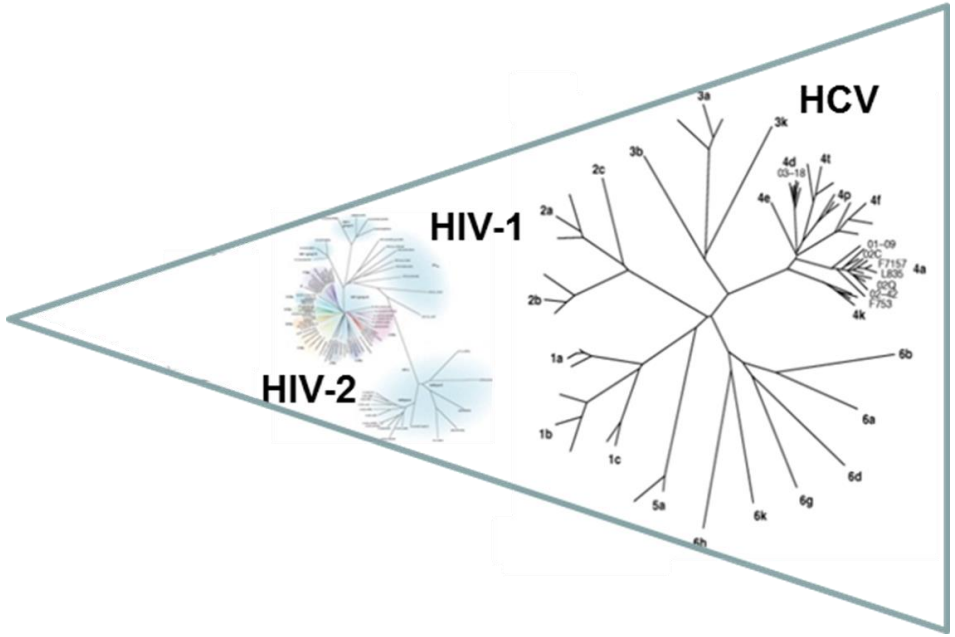
- SVR in > 95%
- Interferon and RBV are out; all-oral pangenotypic regimens in
- “Difficult-to-cure” populations
  - HIV coinfection is not difficult to cure
  - Renal failure patients no longer difficult to cure
  - Cirrhosis
  - Genotype 3
- Resistance…
- DAAs remain overpriced

HCV evolution and resistance

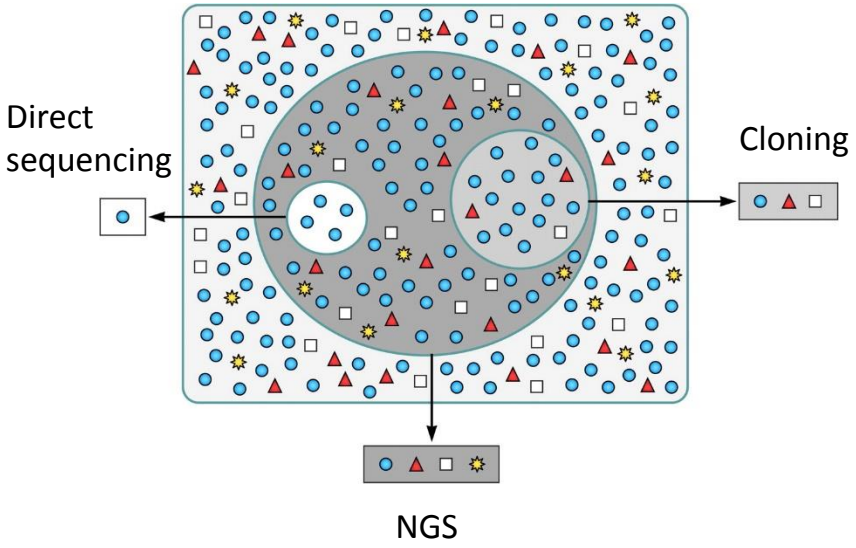


- HCV has been evolving for 2000 years
- 7 genotypes with variable response to treatment
- Natural variations within NS3, NS5A and NS5B confer resistance to DAAs

HCV is a highly variable virus both within populations and within individual hosts

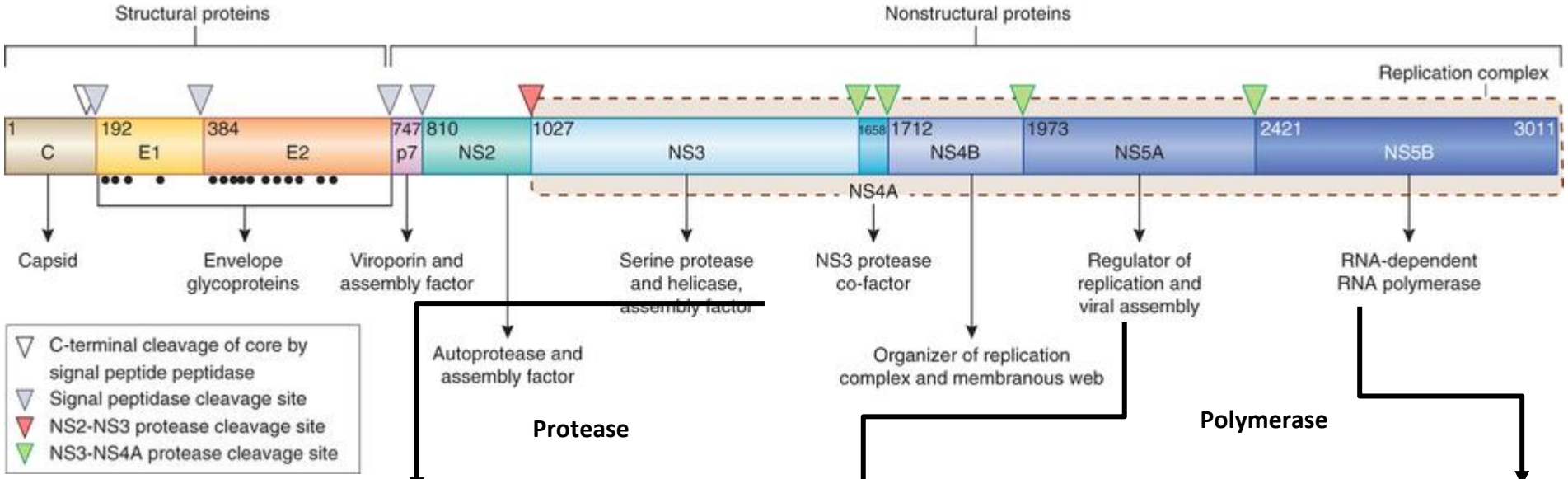


Population



Host

Direct Acting Antivirals (DAAs)



Protease

Polymerase

Ribavirin (RBV)

NS3 Protease Inhibitors

Grazoprevir (GZR)
Paritaprevir/Ritonavir (PTV/RTV)
Simeprevir (SMV)
Voxilaprevir (VOX)
Glecaprevir (GLE)

NS5A Replication Complex Inhibitors

Daclatasvir (DCV)
Elbasvir (EBR)
Ledipasvir (LDV)
Ombitasvir (OBV)
Velpatasvir (VEL)
Pibrentasvir (PIB)

NS5B NUC Inhibitors

Sofosbuvir (SOF)

NS5B Non-NUC Inhibitors (NNI)

Dasabuvir (DSV)

Direct Acting Antivirals (DAAs)

2014

Simeprevir	1,4
Sofosbuvir	1-6
Daclatasvir	1-6

2015

Sofosbuvir/ledipasvir	1,4,5,6
Ombitasvir, paritaprevir, dasabuvir, ritonavir	1
Ombitasvir, paritaprevir, ritonavir	4

