Resistencias & Epidemiología

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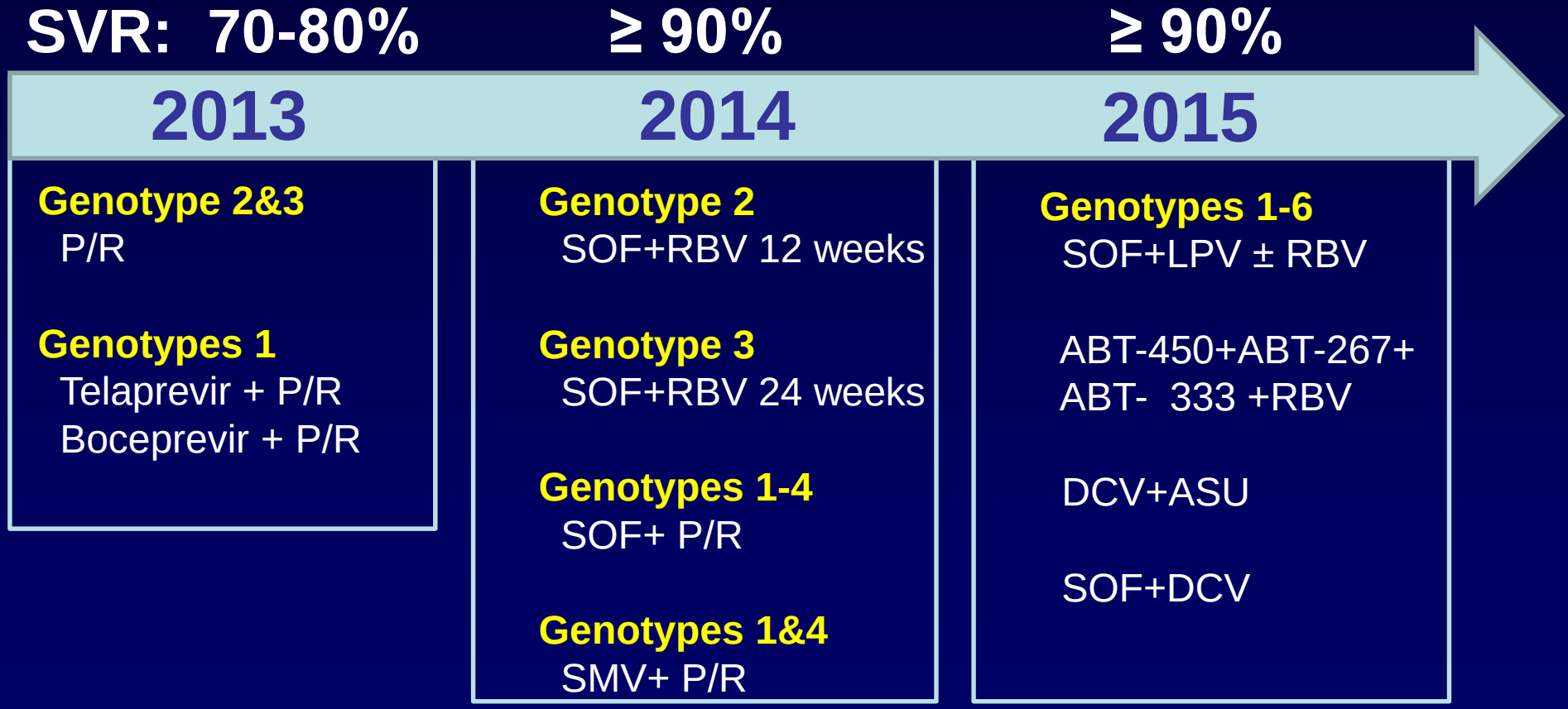
Rapid Evolution of HCV Regimens:

Easier to take/tolerate, Short Duration, Pangenotypic, Higher SVR, Eventually Oral for all patients



HCV Resistance to DAA

During DAA-based treatment:

- Rapid selection of resistance mutation may occur, eventually leading to viral break-through.

Kieffer et al. Hepatology 2007; 46:631-9
Pilot-Matias et al. 46th EASL 2011, Abs1107

- Several changes at different positions at the NS3 protease, NS5B polymerase, and NS5A protein have been associated with loss of susceptibility to DAAs.

Sarrazin et al. Gastroenterology 2010;138:447-62

Main characteristics of the genotype activity and resistance of DAA classes.

