Section 6: Treatment of Hepatitis C virus (HCV)

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Training "Hepatitis C and HR for PWUD",

9th-13th May 2016, Hanoi, Vietnam

Learning objective of the session:

understanding and explaining key elements of HCV treatment

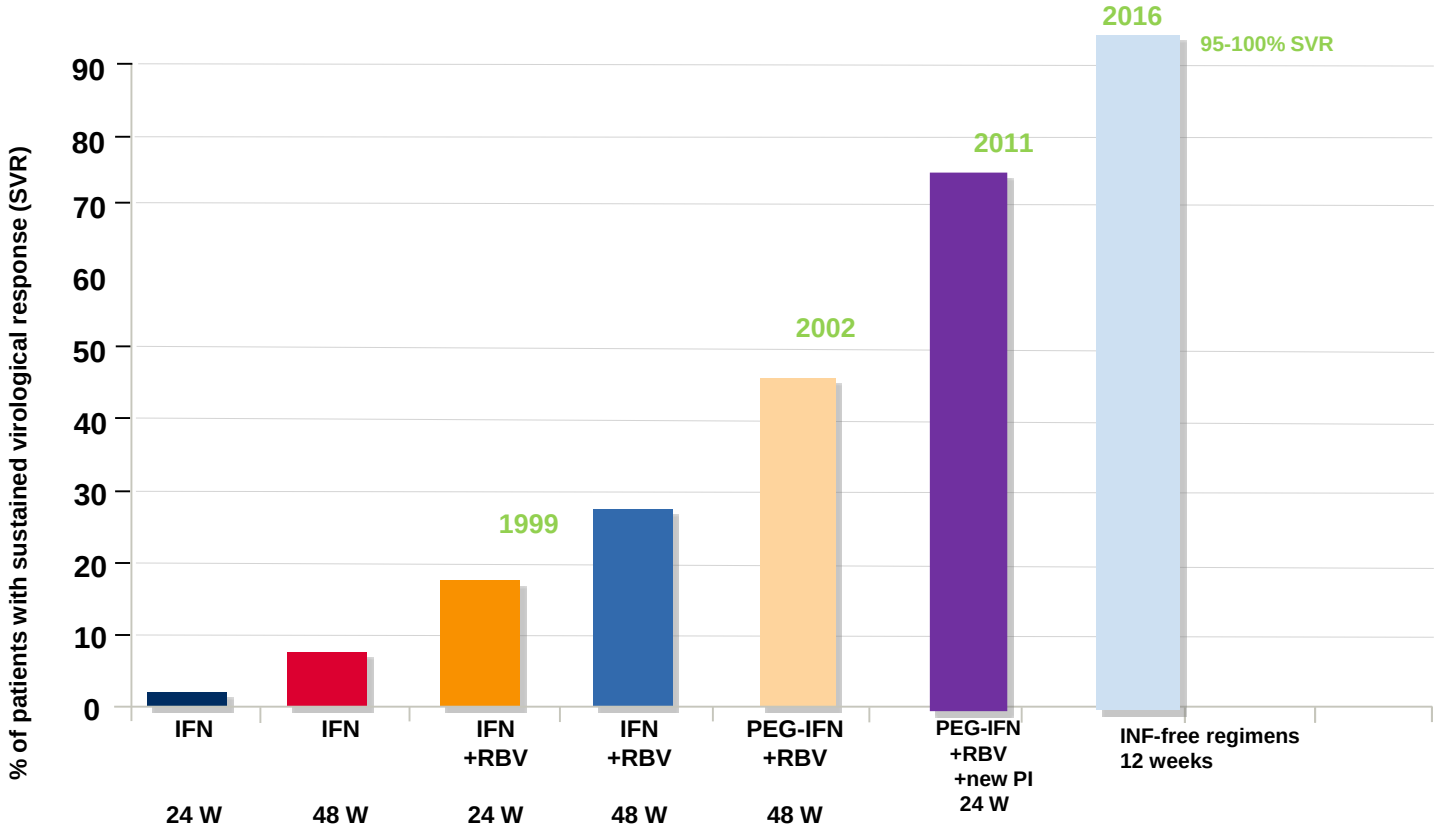
Objective of HCV treatment

- 1st goal of HCV treatment : **cure/to get rid of the virus.** People have cured their HCV when there is no virus in their bloodstream 3 months (12 weeks) after they have finished treatment (this is called **sustained virological response**, or **SVR**).
- 2nd goal of treatment : **reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma.**

