I nuovi farmaci per HCV: frequenza della patologia, evidenze di efficacia e sicurezza, strategie di gestione

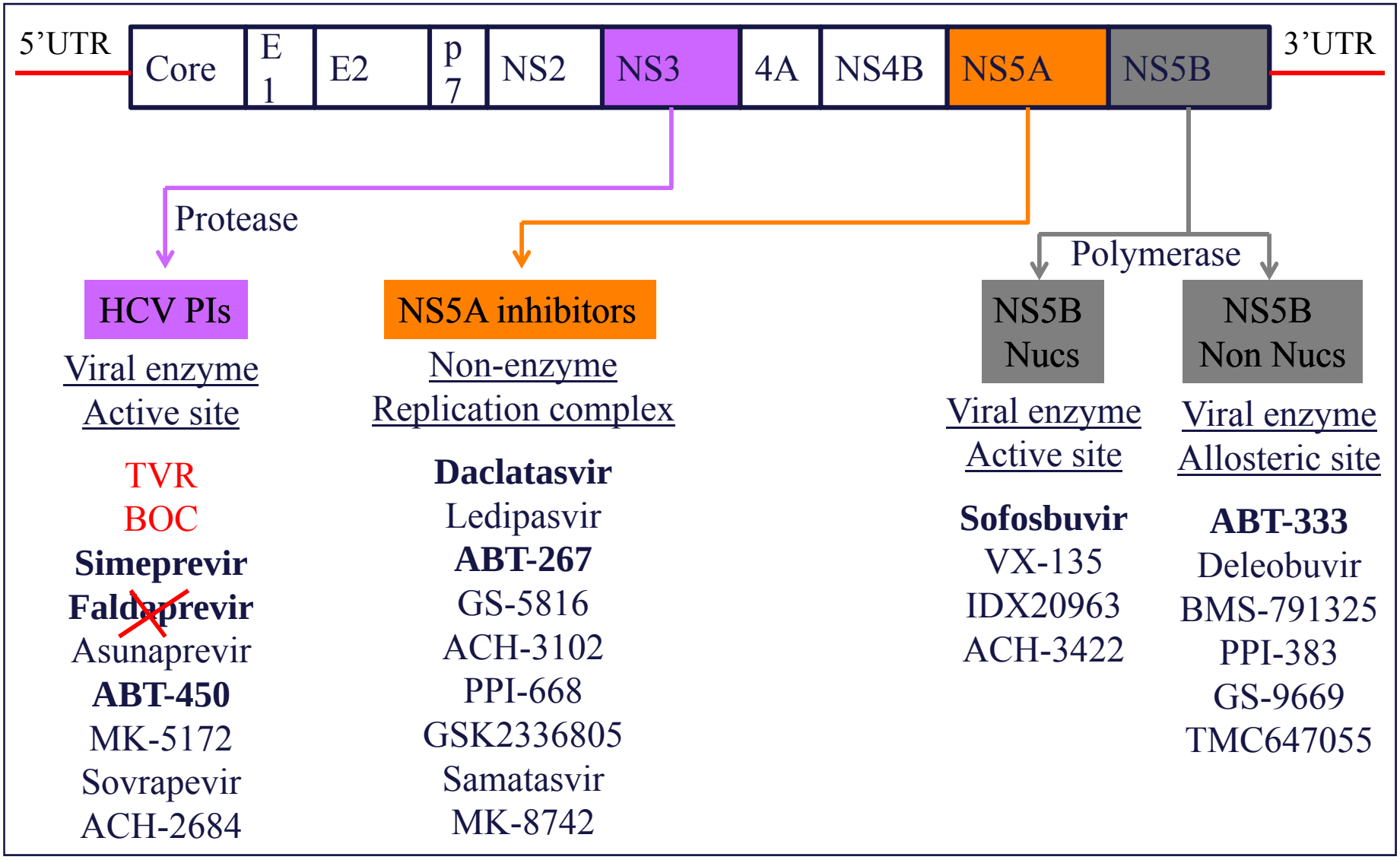
La revisione delle evidenze e indicazioni per la pratica clinica

Marco Marzioni
Segretario AISF

THE BURDEN OF HEPATITIS C IN ITALY

- The cause of death in at least 10.000 persons each year
- The single etiologic agent in half the patients with cirrhosis
- The single etiologic agent in more than half the patients with a liver cancer
- The indication for liver transplantation in half the patients with ESLD
- Each year 67.460 patients with cirrhosis or HCC hospitalized for 11 days on average, 50% HCV (SIS)

MULTIPLE DIRECT ATIVIRAL AGENTS



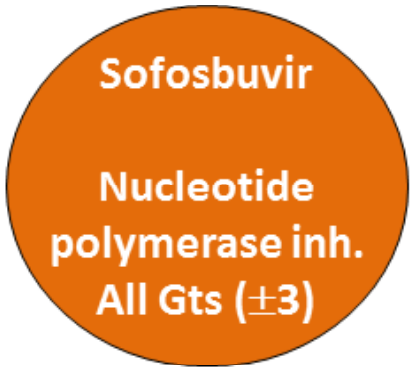
NOT ALL DIRECT-ACTING ANTIVIRALS ARE CREATED EQUAL

Characteristic	Protease Inhibitor*	Protease Inhibitor**	NS5A Inhibitor	Nuc Polymerase Inhibitor	Non-Nuc Polymerase Inhibitor
Resistance profile	🔴	🟡	🟡	🟢	🔴
Pangenotypic efficacy	🔴	🟡	🟡	🟢	🟡
Antiviral potency	🟡	🟢	🟢	🟢	🟡
Adverse events	🔴	🟢	🟢	🟡	🟡

🟢 Good profile 🟡 Average profile 🔴 Least favorable profile

*First generation. **Second generation.