	Genotype activity	Resistance	Key resistance mutations
NS3 protease inhibitors	■ ***First PI generation***: genotypes 1 (1b >1a) (**Telaprevir & Boceprevir**) ■ ***Second wave and second PI generation***: across all but genotype 3 (D168Q) (**Simeprevir**, faldaprevir, vaniprevir, asunaprevir, sovaprevir, MK-5172, ACH-2684)	**Low genetic barrier** **High cross-resistance**	**First PI generation:** G1a: **R155K**, V36M G1b: V36M, T54A/S, A156T **Second wave and second PI generation:** F43S, Q80K, **R155K**, D168A/E/H/T/V
NS5 nucleos(ti)de analogues inhibitors	Across all genotypes **Sofosbuvir** displays less antiviral activity againts genotypes 3 (treatment duration 24 weeks of sofosbuvir+RBV).	**High genetic barrier** **High cross-resistance**	Sofosbuvir*: G1a: **S282T**+(I434M) G1b: S282T G2a: S282T+(T179A, M289L, I293L, M434T, and H479P) Mericitabine*: **S282T**+(K81R,S84S/P, I239L, A300F/L/C, A421V, and Y586C)
NS5B non-nucleoside analogues inhibitors	Genotypes 1 (1b>1a)	**Low genetic barrier** Overlapping resistance profile for NNI-site 3 and site 5 inhibitors (C316Y/N and Y448H)	NNI-site 1: A421V, P495L/S, V499A NNI-site 2: L419S, R422K, M423I/L/T NNI-site 3: C316Y/NS368T, Y448C/H, S556G NNI-site 5: C316Y/N, Y448C/H
NS5A inhibitors	■ **First NS5A generation:** genotypes 1-4 (1b>1a) (Daclatastivir, Ledipasvir, ABT-267) ■ **Second NS5A generation:** across all genotypes (MK-8742, ACH-3102, GS-5816, ABT-530)	**Low genetic barrier** **High cross-resistance** **Improved genetic barrier**	G1a: M28T, Q30E/R, L31F/M/V, Y93C/H/N G1b: L31F/M/V, Y93C/H/N

Poveda et al, Antivir Research 2014 (in press)

Prevalence of key polymorphisms at NS3/4A, NS5B polymerase and NS5A protein sequences associated with resistance to DAA agents.

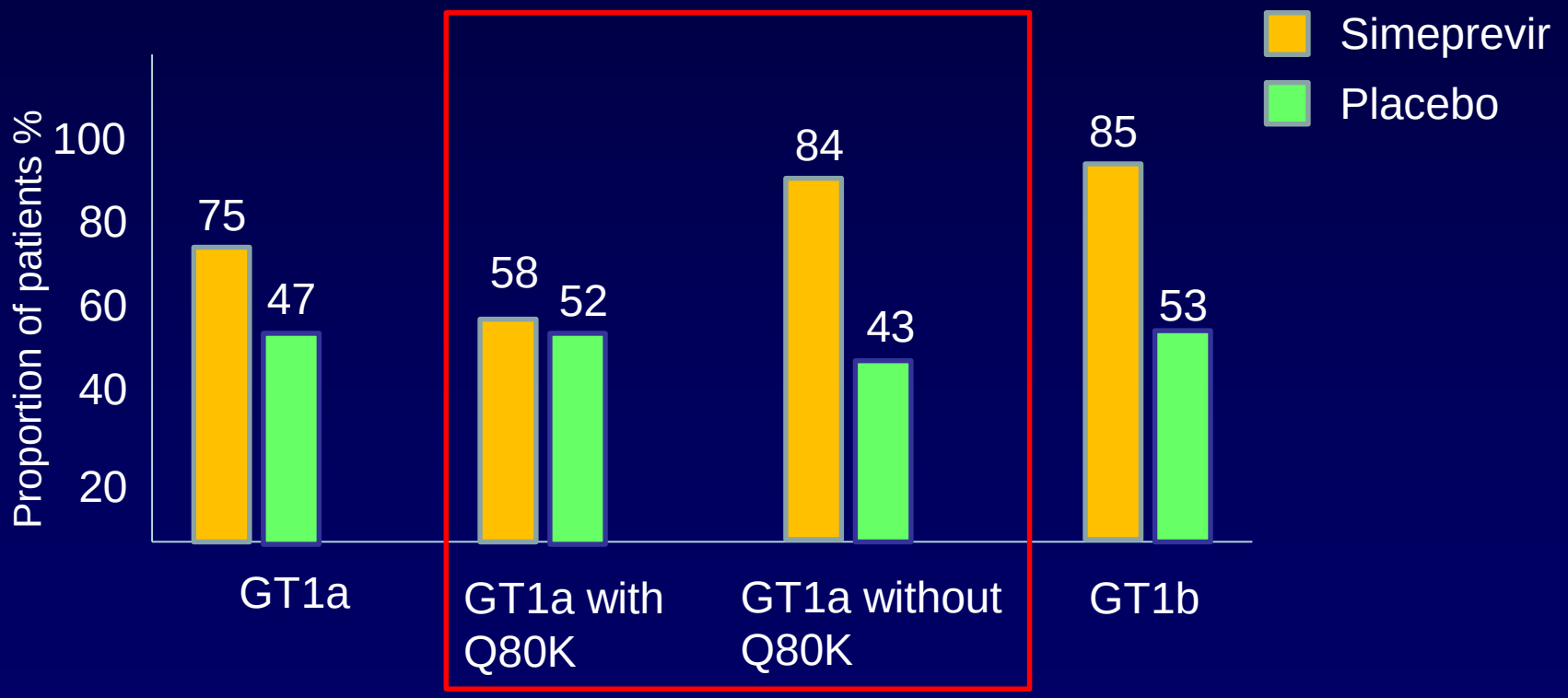
Drug family	Mutation	Fold-change (EC50)	1a	1b	2	3	4	DAA agents potentially affected by specific polymorphisms
NS3/4A protease inhibitors	**Q80K**	10,9	19-48%	0	0	0	0	Simeprevir
	D168Q	> 700	0	0	0	99.2%	0	Second PI generation (with the exception of MK-5172)
NS5B non-nucleoside analogs inhibitors	**C316N**	> 30 *		13,3%				Setrobuvir (NNI-site 3 inhibitors) ABT-072 (NNI-site 3 inhibitors) ABT-333 (NNI-site 3 inhibitors)
	L419V	< 4			13%			Filibuvir (NNI-site 2 inhibitors) VX-222 (NNI-site 2 inhibitors) GS-9669 (NNI-site 2 inhibitors)
NS5A inhibitors	**L31M**	3 - 341		7%				First & second NS5A generation
	Y93H	5,4 - 24		6-12,5%				First & second NS5A generation