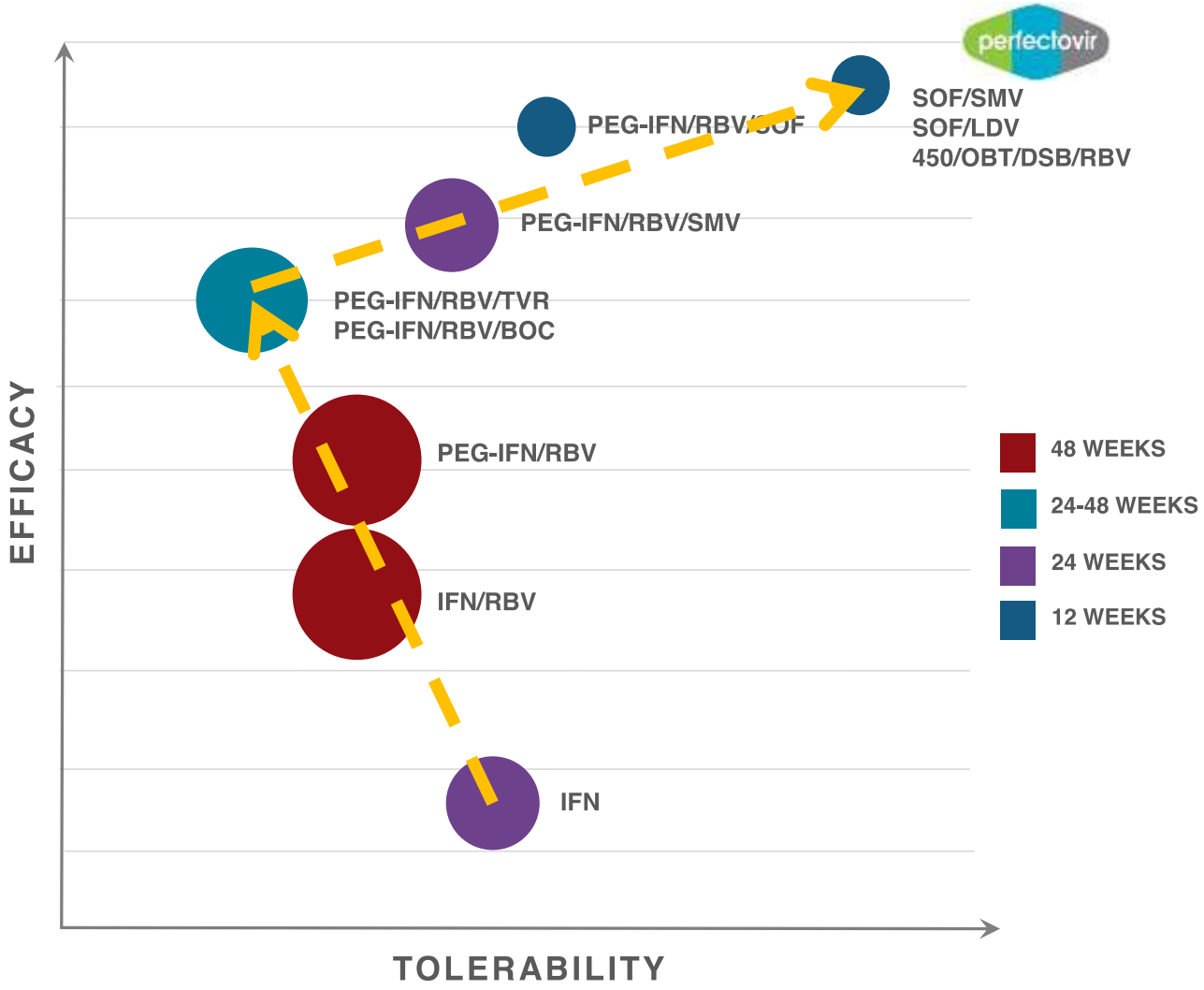
HCV life cycle and treatment

- Hepatitis C virus is replicated in liver cells and can as well be detected in the blood
- Hepatitis C drugs work by blocking different steps in the virus life cycle; this prevents HCV from replicating
- People need to stay on HCV treatment for a certain amount of time to make sure cure is achieved
- Hepatitis C treatment duration depends of the treatment regimen, eventually on the genotypes of the virus, and if the patient has cirrhosis.
- To assess if the treatment has worked, patients need to do a viral load test 12 or 24 weeks after completing the treatment course to measure whether there is still virus in their blood.

Therapeutic development: DAAs



Slide courtesy of Karine Lacombe



Peg-INF + Ribavirin (RBV)

Peg-INF + Ribavirin (RBV)

- General antiviral activity
- Cures rates: 40-80% depending on the genotype
  - **Less effective for people with cirrhosis**
  - **Less effective for people who are HIV+ (especially if they have genotype 1)**
- Duration: 24 to 48 weeks depending of the genotype
- **Heavy side effects:**
  - fatigue (interferon and ribavirin)
  - flulike symptoms: fever, headache, muscle ache (interferon and ribavirin)
  - mild anxiety (interferon)
  - depression (interferon)
  - skin rash (ribavirin)
  - gastrointestinal symptoms: nausea, diarrhea (interferon and ribavirin)
  - Monitoring for severe side effects (eg, marked anemia) is an important part of treatment follow-up

SVR by HCV Genotype with pegylated interferone and RBV

- GENOTYPE 1 ~50%
- GENOTYPE 2 ~75%
- GENOTYPE 3 ~60%
- GENOTYPE 4 40% - 70%
- GENOTYPE 5 49% - 60%
- GENOTYPE 6 60% - 90%

Monitoring in pegINF/RBV treatments

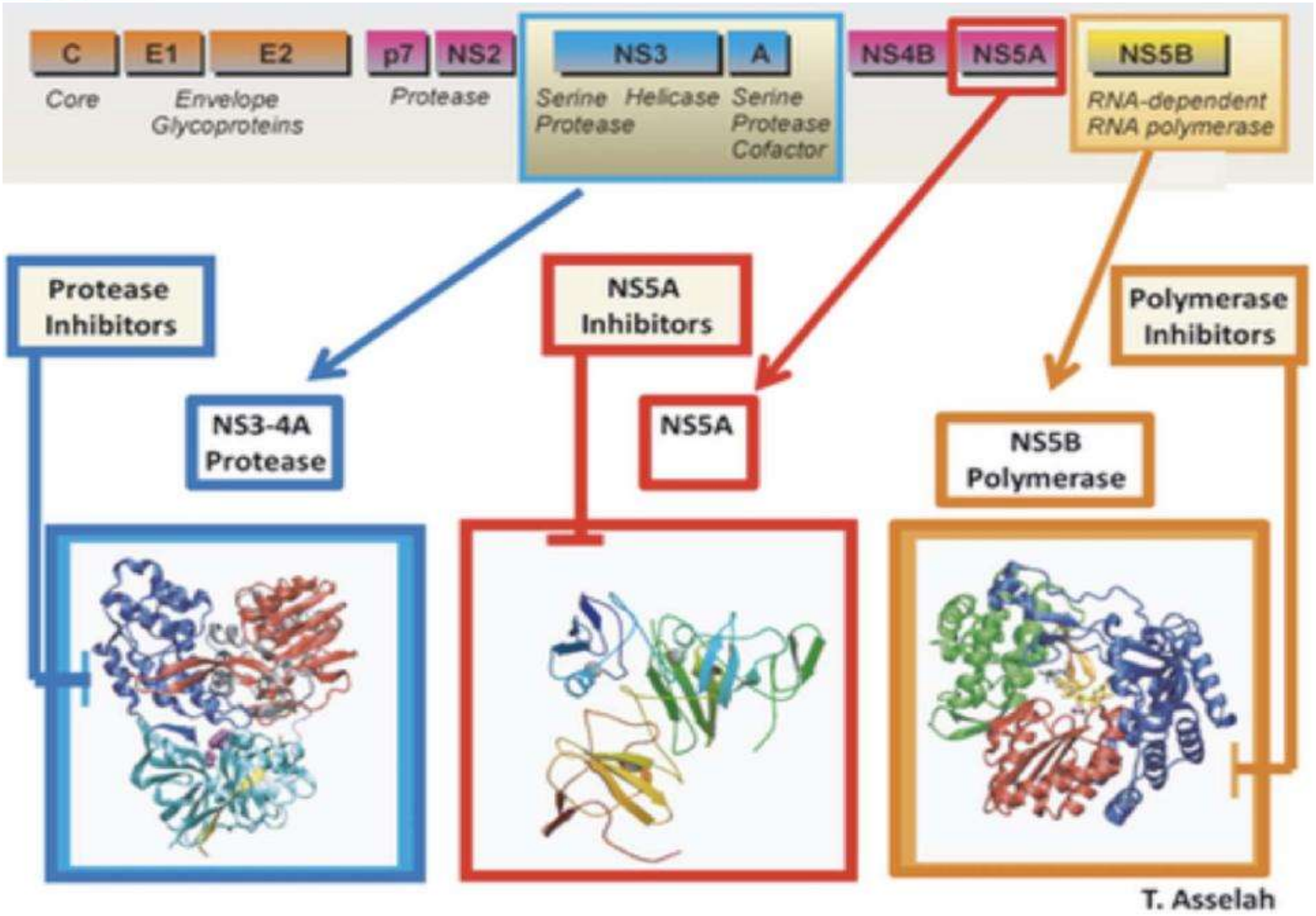
Incidence of side -effects red highest - yellow lowest

	TOXICITY			EFFICACY				
Time	FBC, creatinine, ALT	Thyroid function	Adherence, side effects	IFN/ RBV	IFN/ RBV TEL	IFN/ RBV BOC	IFN/ RBV SMV	IFN/ RBV SOF
● Week 0	X	X	X	X	X	X	X	X
● Week 1[a]	X		X					
● Week 2[a]	X		X					
● Week 4	X		X	X	X	X	X	X
● Week 8	X		X			X		
● Week12 EOT[b]	X	X	X	X	X	X	X	X
● Week24 EOT[c]	X	X	X	X	X	X	X	X
● Week 36	X	X	X			X	X	
● Week48 EOT[d]	X	X	X	X	X	X	X	X[d]
● Week 12 after EOT	X		X					
● Week 24 after EOT	X		X	X	X	X	X	X