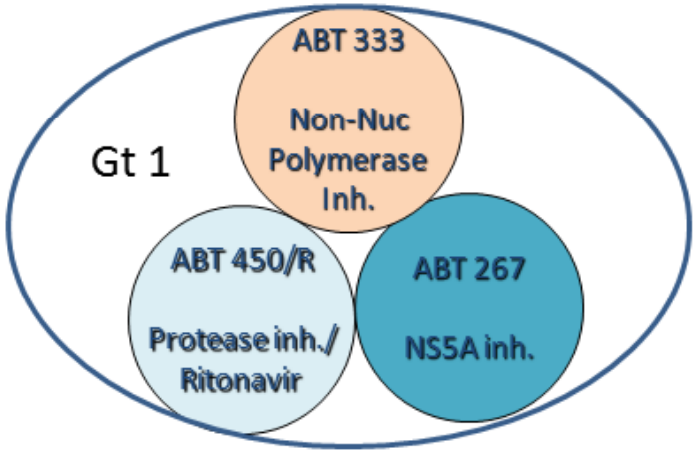
NEW DAAs AVAILABLE OVER THE NEXT 12-18 MONTHS



Triple therapy with PEG IFN and ribavirin

Combination of one DAA and ribavirin

Combination of two DAAs ± ribavirin



Fixed dose combination of three DAAs ± ribavirin.
ABT 450/5 + 267 only for noncirrhotic HCV 1b

Timeline assumes:
- EMA approval ~ 3 months after FDA approval
- AIFA reimbursement granted ~ 9 months after EMA approval

RATIONALE FOR MOVING TO INTERFERON FREE REGIMENS IN TREATING HCV CHRONIC HEPATITIS

- Efficacy
  - IFN intolerant or ineligible
  - Specials populations
- Safety
  - Avoid hematologic, skin and psychiatric side effects
- Tolerability
  - Reduced treatment duration
  - Small number of pills
  - High compliance expected
- Reduce the indirect costs
  - Clinical and biochemical controls
  - Work absences
- Reduce the burden of the disease
  - If costs, availability and affordability of drugs will be optimal

AVAILABILITY OF NEW DAAs IN ITALY

- Often unpredictable
- Different criteria of reimbursement
  - Severe vs mild disease
  - Naïve vs experienced
  - Medical vs financial
- Different regional access to treatment
- Potential disparity among patients from different regions
- Progressive increase in “warehousing effect”

FACTORS INFLUENCING THE "WAREHOUSING EFFECT"

Pro	Cons
Low disease stage	Urgency of HCV clearance
Low probability of SVR	HCV related extrahepatic diseases
Inability	
Comorbi	
Patient's	
Expectar	

Costs and availability of drug (s)

ABOUT COSTS…….

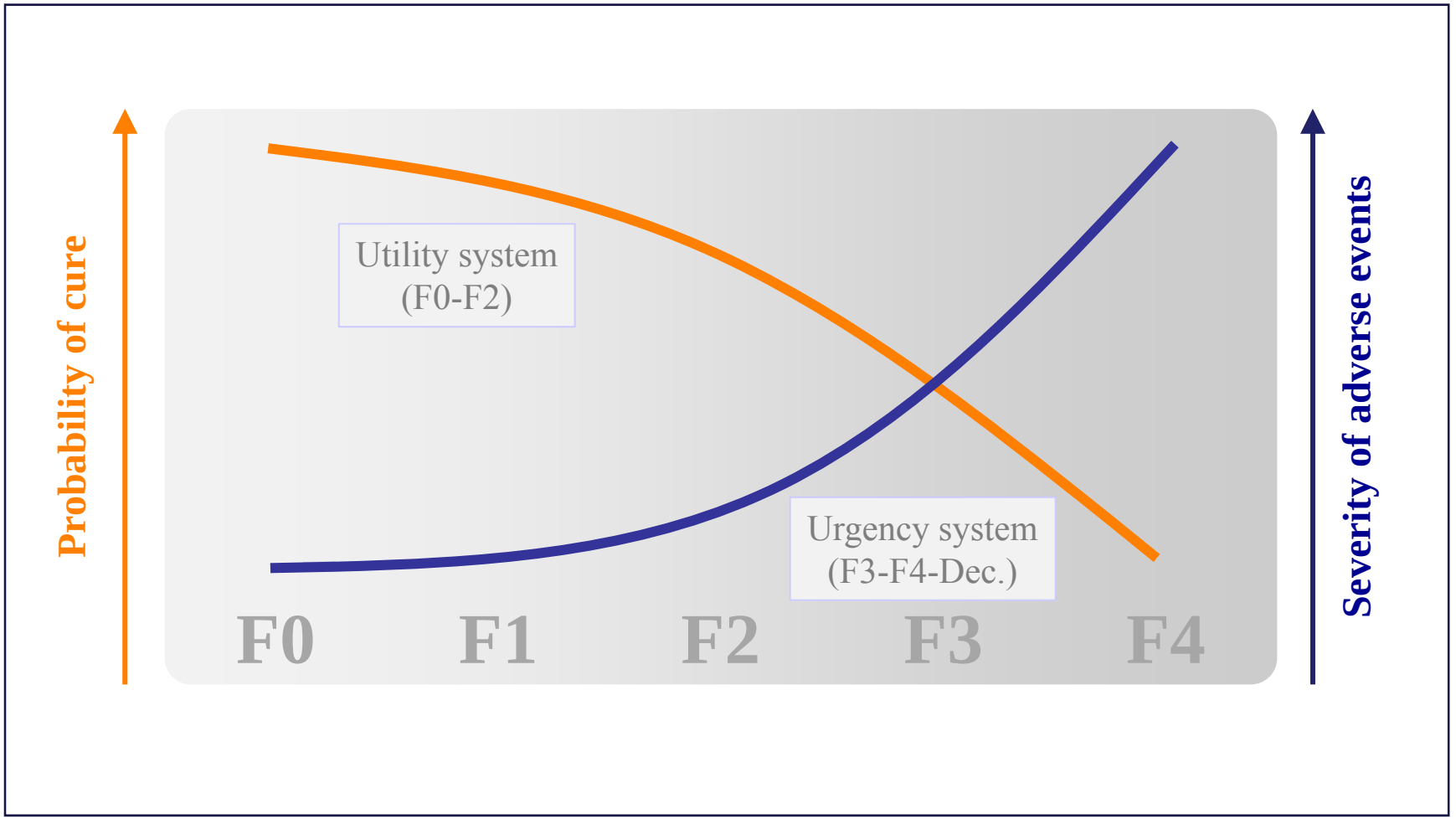
- Physicians must treat the diseases with the most efficacious drugs available
- The cost of drugs should not be the only parameter to be considered for their use
- The responsibility of the restriction of the resources at our disposal should not fall down on the physician
- The physician should use the treatment at a lower cost **ONLY** if this has been shown to have equal efficacy/tolerability profile compared to more expensive treatment