*****In combination with mutations Y448H, D559G or Y555C.

Poveda et al, Antivir Research 2014 (in press)

QUEST 1&2: Lower SVR12 rates to Simeprevir among patients with G1a Q80K polymorphism at baseline

Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naive patients: efficacy in difficult-to-treat patient sub-populations in the QUEST-1 and 2 Phase III trials.



Jacobson et al, EASL 2013, Abs 1122

How common is Q80K?

- Prevalence of Q80K and across different regions in simeprevir phase IIB/III studies

	All HCV GT	HCV GT1a	HCV GT1b
Overall	13.7%	29.5%	0.5%
Europe	6.1%	19.4%	0.3%
North America	34.4%	48.1%	0%
South America	3.3%	9.1%	0%

Lenz O et al. AASLD 2013. Abstract 1101

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AASLD

http://www.hcvguidelines.org/full-report-view

last update April 24

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Infectious Diseases Society of America

EASL

European Association for the Study of the Liver

EASL Recommendations on Treatment of Hepatitis C 2014

APRIL 2014

- When treatment with Simeprevir is considered:

For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present.

- This combination is not recommended in patients infected with subtype 1a who have a detectable Q80K substitution in the NS3 protease sequence at baseline, as assessed by population sequencing (direct sequence analysis) **(Recommendation A2)**

Daclatasvir+RBV+pegIFN *alfa-2a vs. alfa-2b* in treatment-naive and IFN-experienced HCV G1 infected patients.

- N=36 patients (18 treatment naive; 18 IFN-experienced):

  9 experienced virological failure

- Patient's profile at failure:

Treatment naive (n=1):	IFN-experienced (n=8):
- Baseline polymorphism: Y93H - Non-CC IL28	- 7 non-CC IL28B - All baseline polymorphisms :L28M(1),L31V/M(2), R30Q(1), Q54H(5), Q62R(1), A92T(1).

- The most common emergent variants associated with DCV resistance were: L31V/M and Y93H.

McPhee et al, EASL Barcelona 2012

Impact of baseline polymorphism know to confer loss of susceptibility to Daclatasvir among patients receiving Daclatasvir plus Sofosbuvir.

Prevalence of baseline polymorphisms:

8% of G1 untreated patients
8% of G1 treated patients
61% of G2
28% of G3

All patients but one with preexisting daclatasvir resistance variants had a sustained virologic response

Number of Patients	HCV Genotype	Polymorphism(s) at NS5A Amino Acid Positions	Virologic Outcome
1	1a	30H/R	SVR_{48}
1	1a	M28T	SVR_{24}
1	1a	Q30H-Y93H	SVR_{12}
1	1a	Q30E, Y93N	SVR_{48}
1	1a	Y93C	SVR_{36}
1	1a	Q30H	SVR_{36}
1	1a	L31M	SVR_4, then lost to follow-up
1	1a	Q30H-L31M	SVR_{36}
1	1a	Y93N	SVR_{48}
1	1b	R30Q-L31M	SVR_{48}
2	1b	L31M	SVR_{12}, SVR_{36}
1	1b	Y93H	SVR_{36}
13	2	L31M	SVR_{48} (all)
1	2	L31M-P58S	SVR_{24}
1	3	A30K	Relapse
1	3	A30K, L31M	SVR_{48}
3	3	Y93H	SVR_{48} (all)