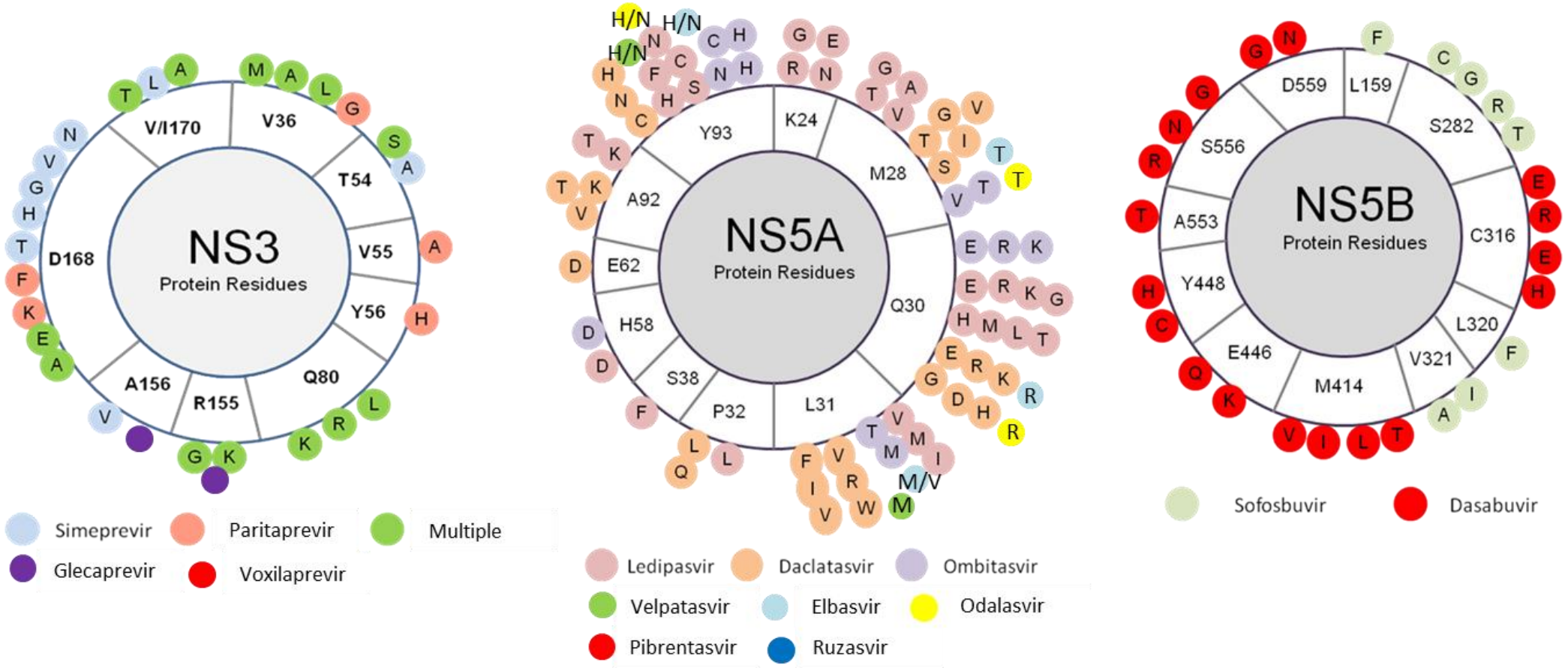
2016

Sofosbuvir/velpatasvir	1-6
Grazoprevir/elbasvir	1,4

2017

Sofosbuvir/velpatasvir/voxilaprevir	1-6
Glecaprevir/pibrentasvir	1-6

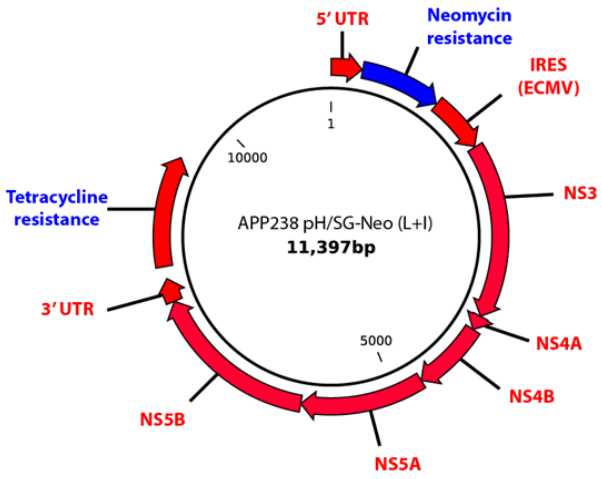
Multiple resistance mutations have been described within NS3, NS5A and NS5B

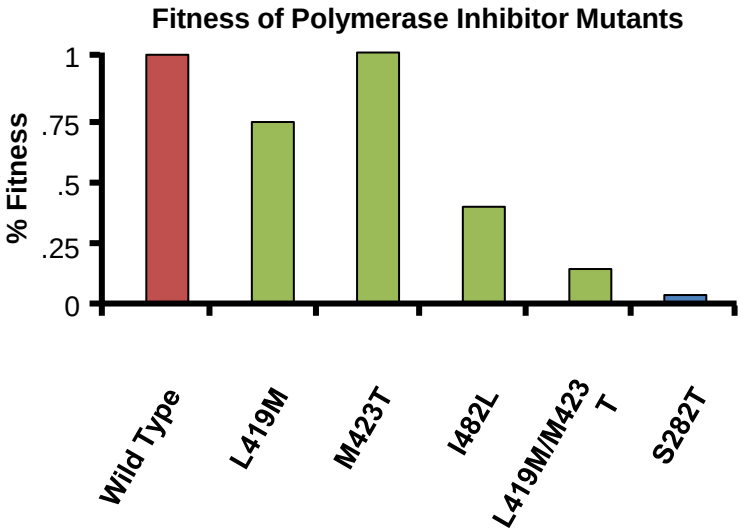


Persistence of resistance mutations in a population is related to replication fitness

Genetic barrier

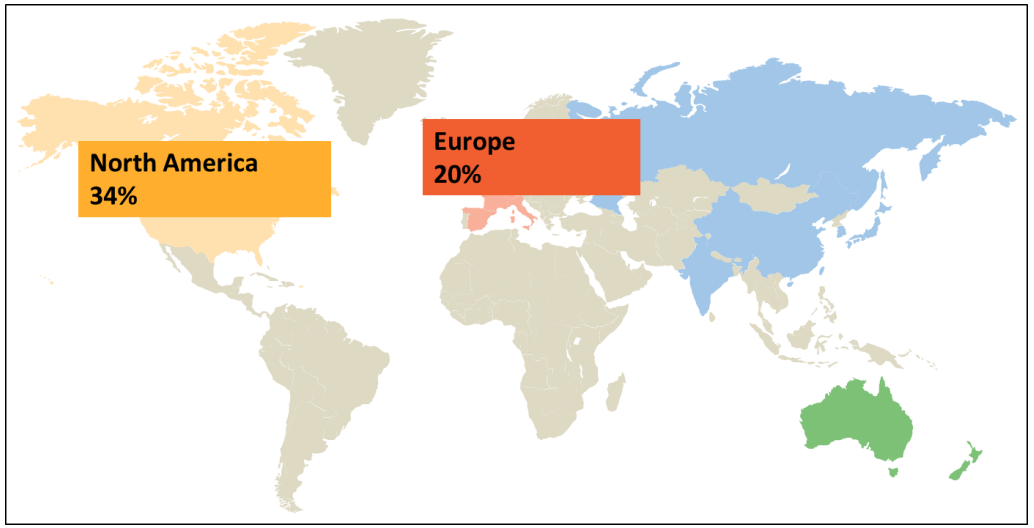
- NS5A and NS3 RAVs at baseline are far more common than NS5B RAVs



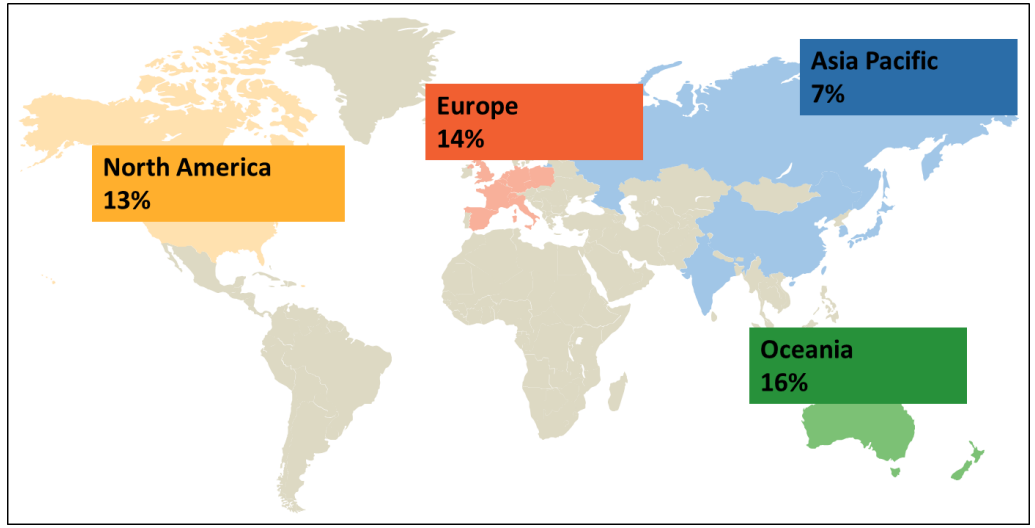


1. Rong L, et al. Sci Transl Med. 2010;2:30ra32. 2. Le Pogam S et al. J Virol. 2006;80:6146-6154. 3. Le Pogam S, et al. J Infect Dis. 2010;202:1510-1519

NS3 and NS5A RAVs occur frequently as natural polymorphisms in genotype 1a HCV



NS3 Q80K RAV



NS5A RAVs

Sarrazin *et al., Antiviral Res* 2015; Zeuzem et al., AASLD 2015

NS5A cross-resistance is less of a problem with newer drugs

Fold-Change in EC50	Genotype 1a				Genotype 1b	
Position	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
Daclatasvir	> 100 x	> 1000 x	> 100 x	> 1000 x	< 10 x	< 100 x
Ledipasvir	20 x	> 100 x	> 100 x	> 1000 x		> 1000 x
Ombitasvir	> 1000 x	> 100 x	< 3 x > 100 x	> 10,000 x	< 10 x	< 100 x
Elbasvir	20 x	>100 x	>10x >100x	>1000x	<10x	>100x
Velpatasvir	<10x	<3x	20x 50x	>100x >1000x	<3x	<3x
Odalasvir	30x	20x	<10x	>100x	<3x	<3x
Pibrentasvir	<3x	<3x	<3x	<10x	<3x	<3x
(Ruzasvir)	<10x	<10x	<10x	<10x	<10x	<10x

The impact of HCV resistance mutations is context specific

Treatment choice

Genotype

Some genotypes are **naturally resistant** to certain DAAs e.g. genotype 3 and protease inhibitors

Viral load

GRZ/ELB, +- RBV extend to 16 weeks if VL >800,000 IU/ml (but not if no NS5A mutations present)