Direct-Acting Antivirals (DAAs) for HCV

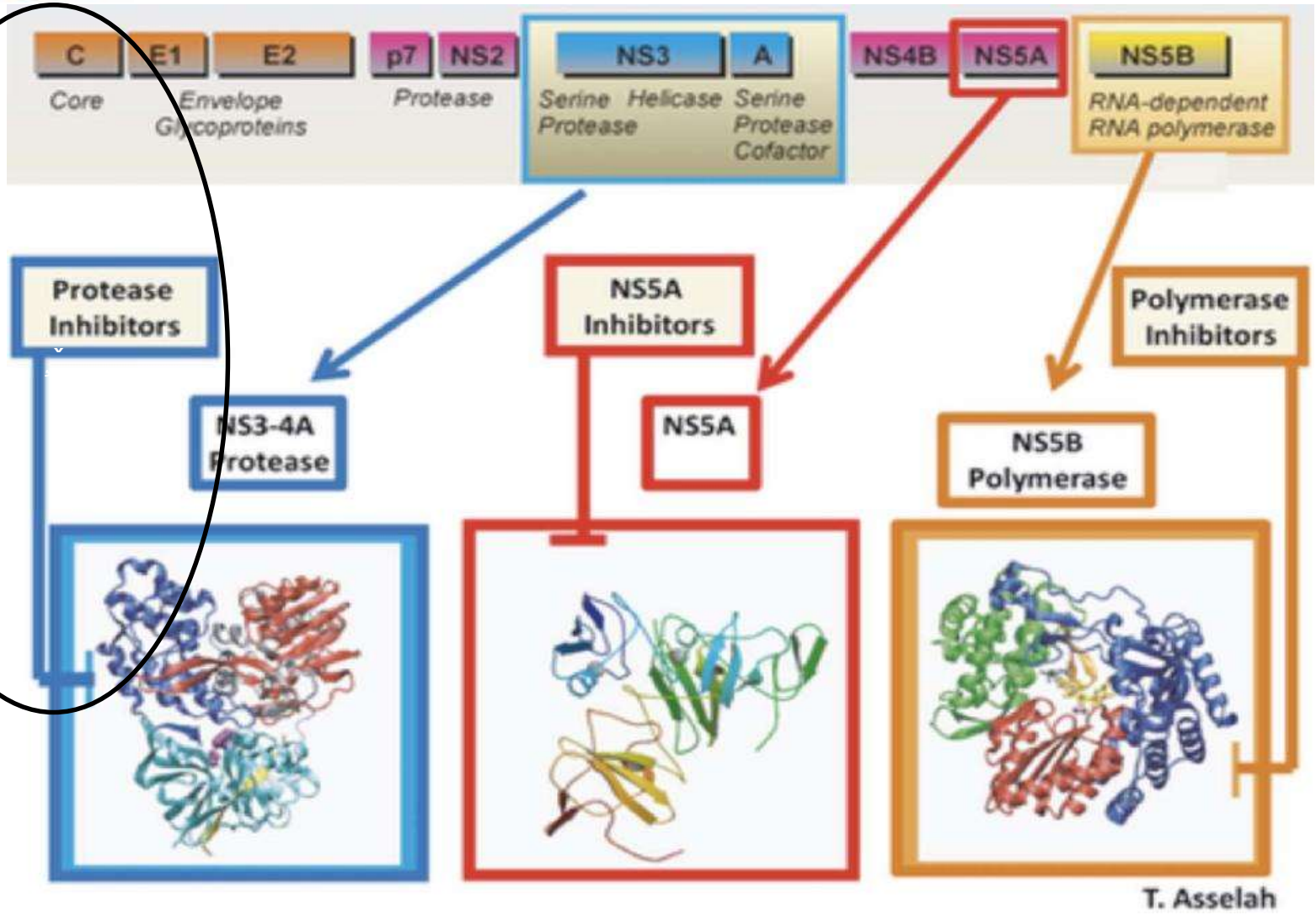
- Oral DAAs are replacing interferon-based treatment as standard of care
- DAAs target different steps of the virus lifecycle, preventing replication

- 4 classes of drugs
  - **(NS3/4A) protease inhibitors (PIs)**
  - **NS5B nucleoside polymerase inhibitors (NPIs)**
  - **NS5B non-nucleoside polymerase inhibitors (NNPIs)**
  - **and NS5A inhibitors**



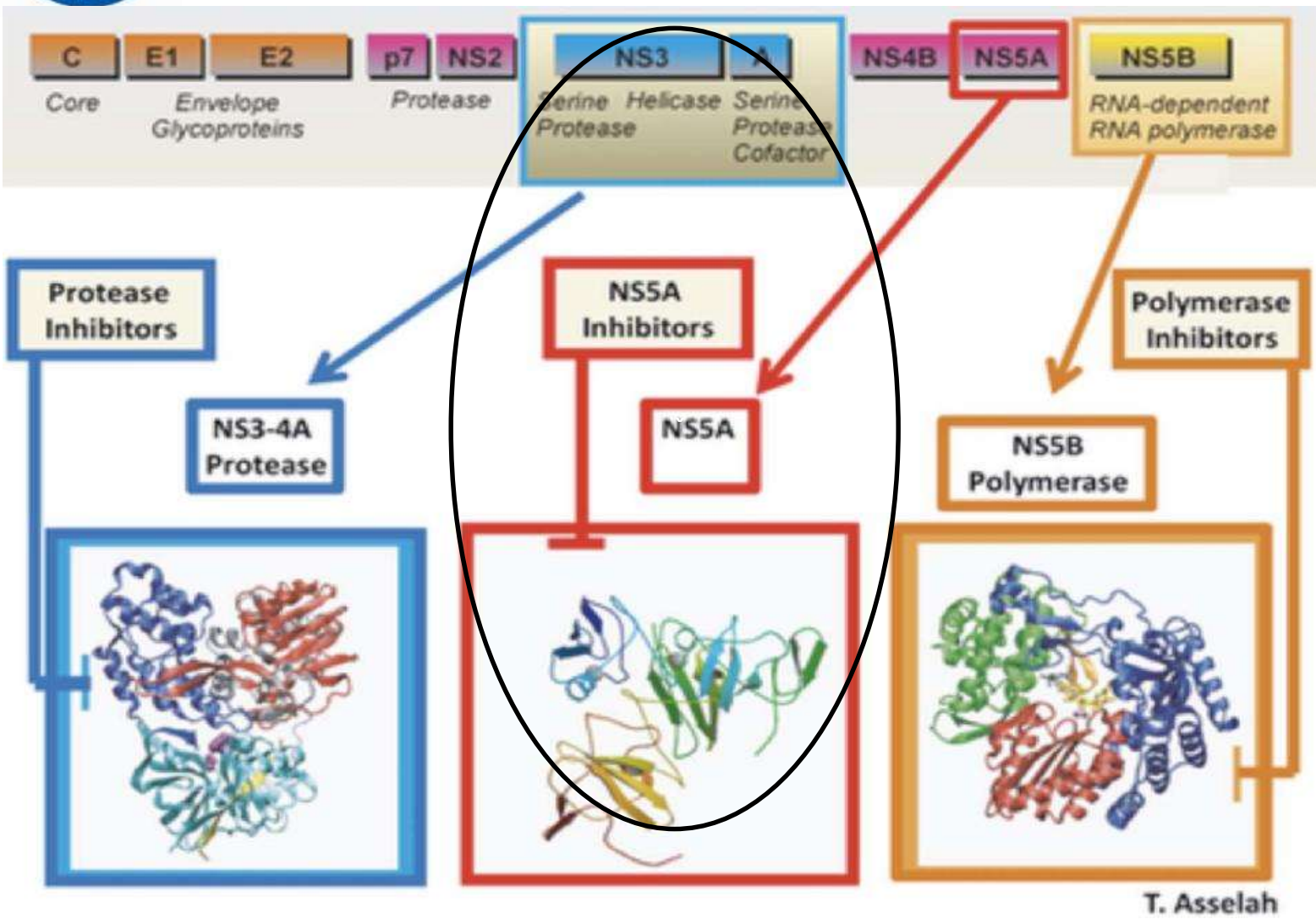
NS5B - HCV Nucleoside/Tide Polymerase Inhibitors: Sofosbuvir