Sulkowski et al., N Engl J Med 2014; 370:211-21

Lack of impact of baseline resistance-associated variants (RAVs) on treatment outcome in the **AVIATOR** study with **ABT-450/r**, **ABT-333**, & **ABT-267**+/- ribavirin

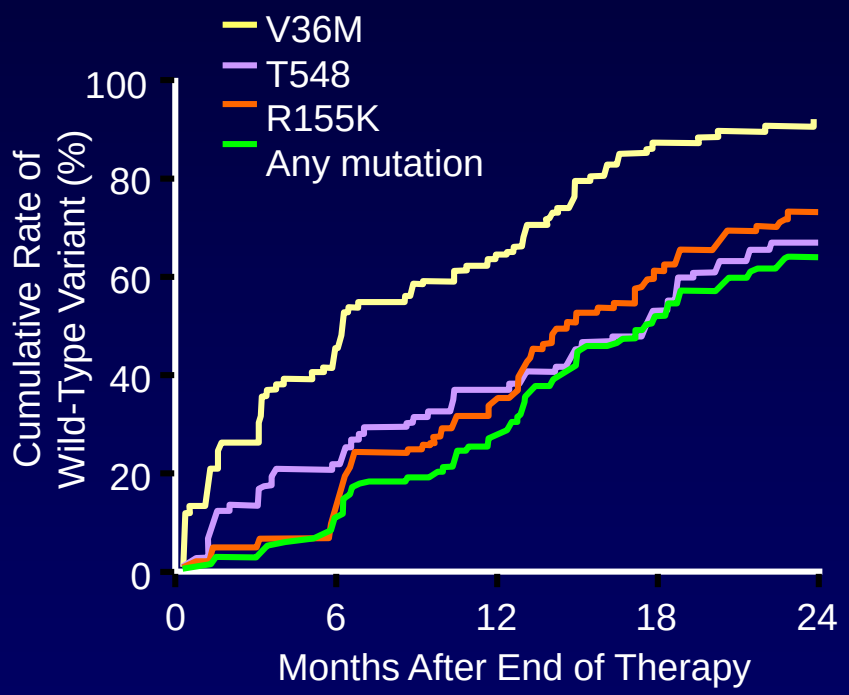
NS3 RAVs	N (%)	NS5A RAVs	N (%)	NS5B RAVs	N (%)
1a- V36A/L/M D168A	7/230 (3) 1/230 (0,4)	**1a-M28T/V** **1a-Q30H/R** 1a-L31M/V 1a-H58C/P/Q/R/Y 1a-Y93C/H/N 1b-R30Q **1b-L31I/M** 1b-P58A/L/R/S/T **1b-Y93H**	**15/235 (6,4)** **8/235 (3,4)** 2/235 (0,8) 11/235 (4,7) 6/235 (2,5) 11/130 (8,5) **8/130 (6,1)** 9/130 (6,9) **7/130 (5,4)**	1a-C316Y 1a-M414T 1a-A553G 1a-S556G/N/R 1b-C316H/K/N/W 1b-S368A 1b-M414L 1b-C445F 1b-S556G	2/258 (0,8) 1/258 (0,4) 1/258 (0,4) 10/258 (3,9) 25/125 (0,2) 1/125 (0,8) 1/125 (0,8) 2/125 (1,6) 20/125 (16)

SVR12 rate of 92,8% in subjects with ≥ 1 RAV was comparable to that subjects with no RAVs, 93,2%)