LED/SOF
Can use 8 weeks if naïve, no cirrhosis and VL < 6 million IU/ml

Stage of disease

Cirrhosis increases the impact of DAA resistance mutations e.g. Q80K and SIM/SOF

Previous treatment

Previous treatment failure is associated with an increased impact from resistance mutations e.g. SOF/LED in treatment experienced patients reduces SVR by 10% and RBV should be added if NS5A res mutations or testing not available

Length of treatment

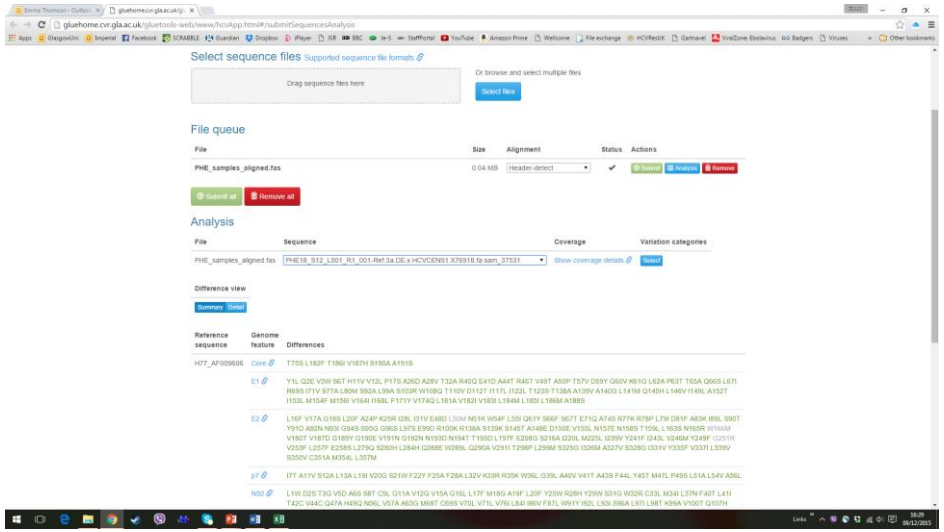
Short treatment courses may be less effective if resistance mutations are present e.g. NS5A mutations (particularly Y93H)

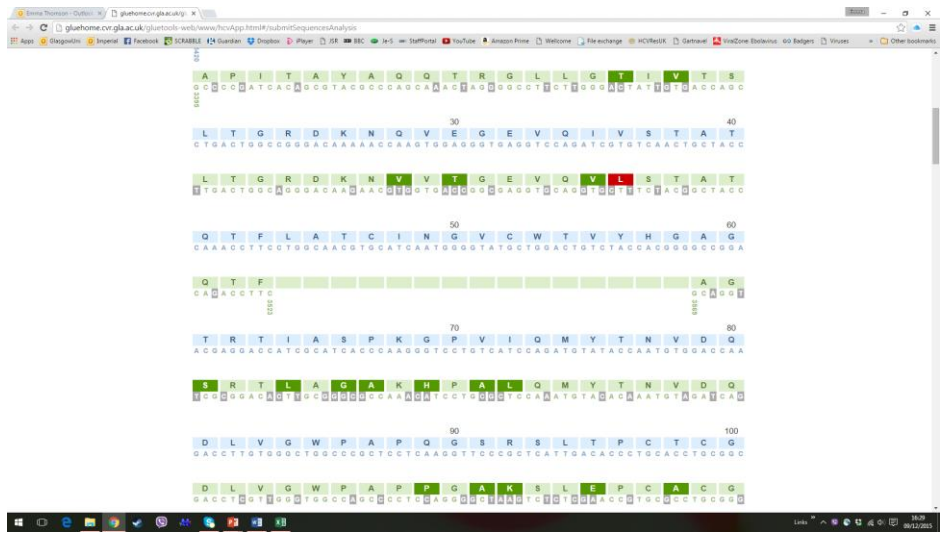
Combined therapy

Monotherapy e.g. in registration trials is invariably associated with the development of resistance

STOP HCV/HCV Res UK resistance database

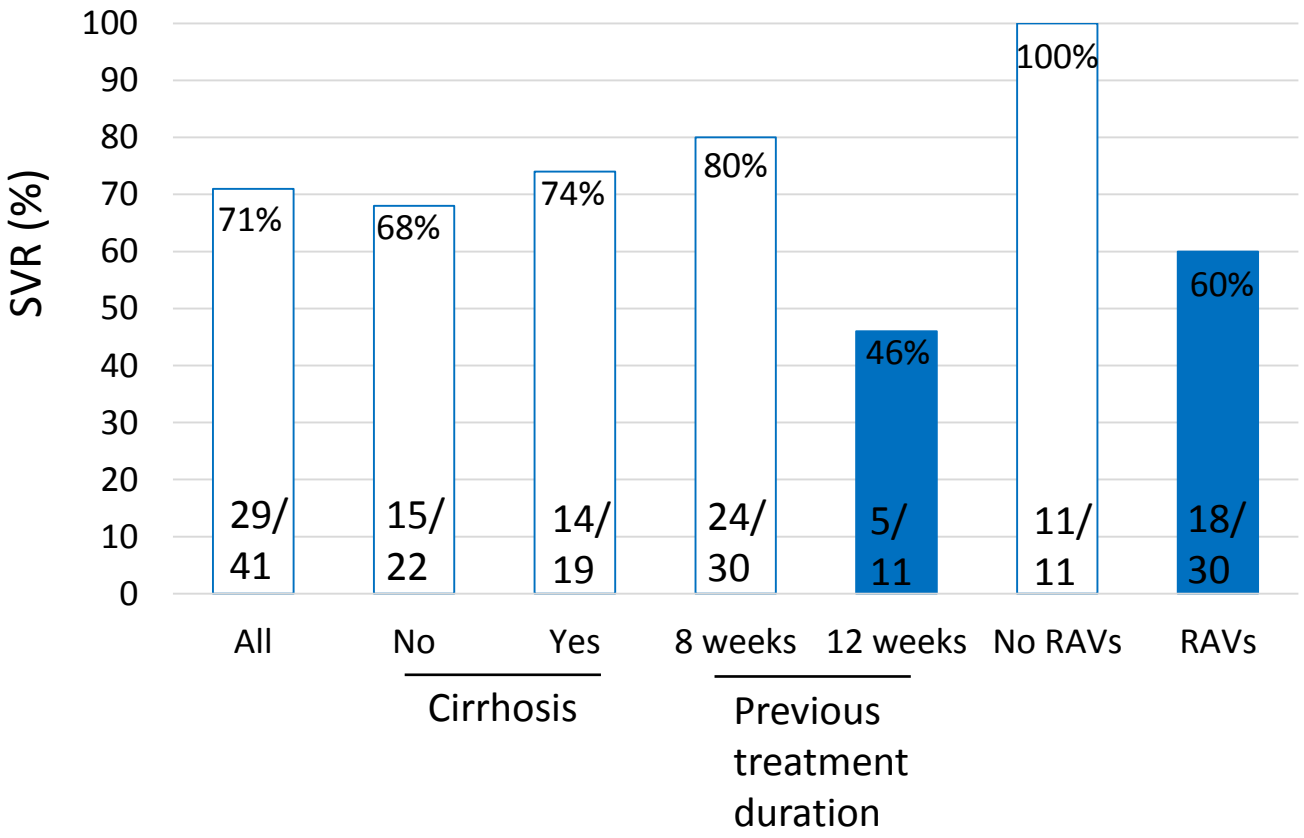
- http://gluehome.cvr.gla.ac.uk/





“Old regimens”: Ledipasvir/sofosbuvir – treatment experienced

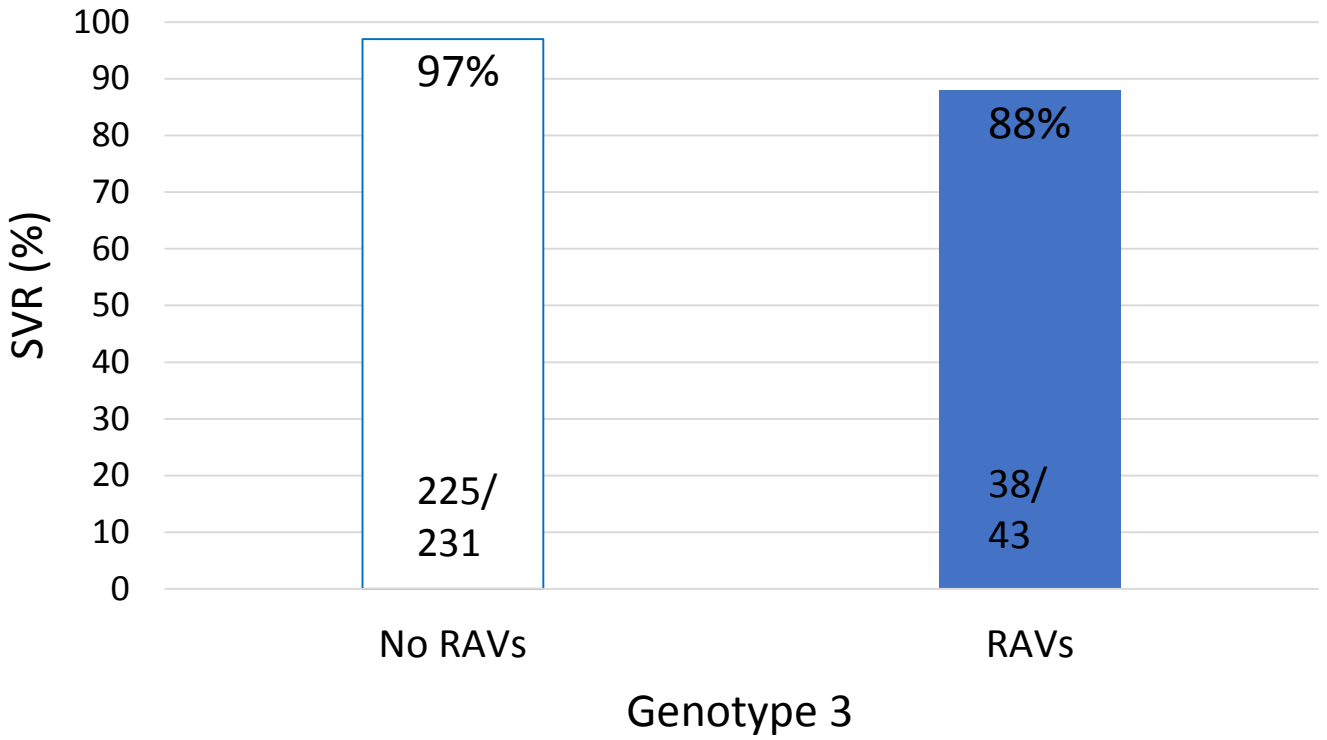
G1 infected patients with and without cirrhosis treated previously with LDV/SOF +- GS-966 retreated with 24 weeks LDV/SOF