- Drugs ending on –BUVIR
- pan-genotypic
- high resistance barrier
- used with PEG-IFN and RBV, RBV alone, and other DAAs
- few DDIs
- few side effects (but hard to tell, since used with other drugs)
- once-daily



HCV Protease Inhibitors: Simeprevir + PARITAPREVIR/RITONAVIR

- Drugs ending on –REVIR
- First generation: BOCEPREVIR+TELAPREVIR not relevant any more
- active against some genotypes (usually 1 & 4)
- low barrier to resistance
- tend to have DDIs with ARVs and other commonly-used drugs (OST is usually OK)
- used with PEG-IFN/RBV or + other DAAs



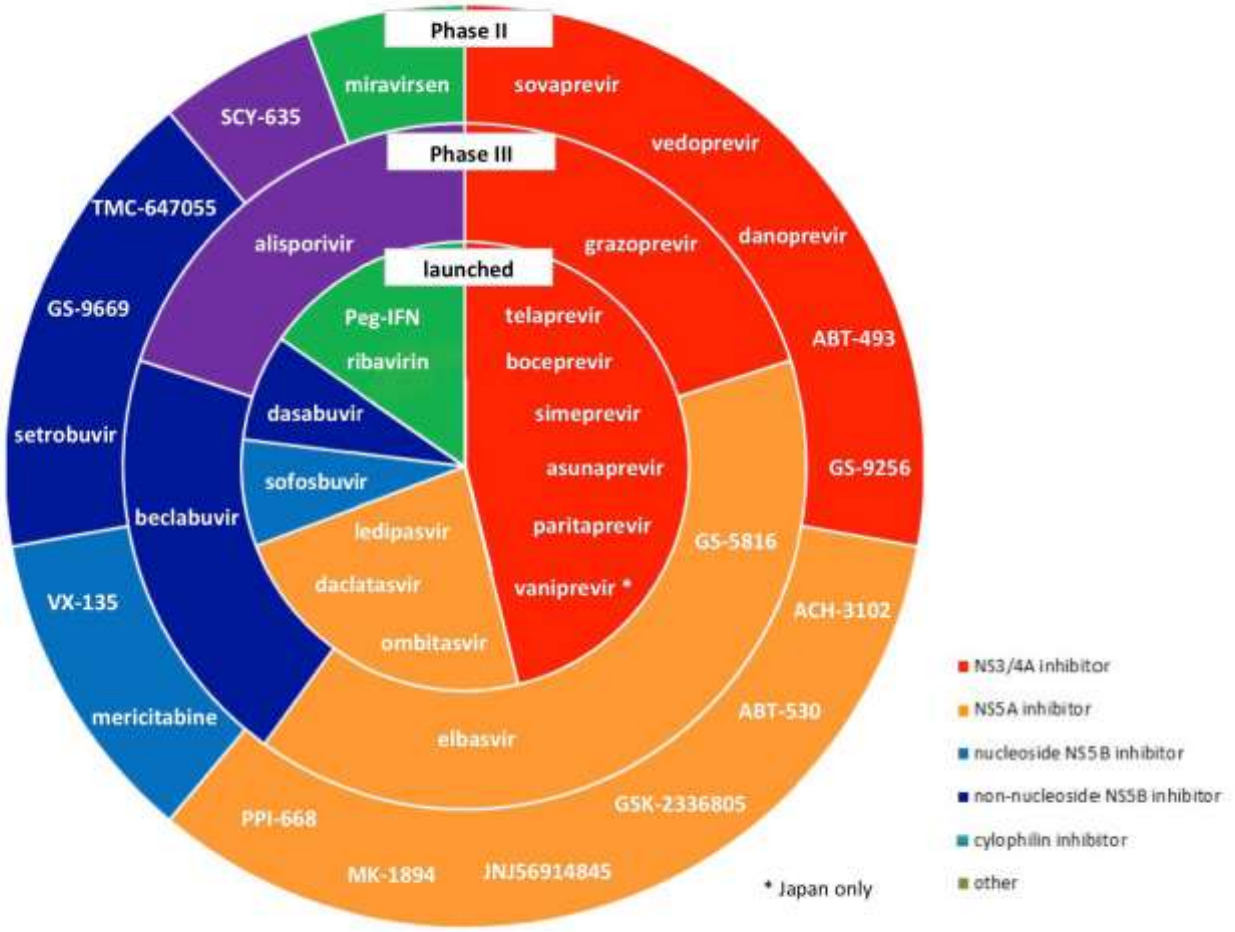
HCV NS5A Inhibitors: LEDIPASVIR + DACLATASVIR (OMBITASVIR)

- Drugs ending on: –ASVIR
- some are pan-genotypic, others not so much
- low resistance barrier
- used with other DAAs, with or without RBV
- Some DDIs
- few side effects
- once-daily

Approved in USA+Europe and evaluated by WHO

- Two fixed-dose combinations
  - **sofosbuvir/ledipasvir (GS)**
  - **and Ombitasvir/paritaprevir/ritonavir plus dasabuvir (Abbvie)**
- Three DAAs
  - **Sofosbuvir (GS)**
  - **Daclatasvir (BMS)**
  - **Simeprevir (J+J)**