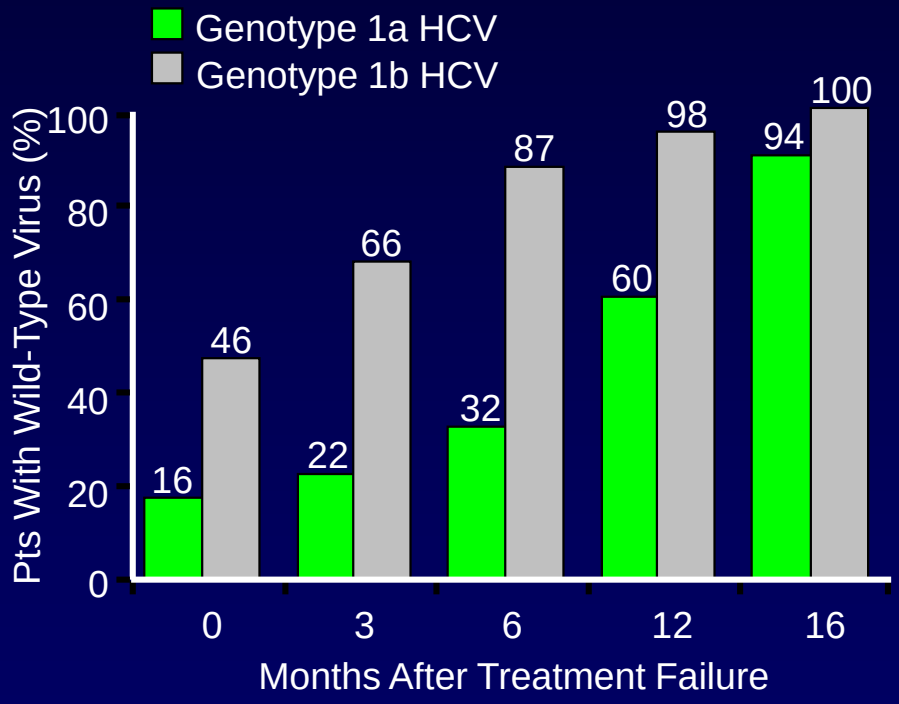
Krishnan et al, EASL London 2014

Loss of Detectable Resistance in Patients Stopping BOC or TVR + PegIFN/RBV

Boceprevir*[1]



Telaprevir[2]



*Data from phase II studies.

1. Vierling JM, et al. EASL 2010. Abstract 2016.
2. Sullivan J, et al. EASL 2011. Abstract 8.

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Patients in whom previous treatment with PEG/RBV plus either telaprevir or boceprevir has failed †† †††***

1	SOF x 12 weeks + PEG/RBV x 12-24 weeks	SOF + RBV x 24 weeks‡	PEG/RBV ± telaprevir or boceprevir or SMV
			Monotherapy with PEG, RBV, or a DAA
		SOF + PEG/RBV x 24 weeks‡‡	Do not treat decompensated cirrhosis with PEG or SMV

*** Non-responder is defined as partial or null response to treatment with PEG/RBV plus telaprevir or boceprevir. Relapse to prior therapy should be treated the same as treatment naive (see Initial Treatment section)

†† A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure not provided due to potential risk of preexistant resistance to protease inhibitor treatment.

Role of HCV resistance in DAA-based therapies

1. *Treatment naive patients and retreatment after PEG/RBV treatment failure.*

- Protease inhibitors: Baseline resistance testing for **Q80K** among genotypes 1a when SMV is considered.
  The impact of Q80K can be minimized with DAAs combinations (i.e. SOF).

- Sofosbuvir: There is no pre-existing RAVs, therefore, resistance testing is not recommended.

- NS5A inhibitors: There is a link between baseline RAVs and treatment failure. However, combined with another potent DAA like SOF the rates of failure is very low and is not associated with pre-existing RAVs.

2. *Retreatment after failure of conventional TVR/BOC triple therapy.*

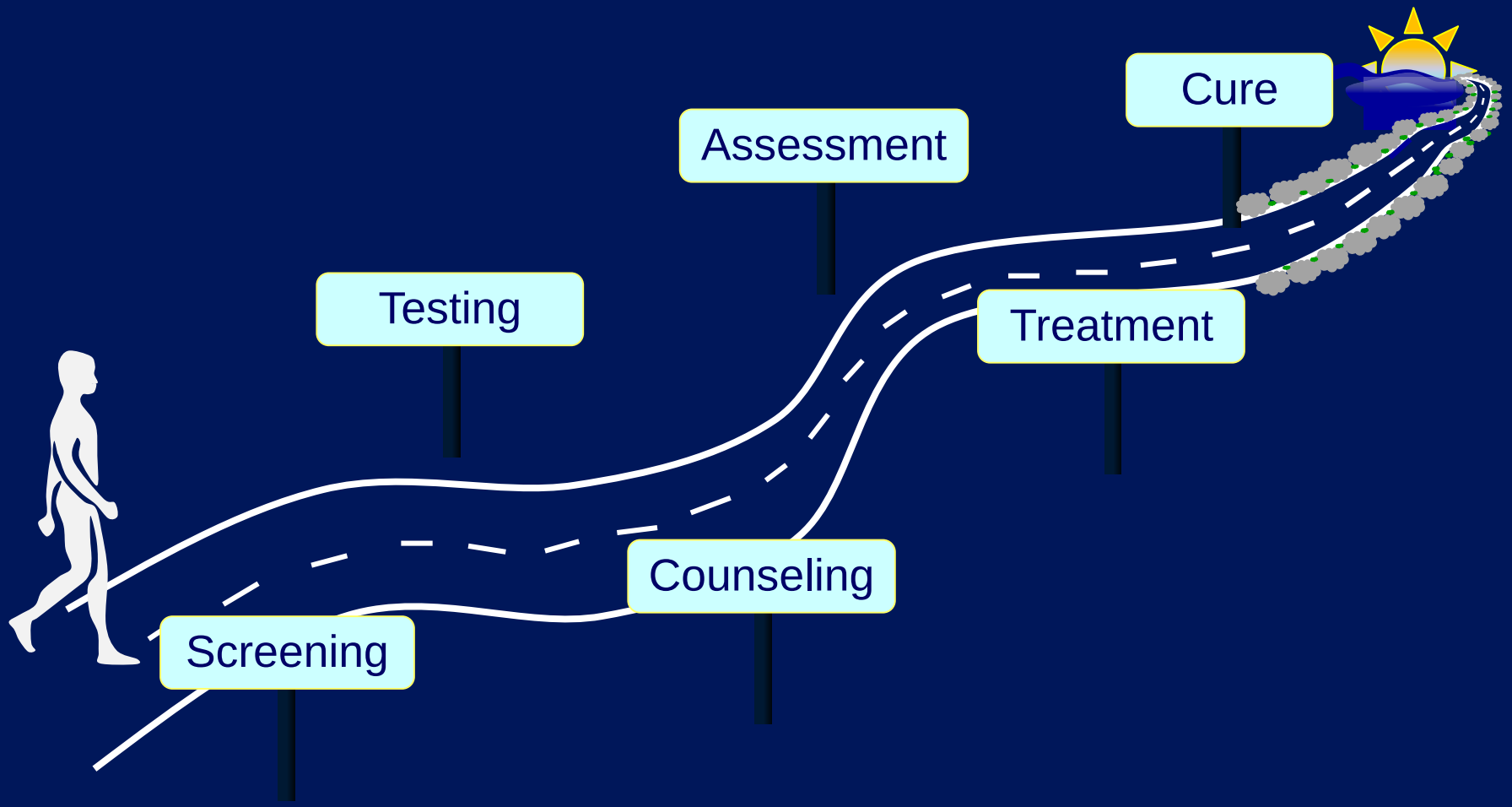
- Protease inhibitors: Cross-resistance and potential risk of pre-existing variants.
  Treatment with PIs is not recommended