PROGNOSTIC MODELS TO ASSIST THERAPEUTIC ALLOCATIONS AND MEDICAL ETHICS IN A CONTEXT OF LIMITED RESOURCES

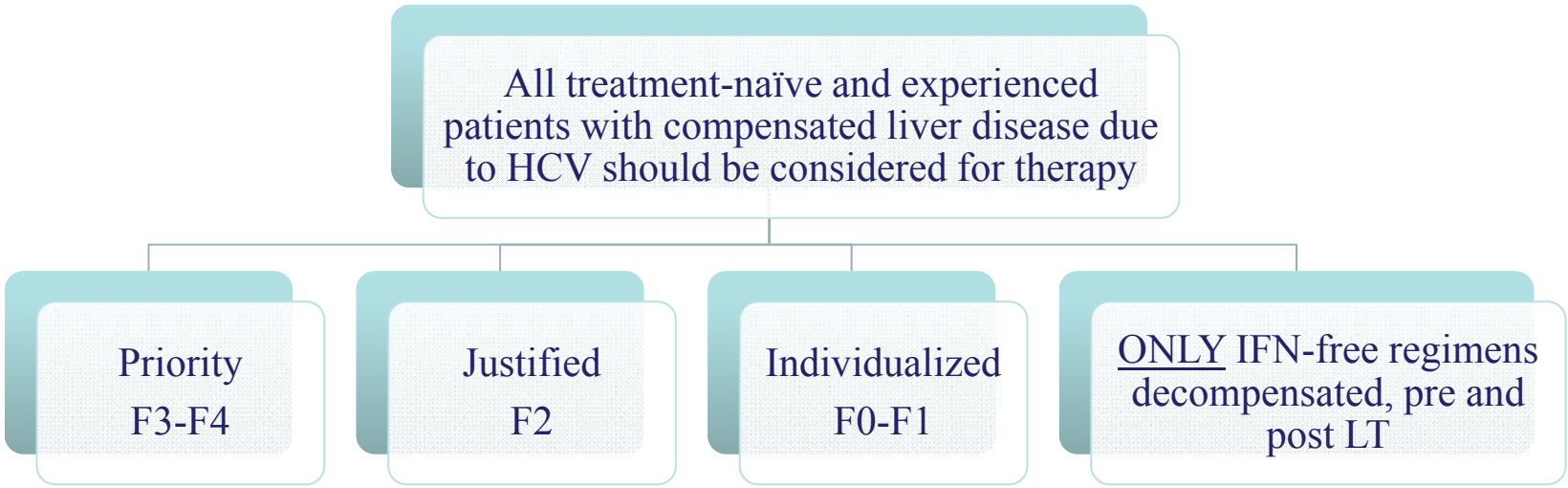
- **EQUITY**: the need to distribute equitably the therapeutic resources available
- **INDIVIDUAL JUSTICE**: the duty to promote the best interest of individual patients
  - **Medical urgency (treat first more advanced liver diseases)**
- **UTILITY**: the duty to strive to obtain the best results for the correct population therapeutic use of the resource
  - **Post treatment outcomes: maximize SVR rates (number of treatments/number of SVR obtained)**

These values should be protected by means of good clinical practice through transparency and verifiability of the procedures and full traceability of individual clinical trial

EFFICACY AND SAFETY WORSEN IN ADVANCED LIVER DISEASE

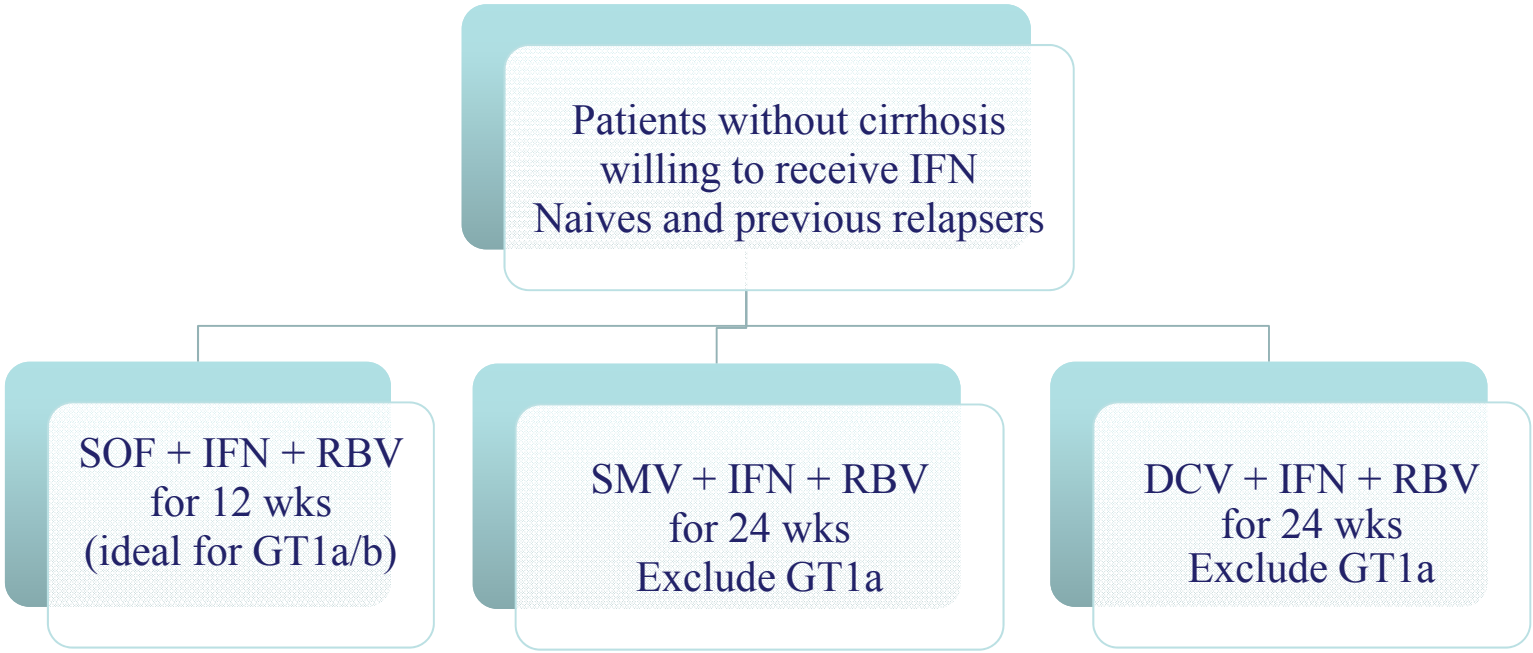


SELECTION OF THE CANDIDATES TO RECEIVE NEW ANTIVIRALS



EASL recommendations on treatment of hepatitis C, J Hepatol, 2014.