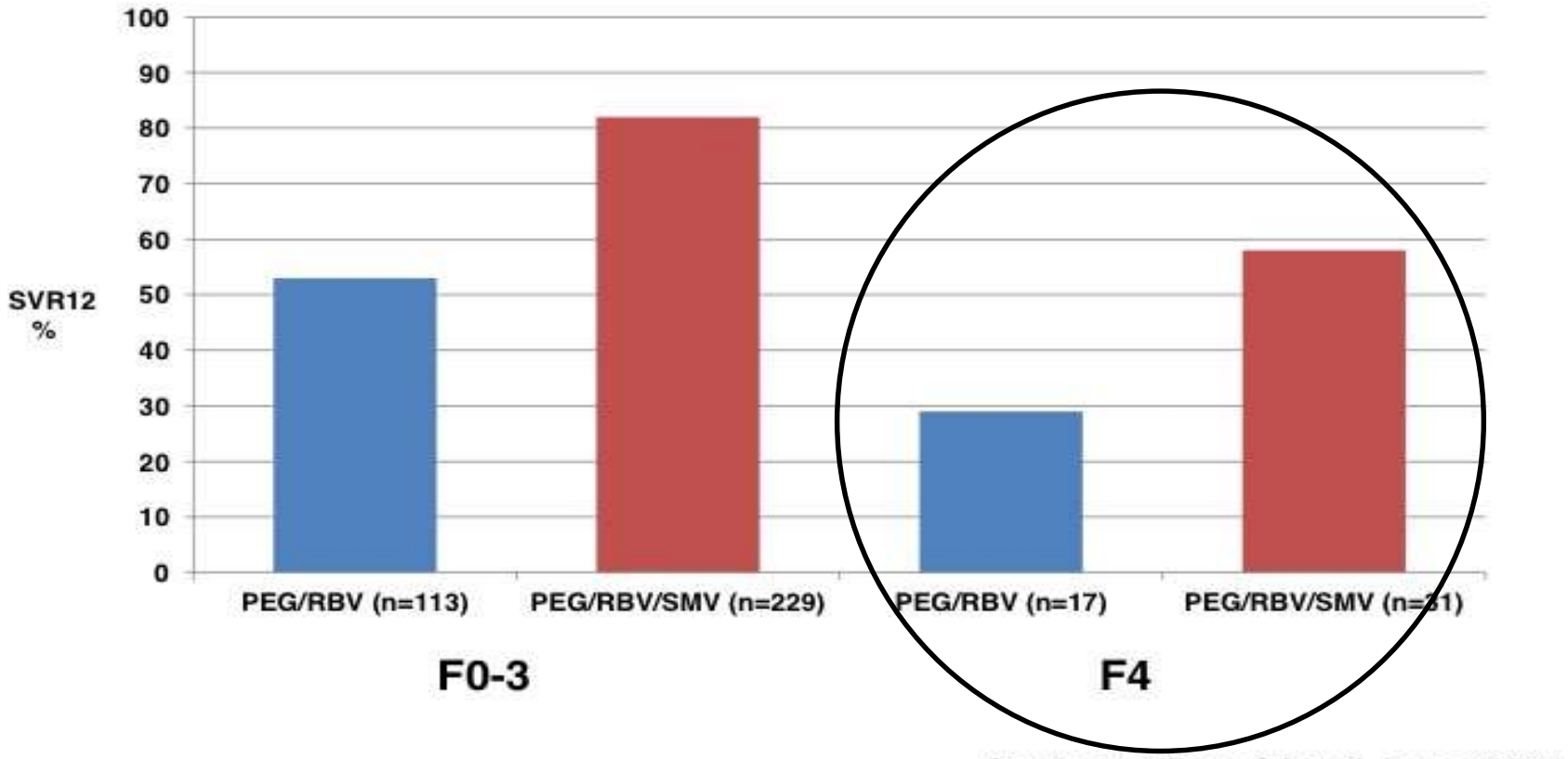
Figure 4. Overview of DAAs on the market and in the pipeline (phase II and III).



Source: UNITAID.