Lawitz et al 2015

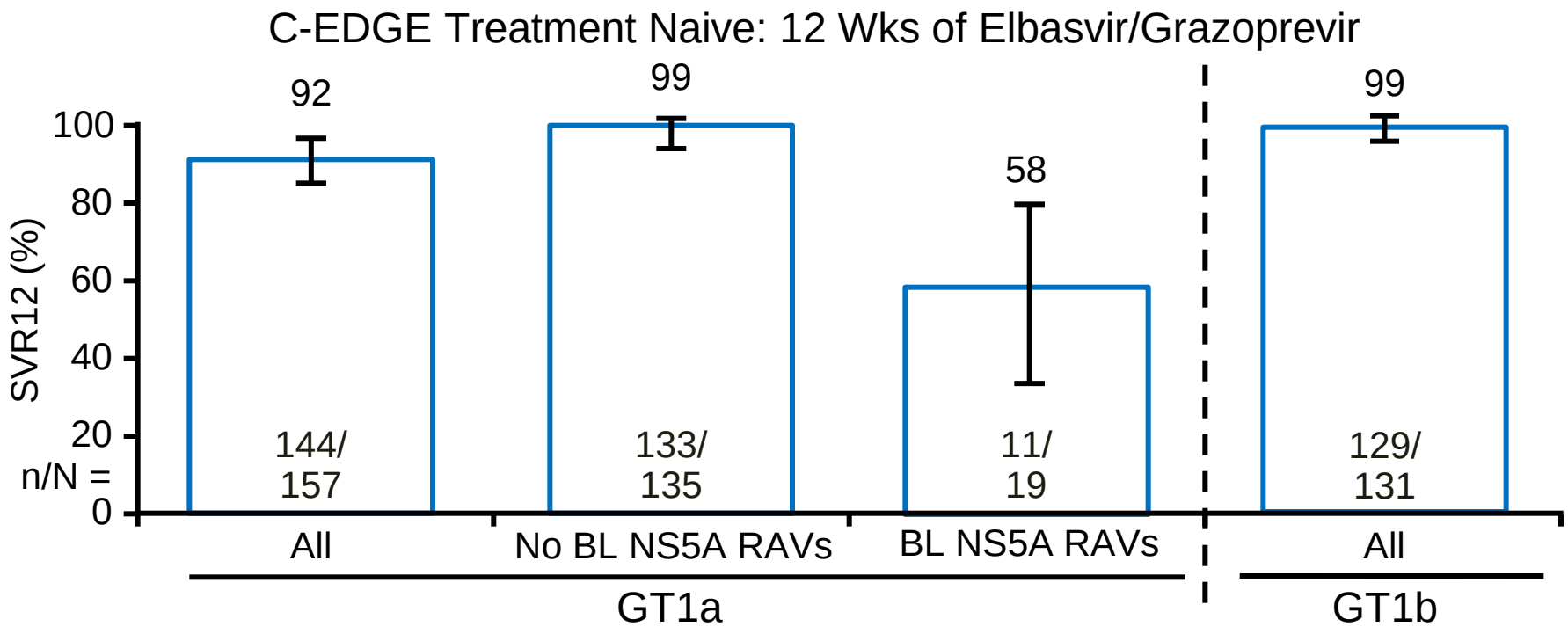
“Old regimens”: sofosbuvir/velpatasvir

ASTRAL-3: 12 weeks of SOF/VEL in tn, te and cirrhotic/non-cirrhotic patients



Recommendation: If SOF/VEL or SOF/DAC is used in g3 tn patients with compensated cirrhosis or in PEG-IFN/RBV TE patients, RAV testing for Y93H is recommended and RBV should be added if present

“Old regimens”: EBR/GZR Duration Based on Baseline NS5A RAVs in GT1a



If NS5A RAVs in GT1a, treat with EBR/GZR + RBV for 16 wks

No baseline RAV testing needed in GT1b pts

New pangenotypic HCV treatments

- Glecaprevir/pibrentasvir

- Sofosbuvir/velpatasvir/voxilaprevir

Sofosbuvir/velpatasvir/voxilaprevir

Study	Genotypes	Tx duration	Population	HIV	Cirrhosis	SVR12
POLARIS 1	1-6	12 weeks	TE (NS5A)	No	Overall Yes (41%) No (59%)	96% 93% 99%
POLARIS 2	1-4	8-12 weeks	TE, TN	No	Overall Yes (18%)	8wk – 95% 12wk – 98% G1 8 wk - 93% 8wk - 90% 12wk – 99%
POLARIS 3	3	8 weeks SOF/VEL/VOX 12 weeks SOF/VEL	TN	No	Yes - all	96% both arms*
POLARIS 4	1-3	12 weeks SOF/VEL/VOX 12 weeks SOF/VEL	TE (DAA)	No	Yes (46%)	97% (SOF/VEL/VOX) 90% (SOF/VEL)

* No RAVs in SOF/VEL/VOX arm but Y93H in SOF/VEL failures

Sofosbuvir/velpatasvir/voxilaprevir

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POLARIS 1	1-6	12 weeks	TE (NS5A)	No	Overall Yes (41%) No (59%)	96% 93% 99%
POLARIS 2	1-4	8-12 weeks	TE, TN	No	Overall	8wk – 95% 12wk – 98%
P		SOF/VEL/VOX 12 weeks SOF/VEL				arms*
POLARIS 4	1-3	12 weeks SOF/VEL/VOX 12 weeks SOF/VEL	TE (DAA)	No	Yes (46%)	97% (SOF/VEL/VOX) 90% (SOF/VEL)

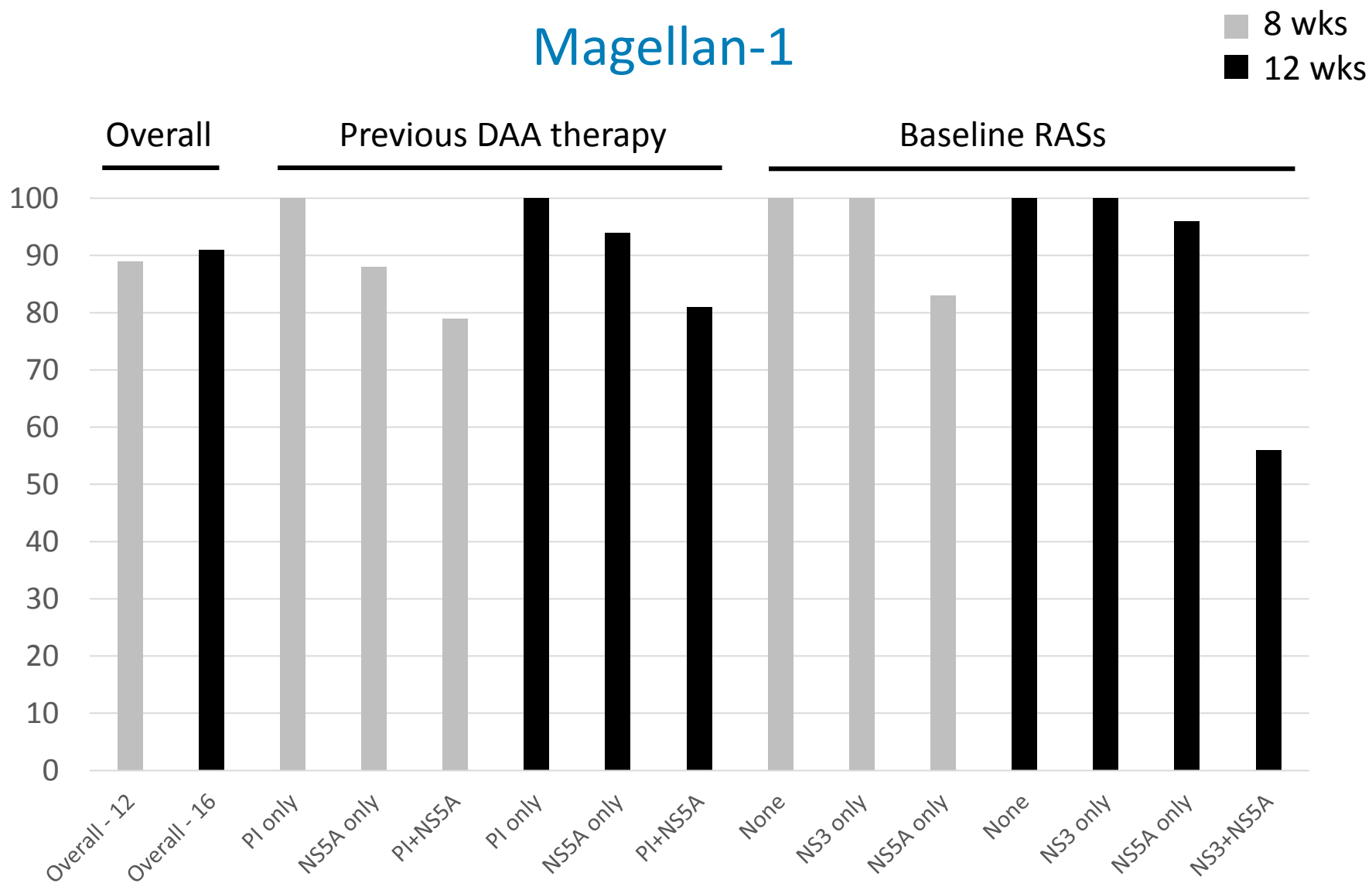
Presence of baseline RAVs had no impact on treatment outcome