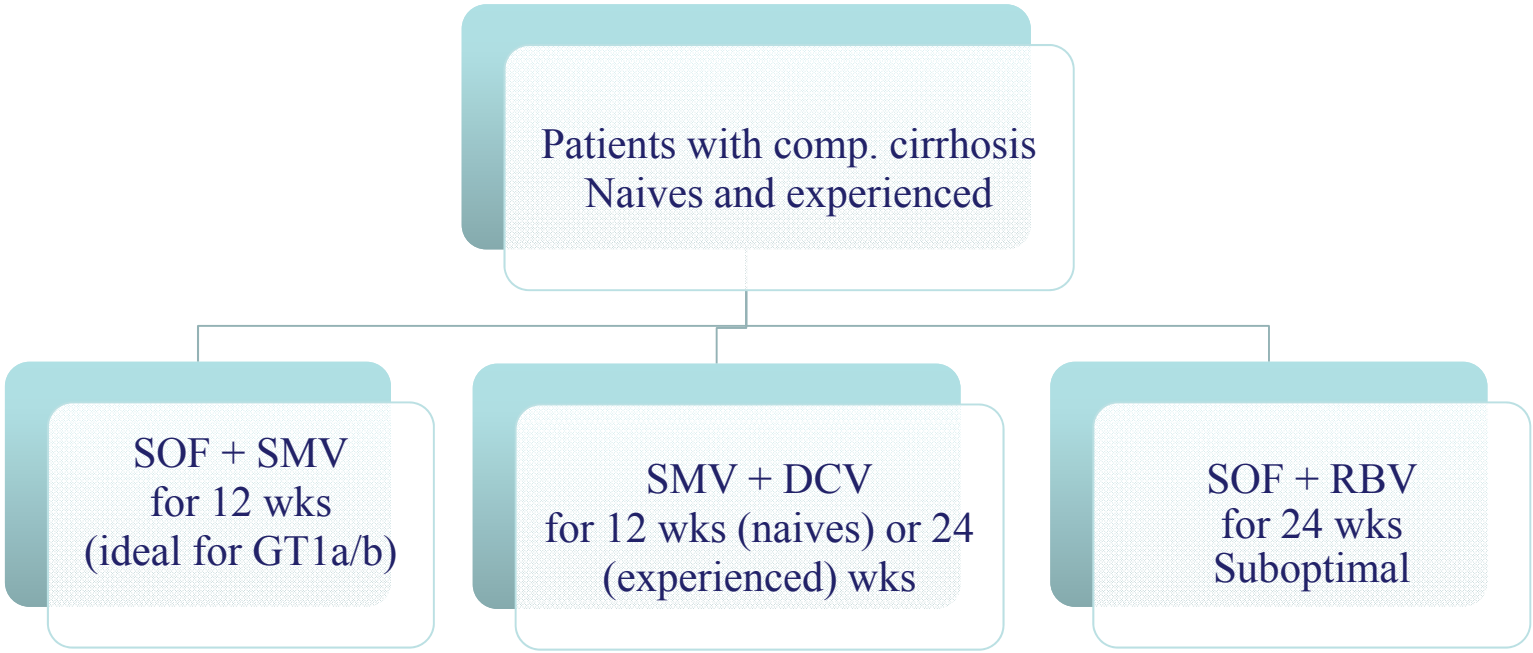
SELECTION OF THE NEW ANTIVIRALS IN TREATING HCV GENOTYPE 1 INFECTED PATIENTS



No indications to use first generation PIs (BOC or TVR)

EASL recommendations on treatment of hepatitis C, J Hepatol, 2014, mod.