QUEST-1: PEG-IFN/RBV/Simeprevir

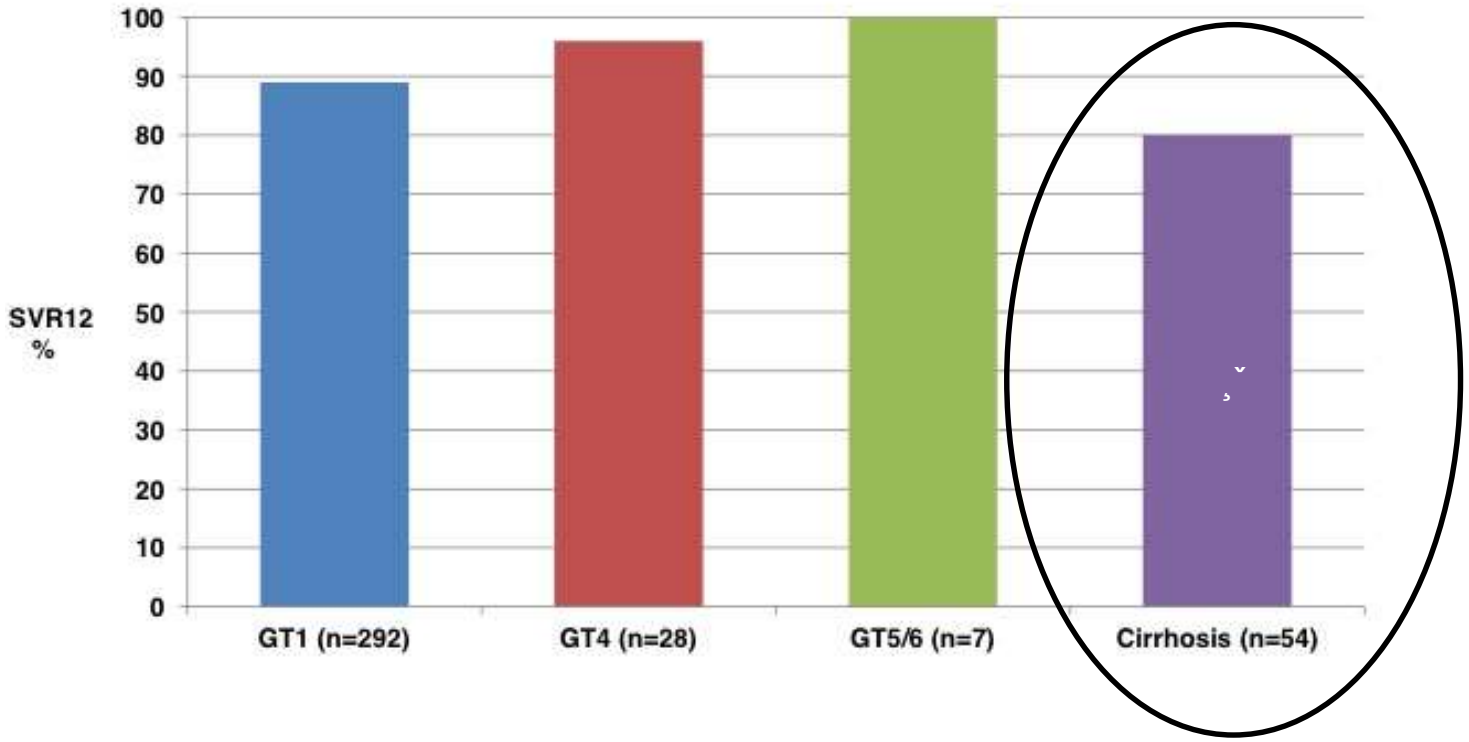
Genotype 1 treatment naïve, 24-48 weeks



Jacobson I, Dore GJ et al. Lancet 2014

NEUTRINO: PEG-IFN/RBV/Sofosbuvir

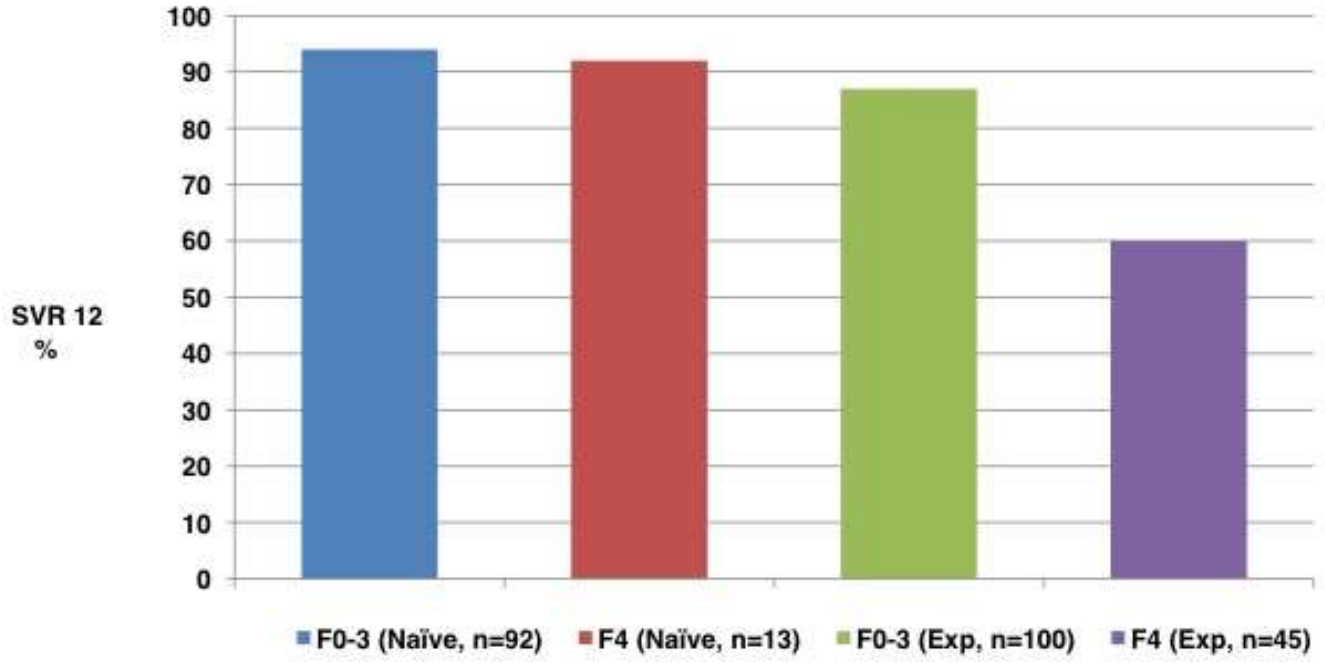
Genotype 1 (+4/5/6) treatment naïve, 12 weeks



Lawitz E et al. NEJM 2013;368:1878-1887

Sofosbuvir/Ribavirin

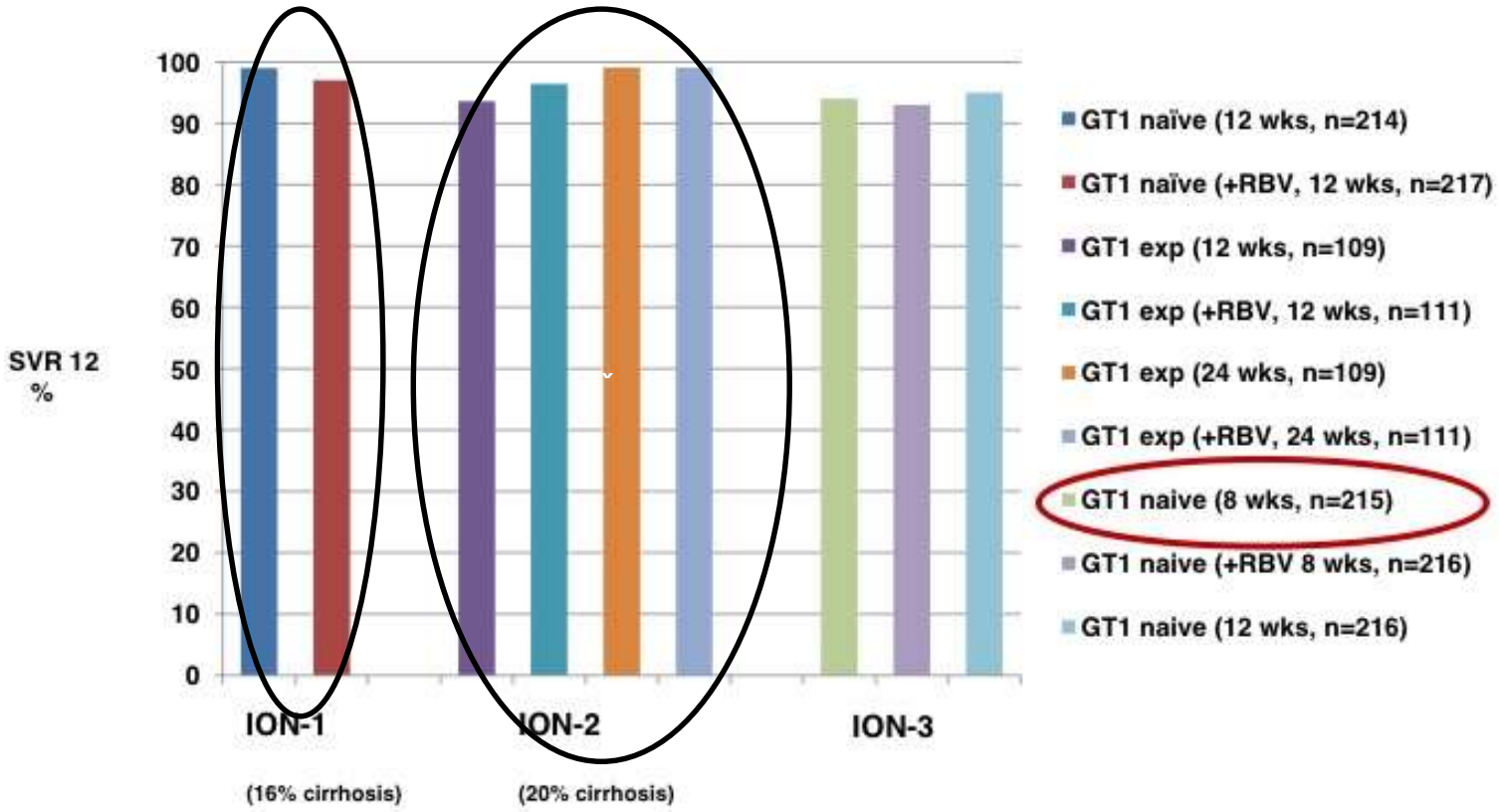
Genotype 3, treatment naïve and experienced, 24 weeks