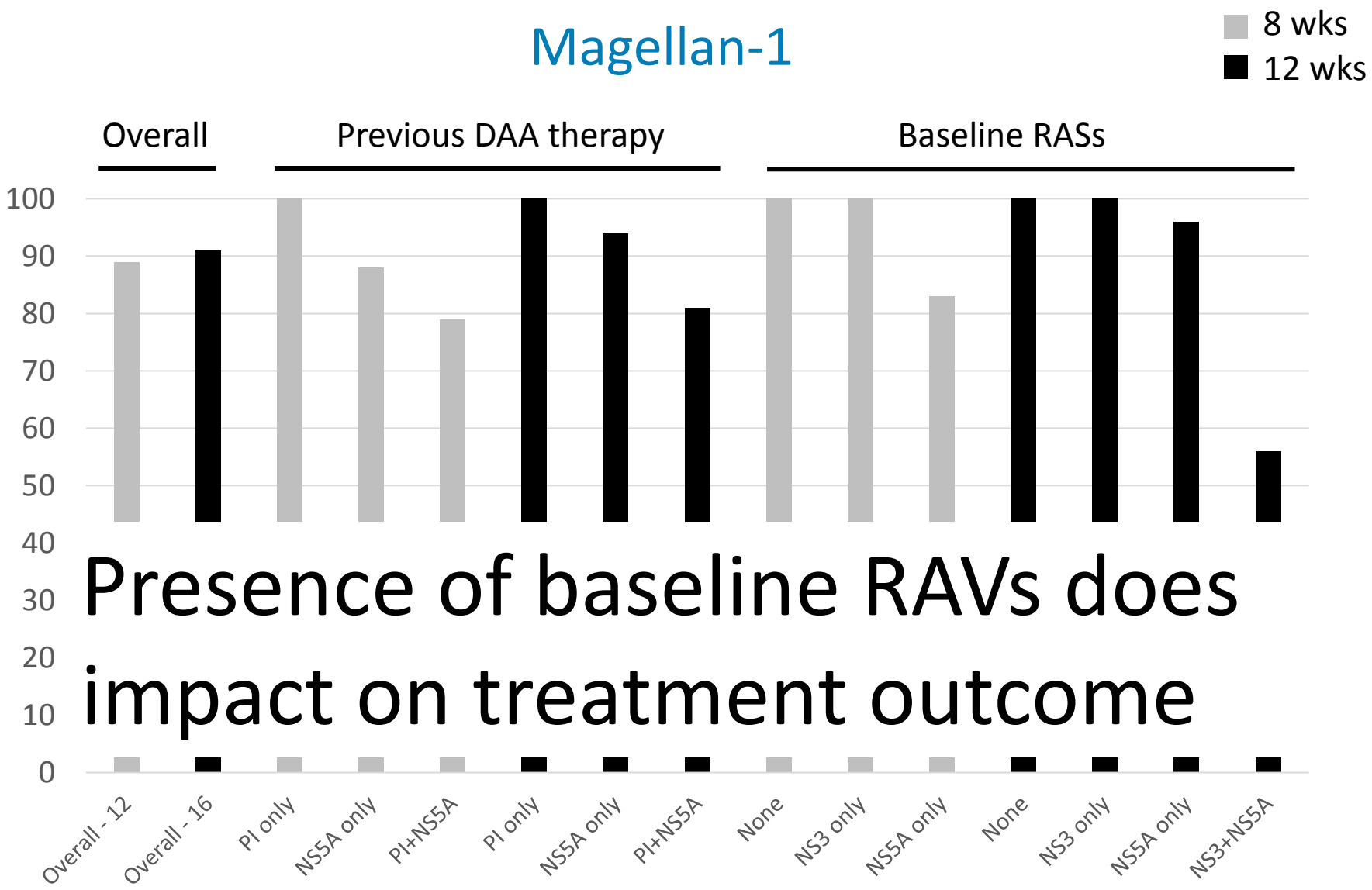
* No RAVs in SOF/VEL/VOX arm but Y93H in SOF/VEL failures

Glecaprevir/pibrentasvir

Study	Genotypes	Tx duration	Population	HIV	Cirrhosis	SVR12
ENDURANCE 1	1	8-12 weeks	TE, TN	Yes	No	99-100%
ENDURANCE 2	2	12 weeks	TE, TN	No	No	99.5%
ENDURANCE 3*	3	8-12 weeks	TN	No	No	95%**
ENDURANCE 4	4-6	12 weeks	TE, TN	No	No	99-100%
EXPEDITION 1	1,2,4,5,6	12 weeks	TE, TN	No	Yes	99-100%
EXPEDITION 2	1-6	8-12 weeks	TE, TN	Yes	Yes	99%
EXPEDITION 4	1-6	12 weeks	Renal	No	Yes	98%
MAGELLAN 1	1	12 weeks	TE (DAA)	No	No	56-100%**
SURVEYOR 1, 2	1-6	8-12 weeks	TN or IFN		No	1:97-100% 2:96-100% 3:83-94% 4-6:100%
MAGELLAN 3	1-6	12-16 weeks (+ SOF/RBV)	TE (AbbVie)	Ongoing		

*ENDURANCE 3 was carried out with a SOF-DAC arm – SVR 97% ** NS3/NS5A mutations ass. with lack of response


Magellan-1
8 wks
12 wks
Overall
Previous DAA therapy
Baseline RASs
100
90
80
70
60
50
40
30
20
10
0
Overall - 12
Overall - 16
PI only
NS5A only
PI+NS5A
PI only
NS5A only
PI+NS5A
None
NS3 only
NS5A only
None
NS3 only
NS5A only
NS3+NS5A



Presence of baseline RAVs does impact on treatment outcome

Resistance testing – take-home messages

- Baseline for first-line therapy
  - Required for grazoprevir/elbasvir therapy if VL>800,000 IU/ml
  - Population sequencing or NGS with a cut-off of 15%

- Treatment failure
  - SOF/VEL/VOX – baseline RAVs have no impact on treatment outcome
  - GLE/PIB – baseline RAVs can impact treatment outcome
  - Await GLE/PIB/SOF data (MAGELLAN-3)