- Sofosbuvir&NS5A inhibitors: No cross-resistance. Resistance testing is not recommended.

New Era for the treatmet of HCV infection:

“Test all, Treat hard and short, and Cure most”

HCV Screening Is the First Step on the Road to a Cure



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HCV testing is recommended at least once for persons born between 1945 and 1965.

Rating: Class I, Level B

Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons withbehaviors, exposures, and conditions associated with an increased risk of HCV infection.

45%-

■ Barriers to testing include inadequate health insurance coverage and limited access to regular health.

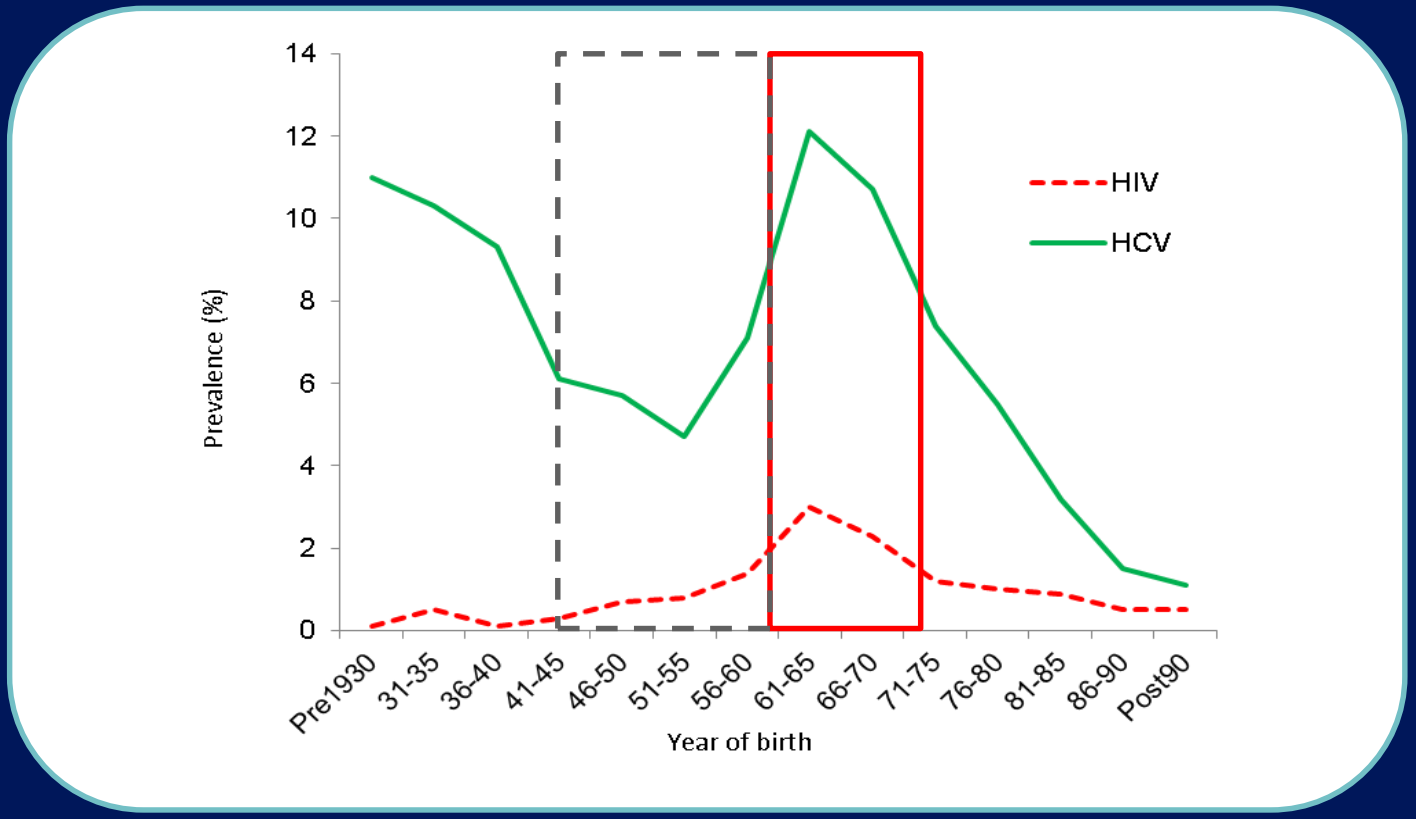
■ 41,7 % of primary care physicians reported being unfamiliar with the guidelines on HCV testing from the American Association for the study of Liver Disease (AASLD).