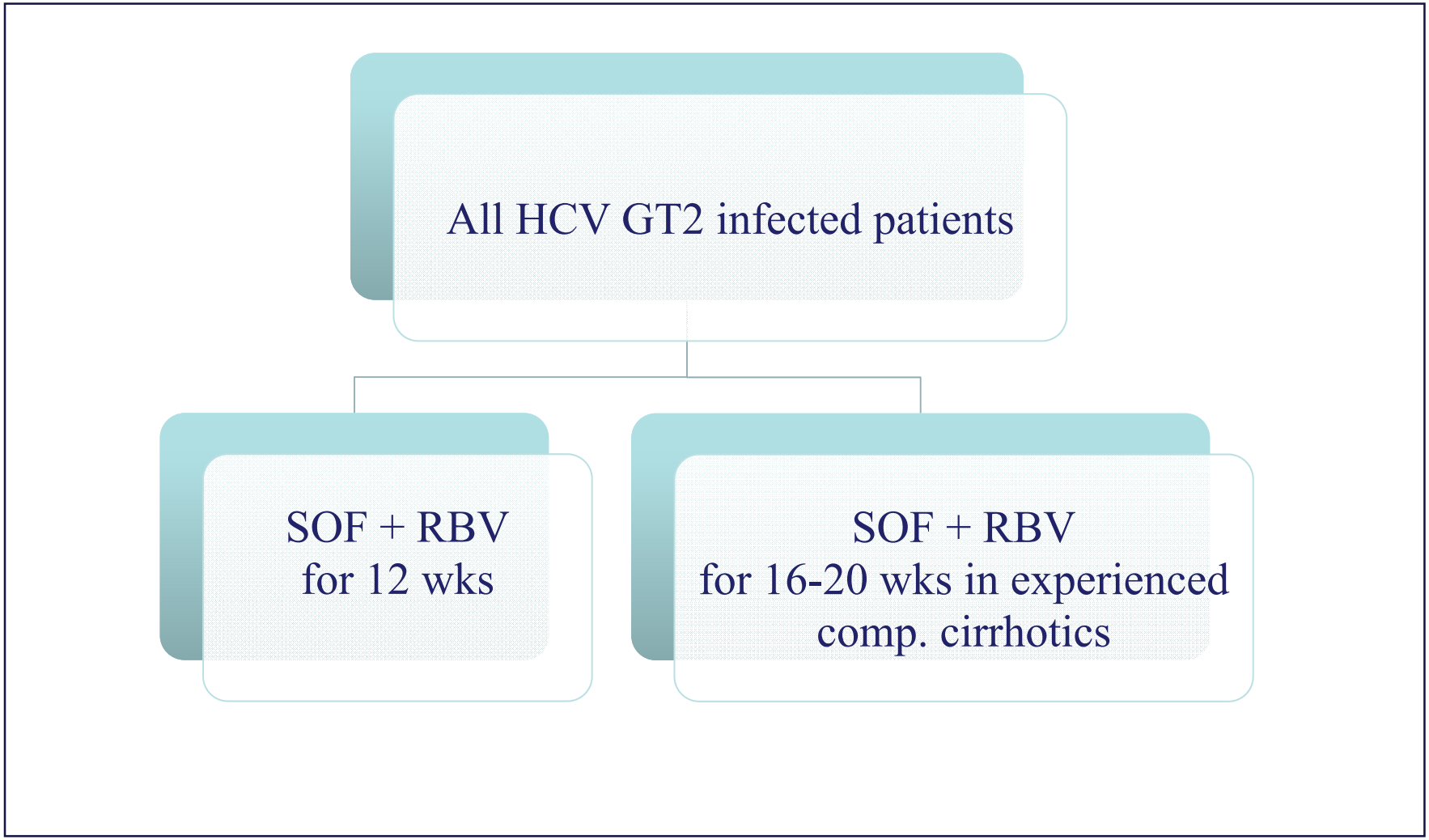
SELECTION OF THE NEW ANTIVIRALS IN TREATING HCV GENOTYPE 1 INFECTED PATIENTS



No indications to use first generation PIs (BOC or TVR)

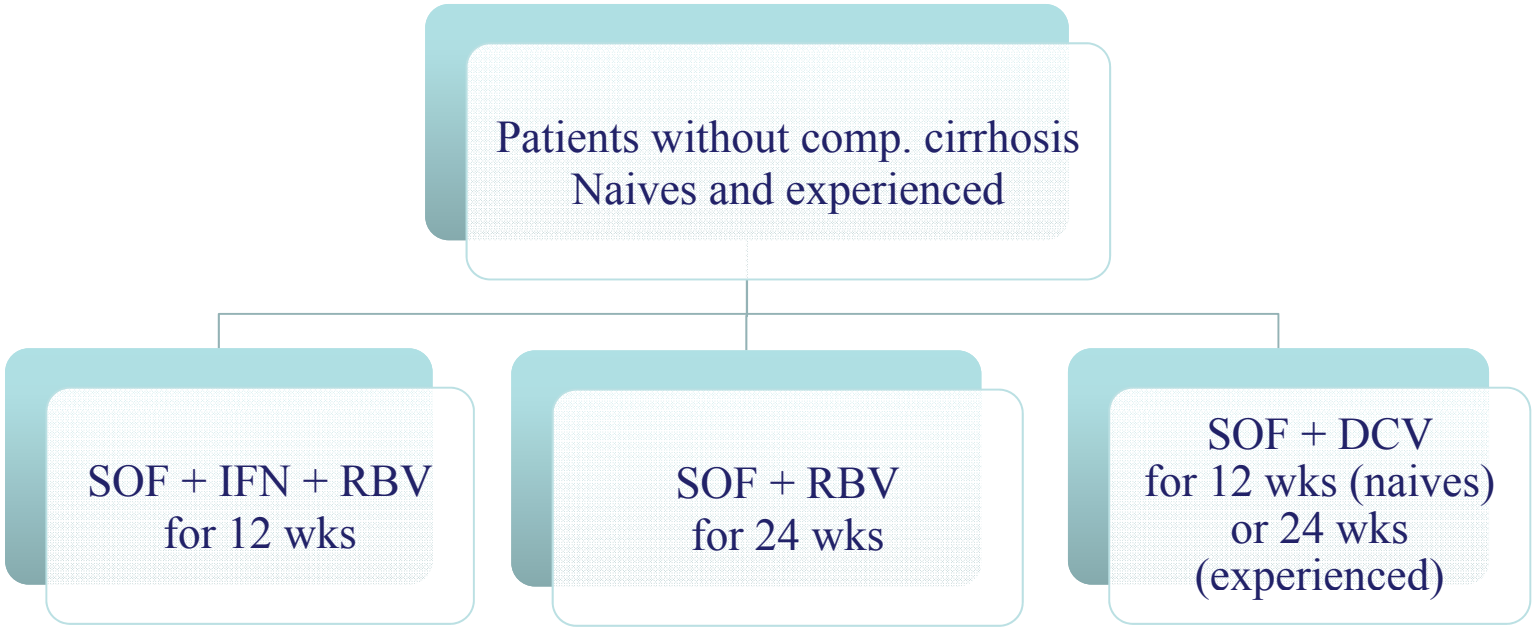
EASL recommendations on treatment of hepatitis C, J Hepatol, 2014, mod.