Zeuzem S et al, AASLD 2013

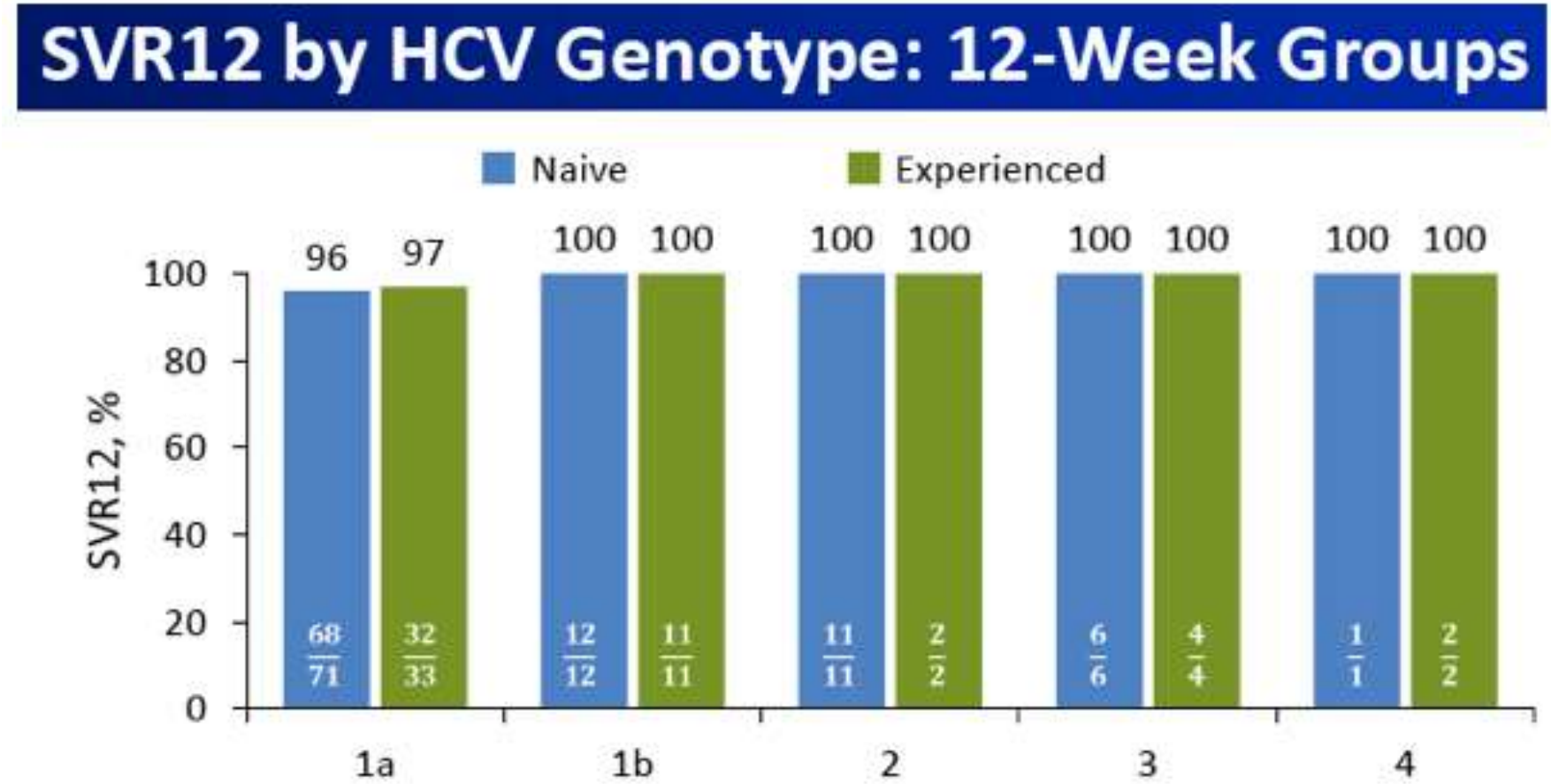
Gilead: Sofosbuvir/Ledipasvir

Genotype 1, treatment naive and experienced



Afdhal N, et al. NEJM 2014;370:1483-1493; Afdhal N, et al. NEJM 2014; Kowdley KV, et al. NEJM 2014

ALLY-2: DAC/SOF in HIV/HCV



DAAs

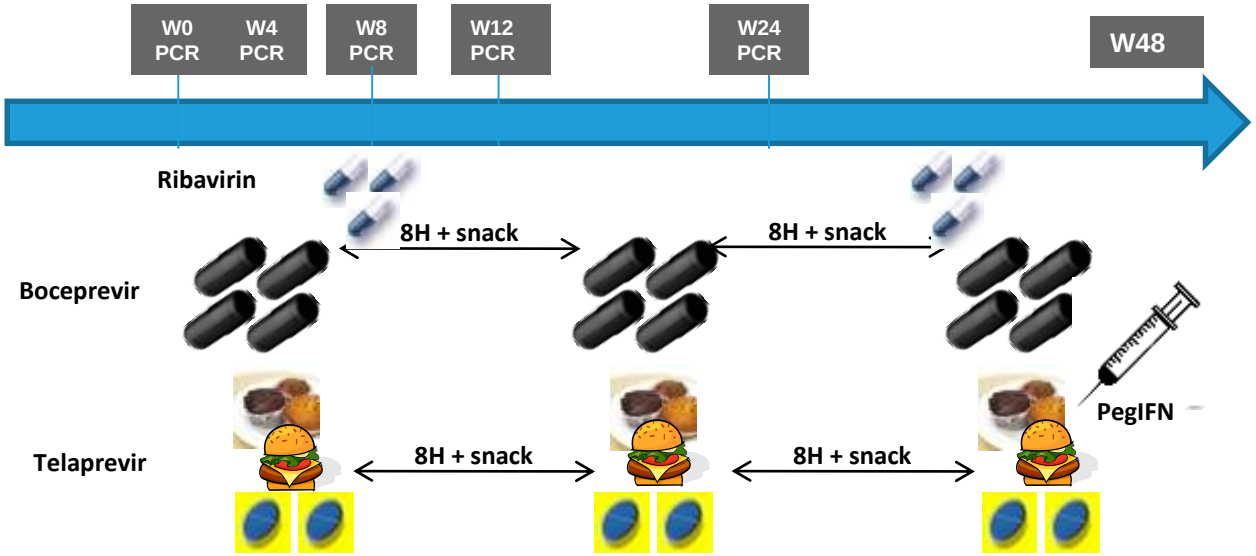
- Radically simplify and improve HCV treatment
- Cure rates have topped 95%—even for people with HIV and people with cirrhosis
- Safe; tolerable: AE-associated discontinuation rates were < 3% across DAA clinical trials, even with RBV
- Because DAAs are so safe and effective, monitoring requirements are minimized – increases feasibility in RLS
- HIV does not impair response to IFN-free DAA therapy
- HCV resistance will not be a major clinical issue

- **Challenges : GT3 + F4 and DDI**

DAAs: perfectovir

Desirable characteristics :

- **Short -** treatment duration : 12 weeks
- **Easy to take** – all oral, no injection, does not require refrigeration
- **Pan-genotypic action:** no genotyping required
- **High activity in chirrosis:** less liver disease assessment



Slide courtesy of Karine Lacombe

Approved in USA+Europe and evaluated by WHO

- Two fixed-dose combinations
  - **sofosbuvir/ledipasvir (GS)**
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- Three DAAs
  - **Sofosbuvir (GS)**
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  - **Simeprevir (J+J)**

WHO 2016 HCV treatment guidelines

TABLE 7.5 Summary of recommended preferred regimens with treatment durations*

Persons without cirrhosis

	Daclatasvir/ sofosbuvir	Ledipasvir/ sofosbuvir	Sofosbuvir/ ribavirin
Genotype 1	12 weeks	12 weeks[a]	
Genotype 2			12 weeks
Genotype 3	12 weeks		24 weeks
Genotype 4	12 weeks	12 weeks	
Genotype 5		12 weeks	
Genotype 6		12 weeks	

WHO 2016 HCV treatment guidelines

Persons with cirrhosis

	Daclatasvir/ sofosbuvir	Daclatasvir/ sofosbuvir/ ribavirin	Ledipasvir/ sofosbuvir	Ledipasvir/ sofosbuvir / ribavirin	Sofosbuvir/ ribavirin
Genotype 1	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 2					16 weeks
Genotype 3		24 weeks			
Genotype 4	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 5			24 weeks	12 weeks[b]	
Genotype 6			24 weeks	12 weeks[b]	

* Treatment durations are adapted from the 2015 guidelines of the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL).