Rate of HCV infection in Birth Cohort Testing (1945-1965)

Study	Target population	City/Country	Period	HCV-infection (%)
Backus et al., AASLD 2013	US Veterans	USA	2012	9,9 %
Yartel et al., AASLD 2013	Primary Care Patients	USA	2005-2010 (retrospective)	6,4%
Galbraith et al., AASLD 2013	Emergency Department	Alabama/USA	2012	10,4%
Geboy et al., CROI 2014	Primary Care Patients	Washington/USA	2012-2013	9%

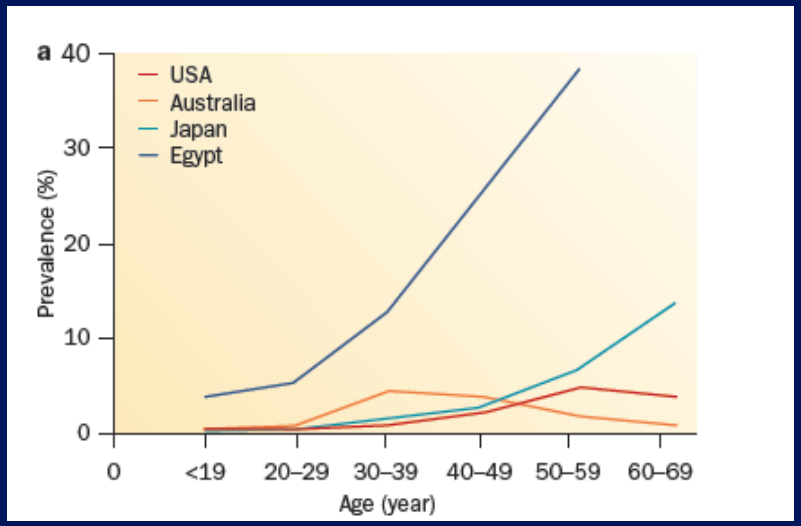
Trends in the seroprevalence of HBV, HCV, and HIV infection at a reference medical center in Spain over the last five years.

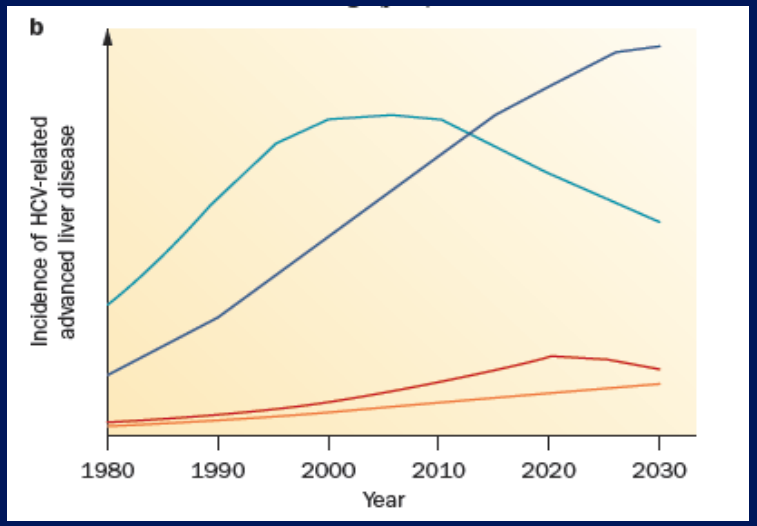
■ A total of **92,143** anti-HCV results were generated during the **last 5 years from** subjects attending our medical care area with a global prevalence of anti-HCV+ of **8,6%**.