What about HCV in the rest of the world? Absence of genomic data in LMICs

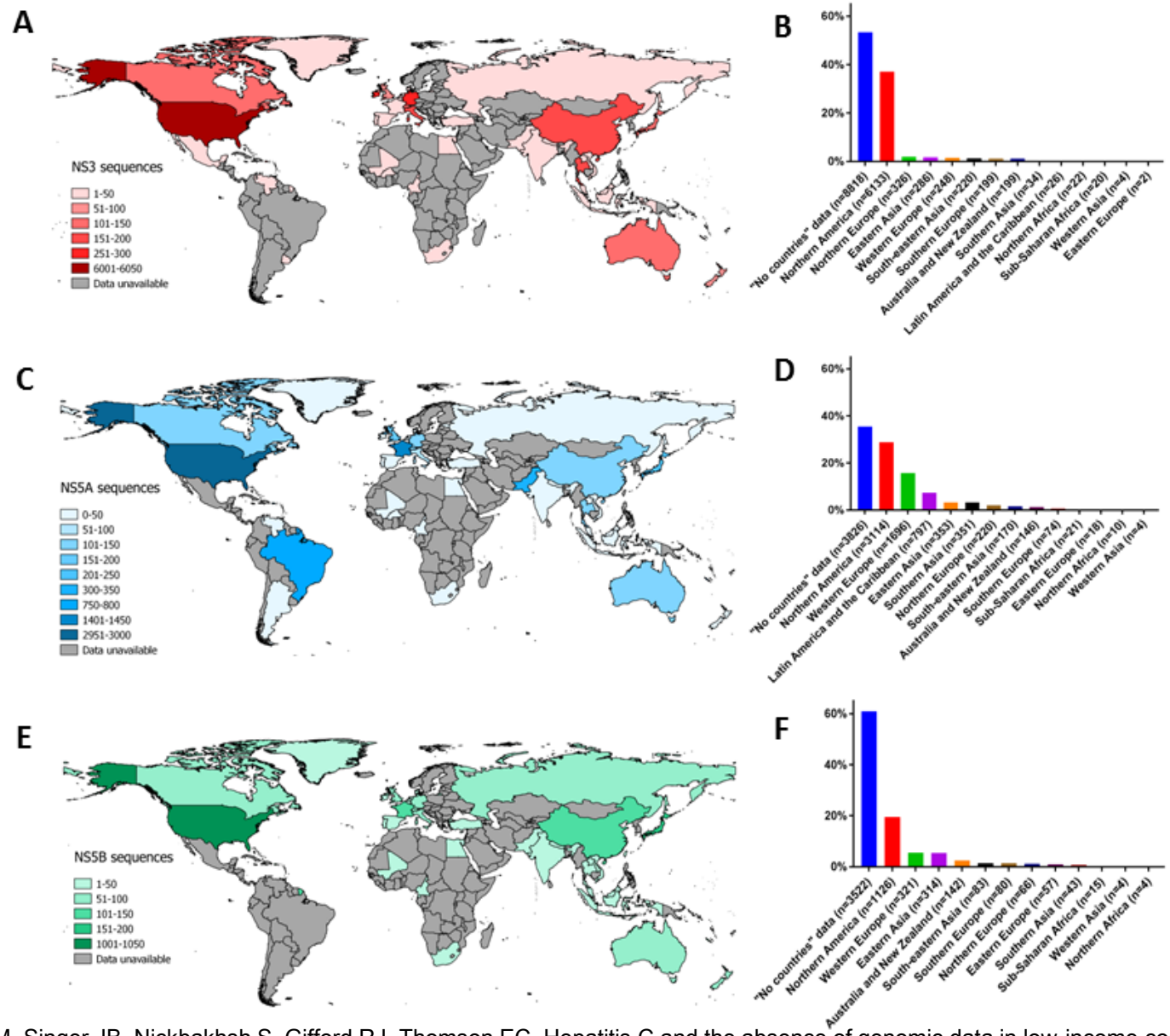


Figure 1. Global distribution of HCV sequence data based on the genes of DAA treatment targets. (A) NS3 protease sequences by country (B) Abundance of NS3 sequences by UN sub-regions. (C) NS5A sequences by country. (D)Abundance of NS5A sequences by UN sub-regions. (E) NS5B sequences by country. (F) Abundance of NS5B sequences by UN sub-regions.

Niebel M, Singer JB, Nickbakhsh S, Gifford RJ, Thomson EC. Hepatitis C and the absence of genomic data in low-income countries: a barrier on the road to elimination? Lancet Gastroenterol Hepatol. 2017 Oct;2(10):700-701

Outcomes of “rare genotypes” in the NHS England Early Access Programme

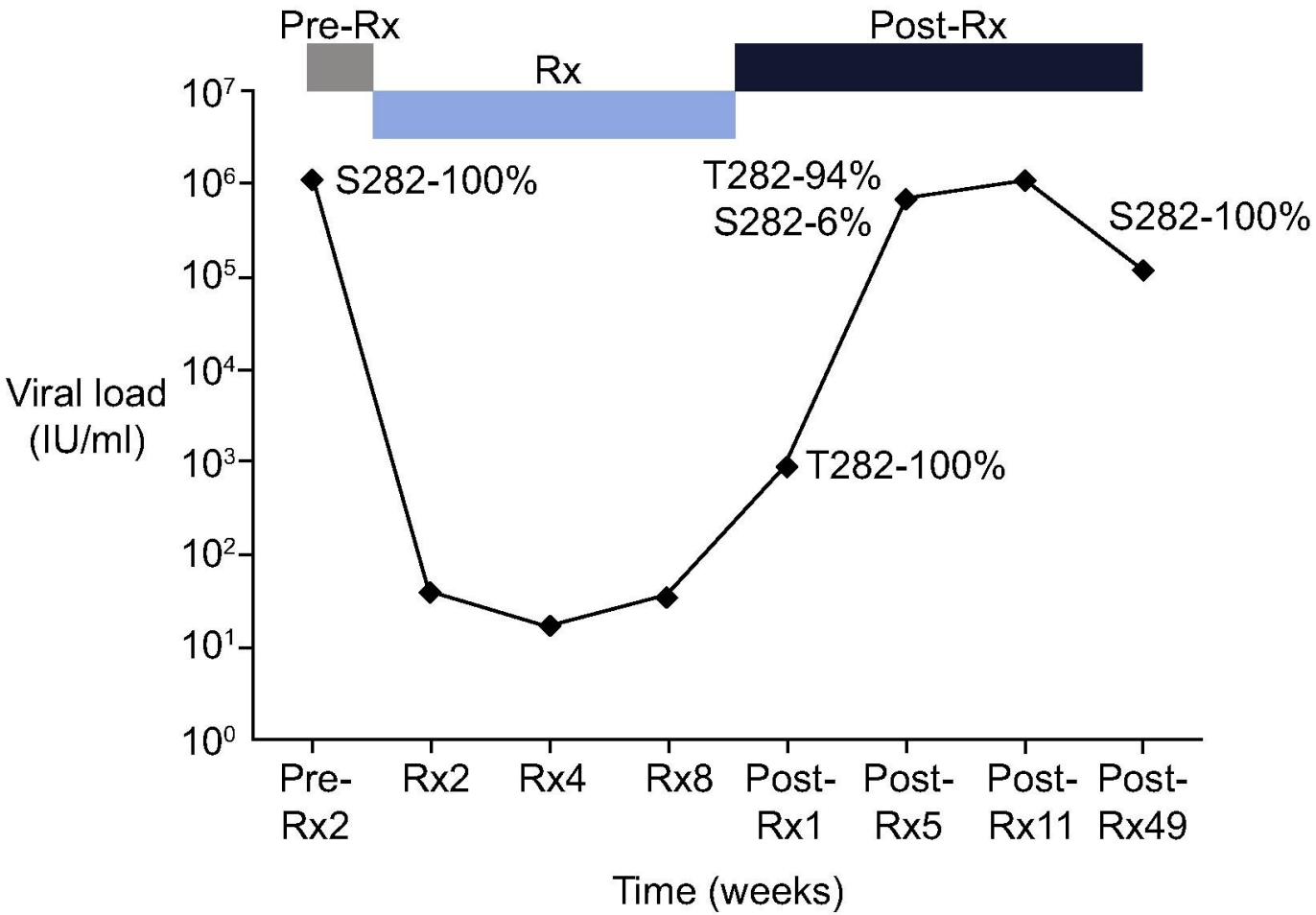
HCV Gt	Subjects/ Reference	DAA Rx	Rx Outcome (1)	Rx Outcome (2)
Gt1l	P1	SOF/LDV/ RBV	Resp-Rel	Resp-Rel
	P2	SOF/DCV	Resp-Rel	Resp-Rel
	P3	SOF/LDV/ RBV	Resp-Rel	Resp-Rel
Gt4r	P4	SOF/LDV	Non-Resp	Not re-treated
	P5	SOF/LDV/ RBV	Resp-Rel	Not re-treated

da Silva Filipe A, Sreenu V, Hughes J, Aranday-Cortes E, Irving WL, Foster GR, Agarwal K, Rosenberg W, Macdonald D, Richardson P, Aldersley MA, Wiselka M, Ustianowski A, McLauchlan J, Thomson EC. Response to DAA therapy in the NHS England Early Access Programme for rare HCV subtypes from low and middle income countries. J Hepatol. 2017 Aug 5. pii: S0168-8278(17)32195-5.