SELECTION OF THE NEW ANTIVIRALS IN TREATING HCV GENOTYPE 2 INFECTED PATIENTS



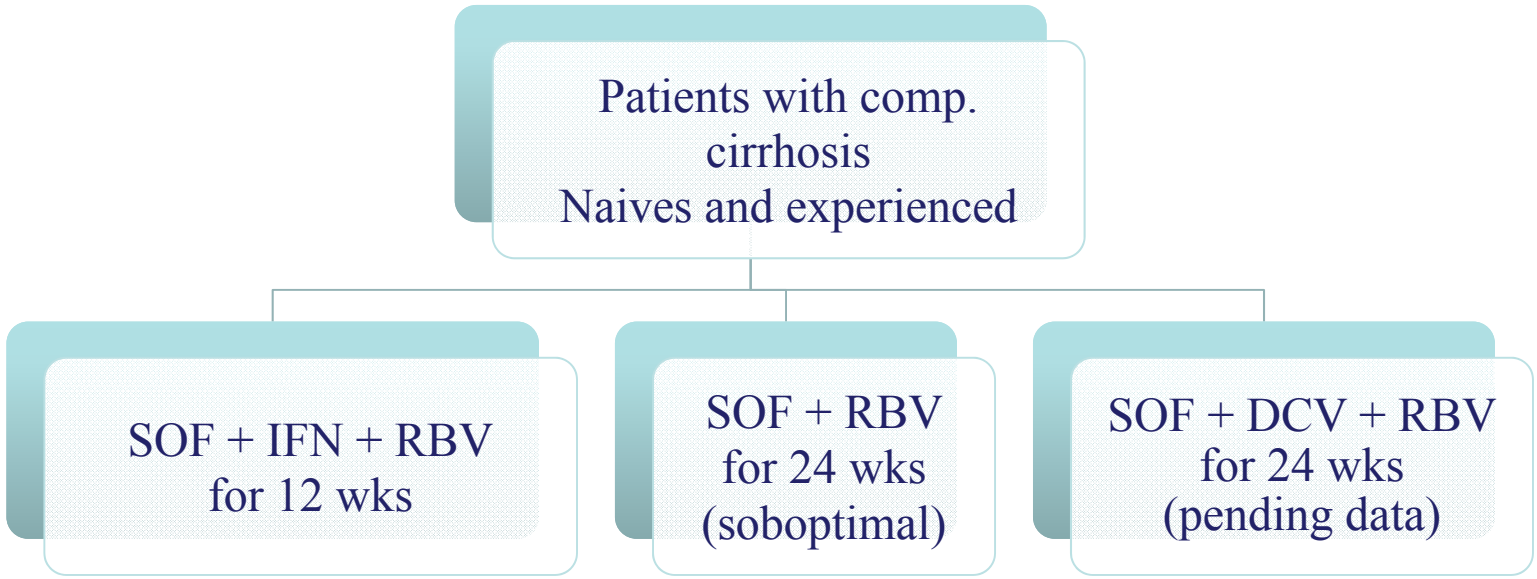
EASL recommendations on treatment of hepatitis C, J Hepatol, 2014, mod.

SELECTION OF THE NEW ANTIVIRALS IN TREATING HCV GENOTYPE 3 INFECTED PATIENTS



EASL recommendations on treatment of hepatitis C, J Hepatol, 2014, mod.

SELECTION OF THE NEW ANTIVIRALS IN TREATING HCV GENOTYPE 3 INFECTED PATIENTS



WILL THERE STILL BE A ROLE FOR IFN DURING 2014-2016 IN A IDEAL TREATMENT SCENARIO?

- Hard to cure
  - GT3
  - DAA failures – multi-DAA resistant
  - Prior non-responders → Quad?
- Easy to cure
  - *IL28B* CC – high efficacy, short duration → Asia?
  - Mild disease – option of IFN vs waiting for progression
- Cost containment
  - Fewer or less effective DAAs
  - GT2?

KEY CONCEPTS CONCERNING THE IDEAL SCENARIO FOR TREATMENT IN 2014-2016

- For the first time a real effective and safety options for treating patients with compensated severe liver disease is available
- The extension to access of patients with less severe liver disease to the new IFN free regimens will be associated with expected SVR rates near to 90%
- Considering the imminent availability of the newest IFN-free antiviral regimens (ABT combinations, SOF+LDV, MK combinations) it could be expected that costs will be redefined

TREATMENT DECISIONS IN 2014 AND EARLY 2016: GENERAL CONSIDERATIONS

- Scientific treatment scenario is evolving rapidly
- Access to treatment probably will not follow this rapidity
  - Bureaucracy
  - Trading costs
  - Different region reimbursement criteria
- Considering efficacy and safety of new antivirals, treat now or defer can not be more decided taking into account only the costs but considering that patients should be cured with current and future regimens
- This will generate a huge gain in the future in terms of reduction of morbidity, mortality and hospitalization for liver disease only if the therapy will be available for the majority of patients

And next?

How Many DAAs Do We Need?

Assumptions:

1) Production of new virions = ~10^{12}/day

2) HCV genome length = ~9600 nucleotides

3) Error rate = ~10^{-5}/per nucleotide copied

Therefore, average number of changes/genome = 0.096/replication cycle

# of Nucleotide Changes	Probability	# of Virions/Day	# of All Possible Mutants	% of All Possible Mutants/Day
0	0.91	9.1×10^{11}		
1	0.087	8.7×10^{10}	2.9×10^{4}	100
2	0.0042	4.2×10^{9}	4.1×10^{8}	100
3	0.00013	1.3×10^{8}	1.0×10^{12}	3.4×10^{-5}

If the theory is right: should need 3 DAAs

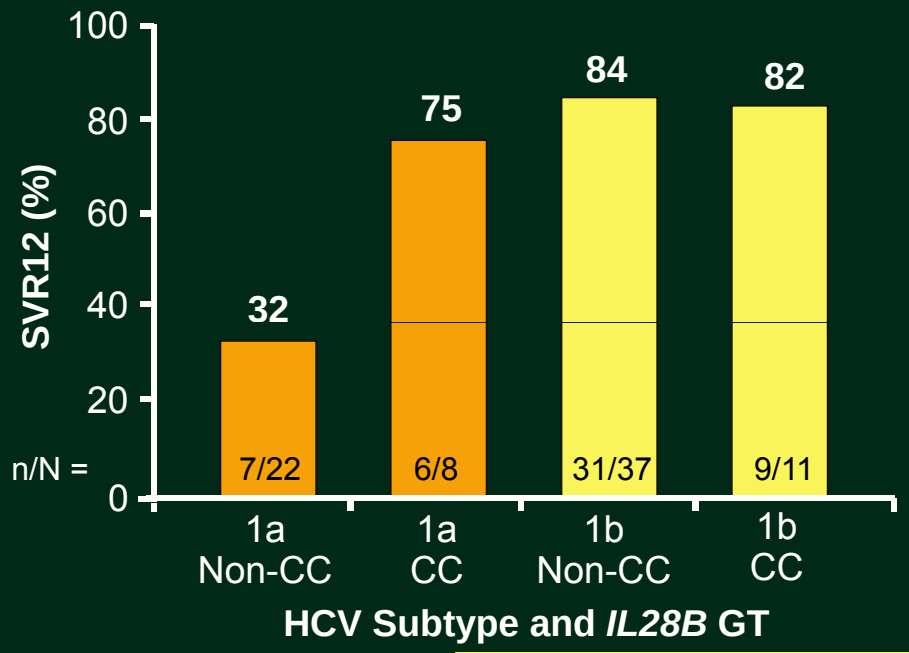
Rong L, et al. Sci Transl Med. 2011;2:30-32.