Mena et al, EASL London 2014

Age-specific prevalence of HCV infection - incidence of HCV-related advanced liver disease





Hajarizadeh et al, Nature Rev 2013

- In Europe patients now chronically infected with HCV will represent a heavy disease burden in the coming years:

The disease burden of chronic hepatitis C virus (HCV) infection in Switzerland.

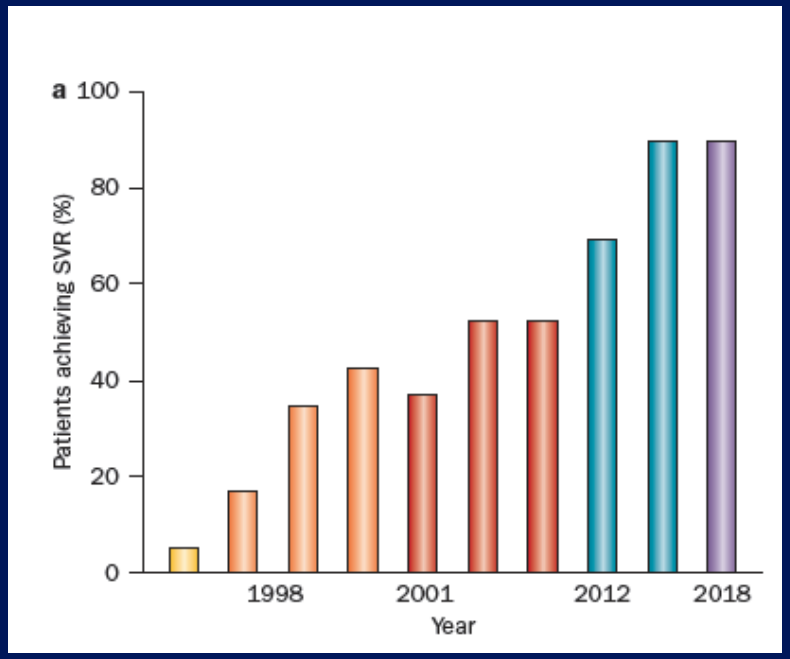
HCV progression and mortality was modeled to 2030:
- Cases of cirrhosis increase by 60%.
- Cases of decompensated cirrhosis by 75%.
- Cases of HCC by 110%.
- Cases of liver-related deaths by 95%.

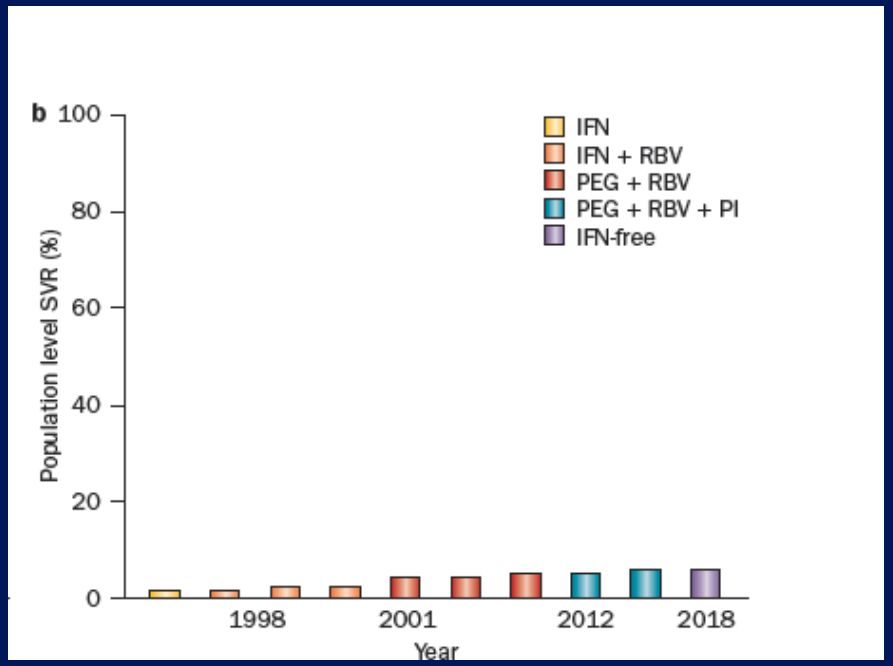
Bruggmann et al EASL London 2014

Low global impact of improving HCV treatment efficacy without expanding HCV testing and treatment initiation

- Most HCV-infected individuals are not patients. Only a small fraction of the estimated 150 million individuals with chronic HCV know they are infected; far fewer ever start treatment.

- USA: 663, 000 of around 4-5 million individuals with chronic HCV were treated (2002-2007).
  Europe: 308, 000 individuals (~ 16% of the HCV-infected patients) received HCV treatment (2006).





Hajarizadeh et al, Nature Rev 2013