[a] Treatment may be shortened to 8 weeks in treatment-naive persons without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 log) IU/mL. The duration of treatment should be shortened with caution.

[b] If platelet count <75 x 10^3/μL, then 24 weeks' treatment with ribavirin should be given.

Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	•	•	•*	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•*	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	•	•	•*	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•*	•
	Fosamprenavir	•	•	•	•*	•
	Lopinavir	•	•	•	•*	•
	Saquinavir	•	•	•	•*	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•*	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

Table 4B. Drug-drug interactions between HCV DAAs and illicit recreational drugs.

	SIM	DCV	SOF	SOF/ LDV	3D
Amphetamine	•	•	•	•	•
Cannabis	•	•	•	•	•
Cocaine	•	•	•	•	•
Diamorphine	•	•	•	•	•
Diazepam	•	•	•	•	•
Gamma-hy-droxybutyrate	•	•	•	•	•
Ketamine	•	•	•	•	•
MDMA (ecstasy)	•	•	•	•	•
Methamphetamine	•	•	•	•	•
Phencyclidine (PCP)	•	•	•	•	•
Temazepam	•	•	•	•	•

TABLE 8.4 Framework for the frequency of monitoring patients undergoing HCV therapy based on type of regimen

Time	DAA alone			DAA + ribavirin			DAA + pegylated interferon + ribavirin			
	FBC, renal, liver function	Adherence, side-effects	HCV RNA	FBC, renal, liver functions	Adherence, side-effects	HCV RNA	FBC, creatinine, ALT	Thyroid function	Adherence, side-effects	HCV RNA
Baseline	X		X	X		X	X	X		X
Week 1				X	X		X		X	
Week 2				X	X		X		X	
Week 4	X	X		X	X		X		X	
Week 8				X	X		X		X	
Week 12				X	X		X	X	X	
Week 12 after end of treatment			X	X		X	X	X		X
Week 24 after end of treatment										X

ALT: alanine aminotransferase; DAA: direct-acting antiviral; FBC: full blood count

DAAs and the question of price

5g of diamonds

25 1-carat ($1900 each)

Cost = $48,000

5g of daclatasvir

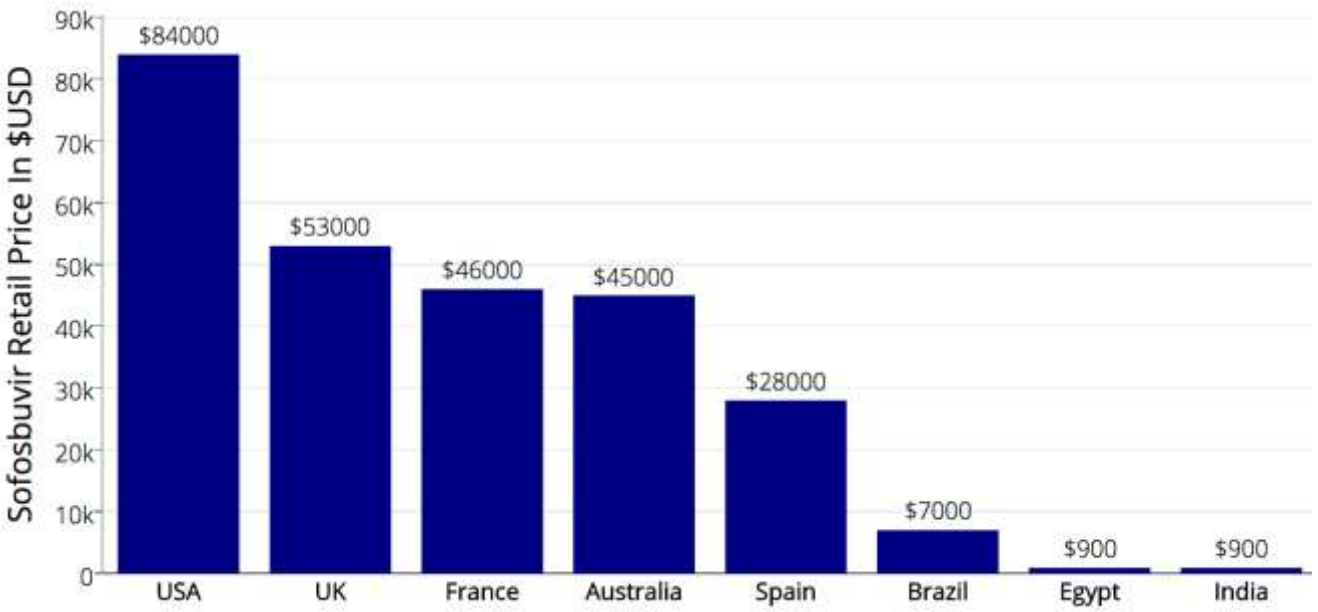
12 weeks of treatment, 60mg/day

Cost = $63,000 (US price)

Slide Courtesy of Andrew Hill

DAAs can be affordable

Sofosbuvir Retail Price for 12-weeks treatment in March 2016



Source: significant reductions in costs of generic producSon of sofosbuvir and daclatasvir for treatment of hepatitis C, Hill et al, EASL 2016

Sofosbuvir: generic prices

Cost of API = $4,770/kg

API needed per person = 34g (400mg x 84 days)

API per 12 weeks = $163

Formulation = 40%

Formulated drug = $228

Packaging = $0.35/month

Packaged drug = $229

Profit margin = 50%

Final generic Price = $344

For end 2015, Prices falling rapidly

Slide Courtesy of Andrew Hill

DAAs are cheap to produce

DAAs	Calculated price for 12-week treatment (1)
Sofosbuvir (SOF)	**$95**
Daclatasvir (DCV)	**$17**
Ledipasvir (LED)	**$136**
Sofosbuvir/ daclatasvir	**$112**
sofosbuvir/ ledipasvir	**$231**

Source : Dr Andrew Hill, Presentation in Bangkok mid-March 2016

Price of DAAs generic versions

DAAs	Lowest indian generic price for 12-week treatment (2)
Sofosbuvir (SOF)	$900
Daclatasvir (DCV)	$276
Sofosbuvir/ daclatasvir	
sofosbuvir/ ledipasvir	~ $1,152

Source : TreatAsia

SOF/LED
~ 306$/bottle

SOF/LED
~ 380$/bottle

DAAs offer opportunities…

- **DAAs allow for increased treatment access including for hard-to-reach populations through**
  - More **decentralized** models of care
  - **Integration** of treatment in harm reduction, drug dependency programs and HIV program
  - Shorter treatment with less side effects
  - Better adherence

…but challenges remain

- **DAAs are not yet registered in Vietnam and not covered by Health Insurance (HI)**
- **By now DAAs remains expensive in Vietnam (~ 2,700 USD for 12 weeks)**

Need for registration of DAAs + price reduction through generic competition + inclusion of DAAs in HI

…but challenges remain

- **HCV treatment will only be effective to reduce HCV prevalence if strong prevention services are implemented targetting most at risk population**

Need for better coverage of comprehensive harm reduction services

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