DAA Options

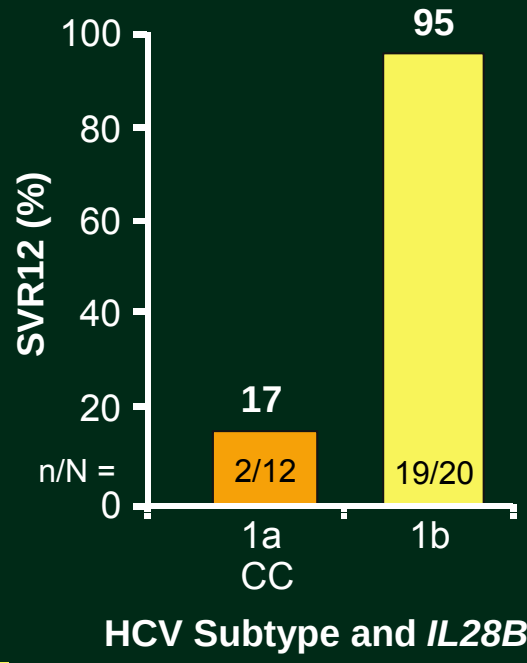
- PI backbone – potent/modest barrier
  - PI + another low-barrier DAA (NNI/NS5A) for GT1b
  - PI + 2 low-barrier DAAs for GT1a
- Nuc backbone – potent/high barrier
  - Nuc + low-barrier DAA for GT1a/b
  - Nuc + PI
- Include ribavirin?
  - May allow fewer DAAs (2 vs 3)
  - May allow shorter therapy

Example of PI Backbone + NNI + RBV for GT1b Only

Faldaprevir (PI) 120 mg QD + deleobuvir (NNI) 600 mg BID + RBV for 28 wks[1,2] (N = 78)



Faldaprevir (PI) 120 mg QD + deleobuvir (NNI) 600 mg BID + RBV for 16 wks[3] (N = 32)

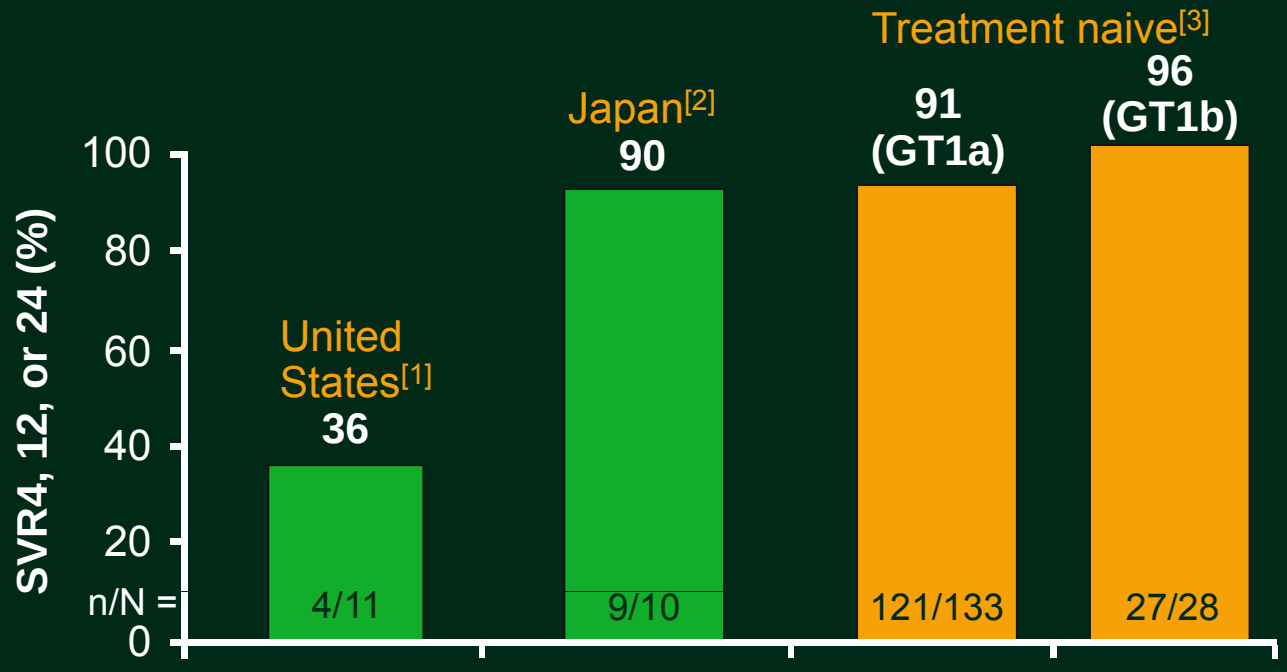


~~Simple regimen for GT1b only?~~

1. Zeuzem S, et al. NEJM. 2013;369:630-639. 2. Zeuzem S, et al. EASL 2012. Abstract 101.
3. Dufour JF, et al. AASLD 2013. Abstract 1102.

Example of PI Backbone + NS5A in Prior Null Responders

- Daclatasvir (NS5A) + Asunaprevir (PI) x 24 wks
- Daclatasvir (NS5A) + Asunaprevir (PI) + BMS 791325 (NNI) x 12 wks