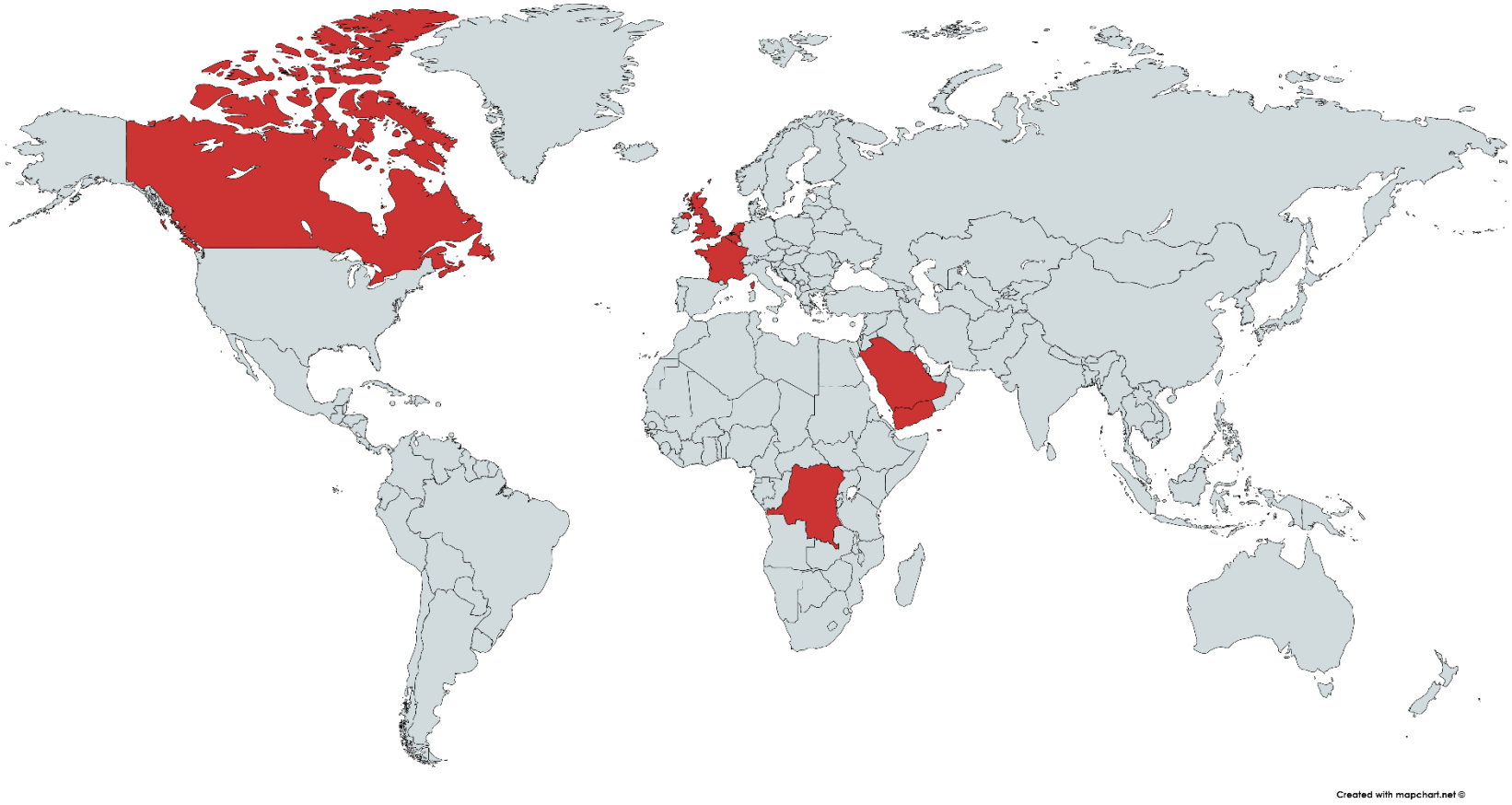
HCV Gt	Subjects/ Reference	DAA Rx	Rx Outcome (1)	Rx Outcome (2)	Timepoint	28	29	30	31	32	58	93
Gt1a	**Gt1a Ref**					M	P	Q	L	P	H	Y
Gt1b	**Gt1b Ref**					L	P	R	L	P	P	Y
Gt1l	**P1**	SOF/LDV / RBV	Resp-Rel	Resp-Rel	Pre-Rx	M	P	R	M	P	P	Y
					Post-Rx	M	P	R	M	P	P	Y
	P2	SOF/DCV	Resp-Rel	Resp-Rel	Pre-Rx	M	P	Q	M	P	P	Y
					Post-Rx	NA						
	P3	SOF/LDV / RBV	Resp-Rel	Resp-Rel	Pre-Rx	M	P	R	M	P	P	Y
					Post-Rx	M	P	R	M	P	P	Y
Gt4a	**Gt4a ref**					V	P	L	M	P	P	Y
Gt4r	**P4**	SOF/LDV	Non-Resp	Not re-treated	Pre-Rx	M	P	R	M	P	P	Y
					Post-Rx	M	P	R	M	P	P	Y
	P5	SOF/LDV / RBV	Resp-Rel	Not re-treated	Pre-Rx	M	P	R	L	P	P	Y

da Silva Filipe A, Sreenu V, Hughes J, Aranday-Cortes E, Irving WL, Foster GR, Agarwal K, Rosenberg W, Macdonald D, Richardson P, Aldersley MA, Wiselka M, Ustianowski A, McLauchlan J, Thomson EC. Response to DAA therapy in the NHS England Early Access Programme for rare HCV subtypes from low and middle income countries. J Hepatol. 2017 Aug 5. pii: S0168-8278(17)32195-5.

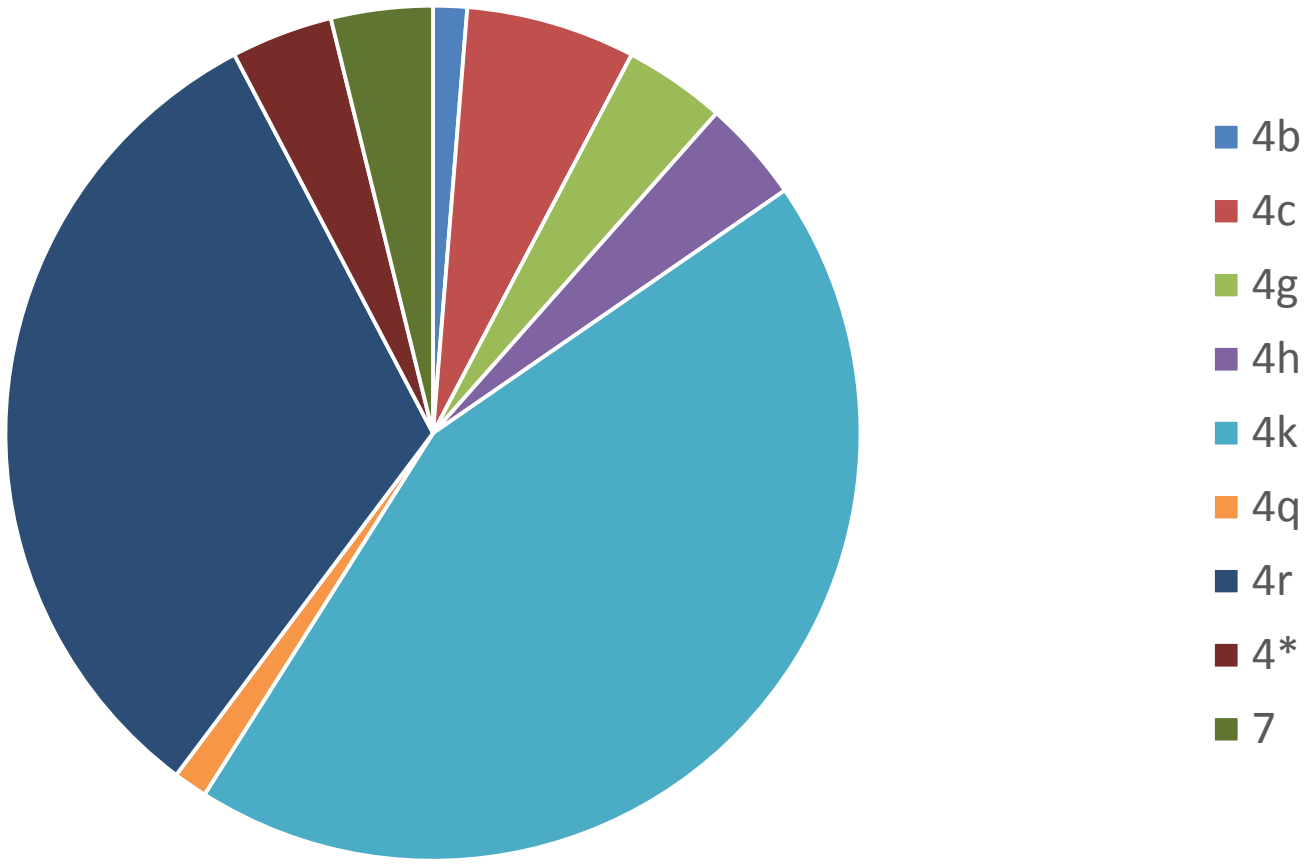
Evolution of S282T mutation in genotype 4r patient in EAP



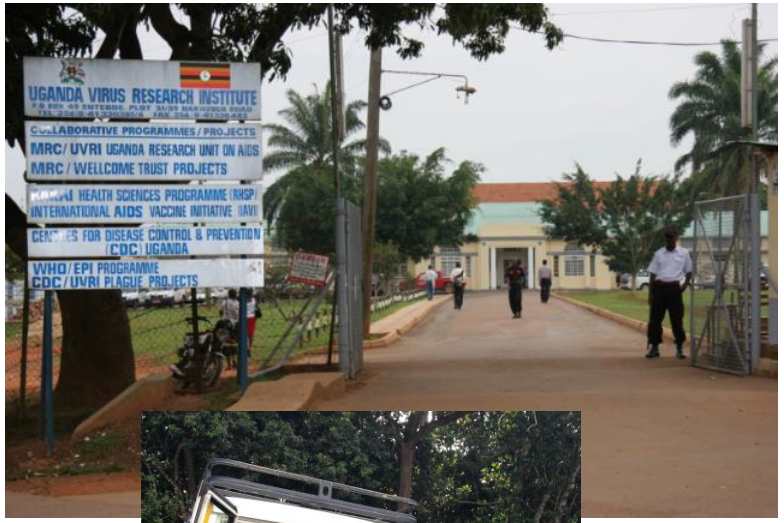
Genotype 4r is rare in Europe and Canada but common in other countries…

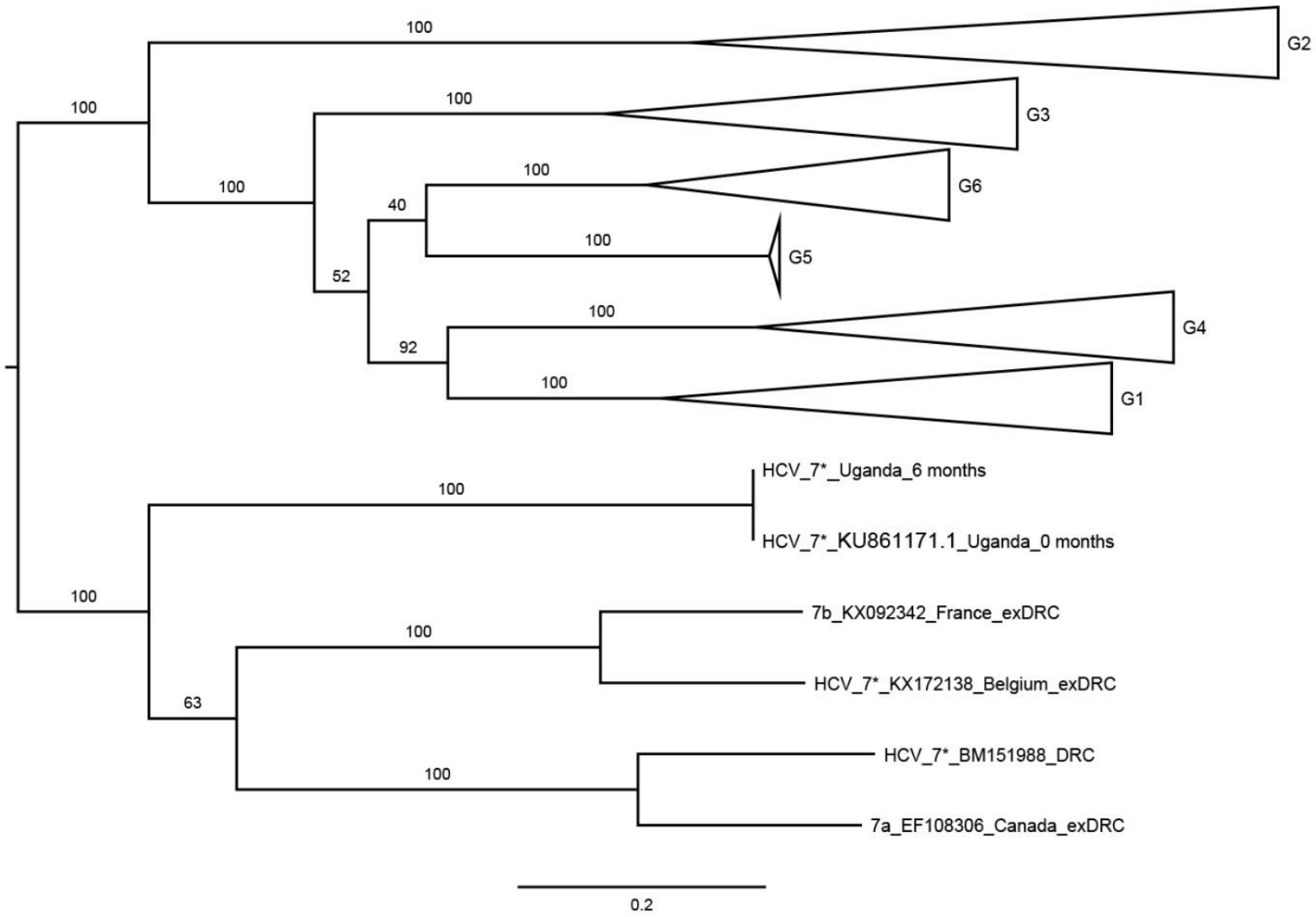


HCV genotype distribution in the Democratic Republic of Congo (DRC)



HCV in Uganda and in DRC





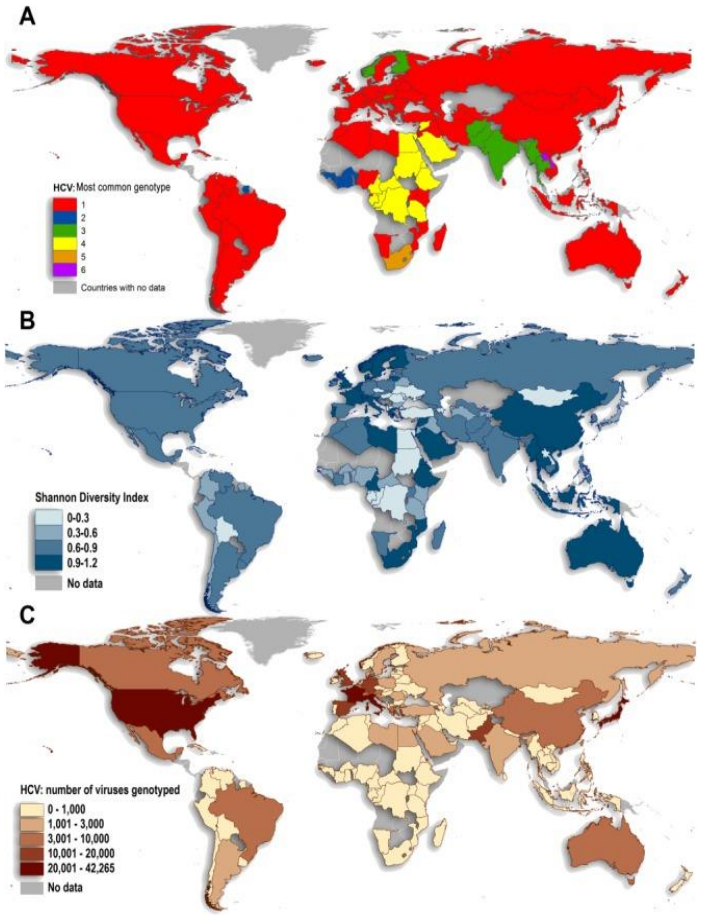
Genotype 7 – predicted resistance

- Genotype 7 is an expanding genotype
- Found in DRC and Uganda
- E2 and NS5A proteins of the 7* sequence contain 1 and 2 additional amino acids compared with genotype 7a.
- Treatment of genotype 7 HCV is not addressed in any treatment guideline…

Gene	Location	*1a	1b	2a	3a	4a	5a	6a	7a	7b	7c	7d
NS3	V36	-	-	L	L	L	L	-	L	L	L	L
NS3	Q41	-	-	-	-	-	-	-	-	-	-	-
NS3	F43	-	-	-	-	-	-	-	-	-	-	-
NS3	T54	-	-	-	-	-	-	-	G	S	-	A
NS3	V55	-	-	-	-	-	L	-	P	-	-	P
NS3	Q80	-	-	G	-	-	K	K	D	E	E	E
NS3	Q86	P	-	P	P	P	P	P	P	P	P	-
NS3	R109	-	-	-	-	-	-	-	-	-	-	-
NS3	R155	-	-	-	-	-	-	-	-	-	-	-
NS3	A156	-	-	-	-	-	-	-	-	-	-	-
NS3	D168	-	-	-	Q	-	E	-	Q	Q	Q	Q
NS3	V170	I	-	I	I	-	-	I	-	R/G	-	-
NS3	E176	-	-	D	S	-	-	-	Q	A	-	Q
NS5A	L23	-	-	-	-	-	-	-	-	-	-	M
NS5A	K24	-	-	T	S	-	Q	Q	-	-	-	-
NS5A	M28	-	-	-	-	V	L	F	L	L	-	L
NS5A	Q30	-	-	-	A	L	-	R	S	S	S	C
NS5A	L31	-	-	M	-	M	-	-	-	-	-	-
NS5A	P32	-	-	-	-	-	-	-	-	-	-	-
NS5A	F37	-	-	-	-	L	-	-	L	L	I	L
NS5A	S38	-	-	-	-	-	-	-	-	-	-	-
NS5A	H54	-	-	T	T	-	S	-	N	T	T	N
NS5A	K56	R	-	R	R	T	-	T	-	M	-	K
NS5A	H58	-	-	P	P	P	P	T	P	P	G	P
NS5A	E62	-	-	N	T	D	T	V	L	N	S	L
NS5A	A92	-	-	C	E	-	-	-	S	-	-	S
NS5A	Y93	-	-	-	-	-	T	T	H	H	H	-
NS5B	L159	-	-	-	-	-	-	-	-	-	-	-
NS5B	S282	-	-	-	-	T	-	-	-	-	-	-
NS5B	C316	-	-	-	-	-	-	-	-	-	-	-
NS5B	L320	-	-	-	-	-	-	-	-	-	-	-

HCV in Uganda and DRC

- Diversity of HCV in sub-Saharan Africa still uncharted territory
- In Uganda genotypes 4q and 4k were found most frequently
- New sub-genotypes of genotype 7 was identified
- *In vitro* and *in vivo* susceptibility to DAAs awaited – no guidelines on genotype 7 treatment
- SOF/VEL effective in 1 patient



Summary

- HCV is now curable in most people and we have pangenotypic regimens
- HCV resistance is currently a problem (when you want to cut costs) and we need to remain vigilant
- There are still gaps in our knowledge about HCV diversity esp in Africa
- We need to eradicate it by 2030!

Acknowledgements

- Oxford
  - –Ellie Barnes
-
- MRC CVR, Glasgow
  - –John McLauchlan
  - –Sreenu Vattipally
  - –Walt Adamson
  - –Ana Filipe
- PHE, Colindale
  - –Tamyo Mbisa
- UCL, London
  - –Judy Breuer
- HCV Research UK
  - –Will Irving
  - –John McLauchlan