US study
9/11 GT1a

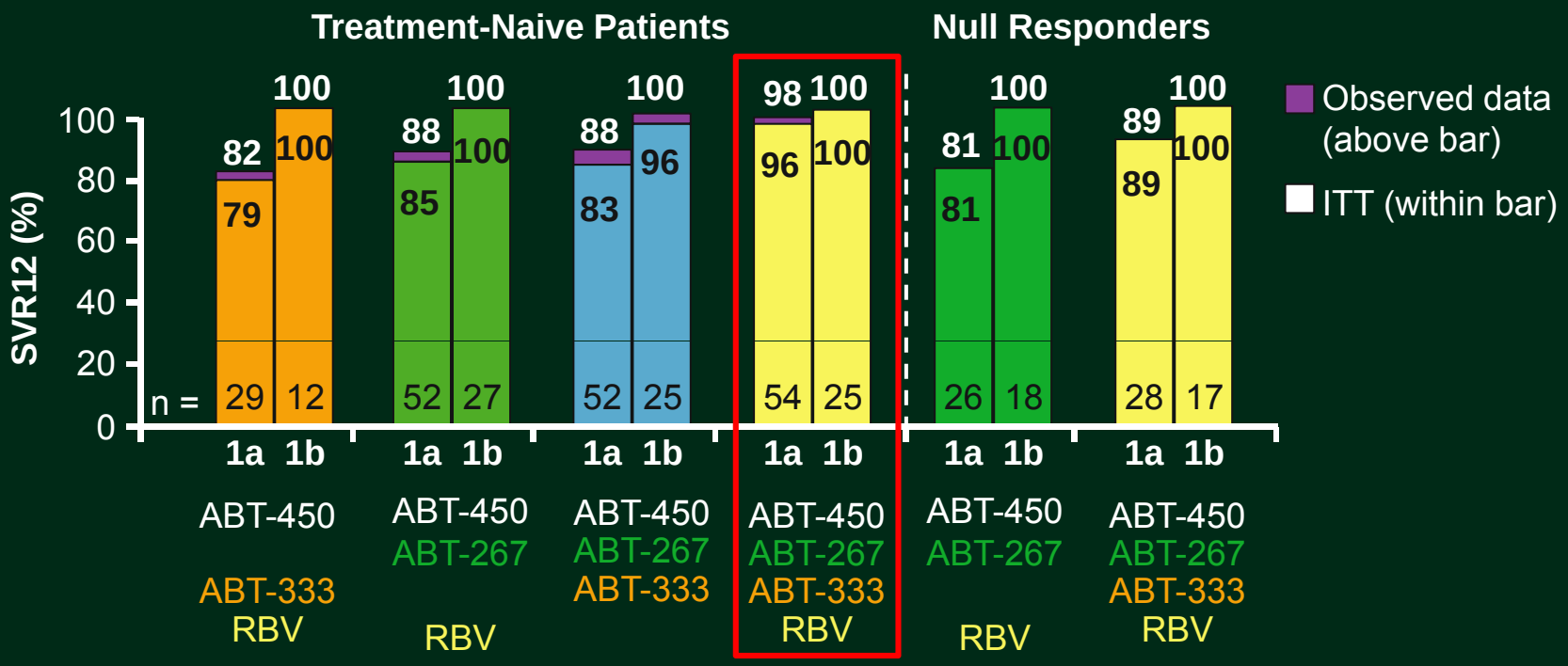
Japanese study
10/10 GT1b

- Likely adequate for GT1b but not for GT1a
- Overcome by addition of third drug: only 12 wks

1. Lok AS, et al. N Engl J Med. 2012;366:216-224. 2. Chayama K, et al. Hepatology. 2012;55:742-748.
3. Everson G, et al. AASLD 2013. Abstract LB-1.

Example of PI Backbone + 2 Other DAAs

ABT-450/RTV (PI) ± **ABT-333** (NNI) +
ABT-267 (NS5A) ± **RBV** x 12 wks

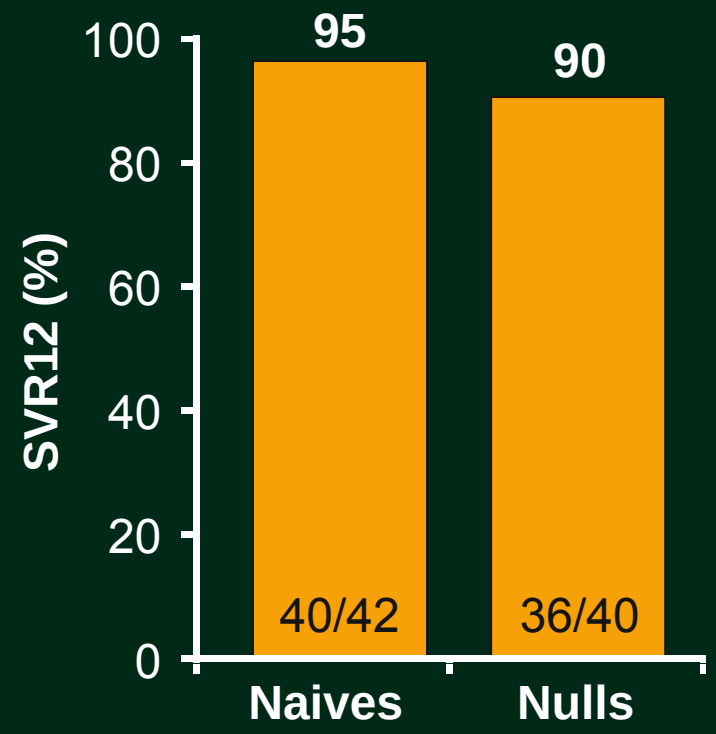


5 drugs (3 pills) but 12 weeks, one size fits all

Kowdley KV, et al. AASLD 2012. Abstract LB-1.

Example of PI Backbone + NS5A in GT1b Trt-Naive Pts and Nulls (PEARL-1)

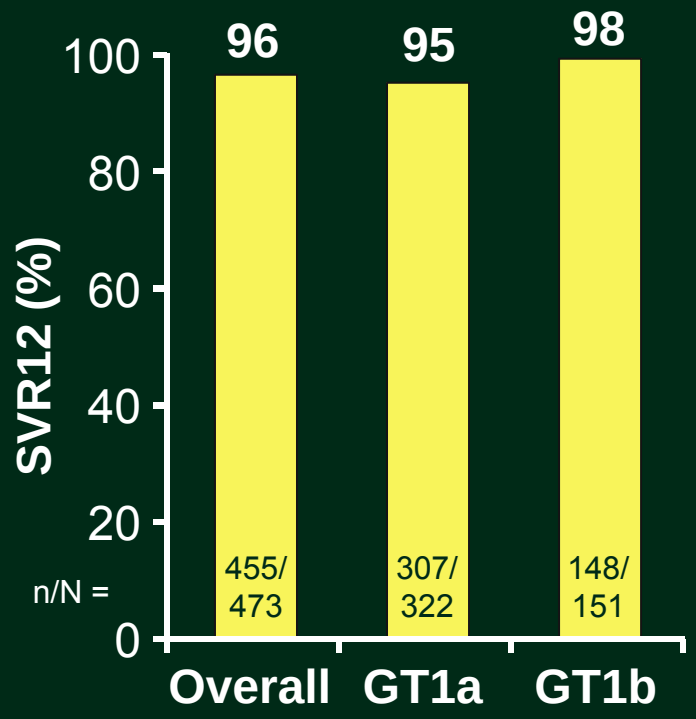
ABT-450/RTV (PI) +
ABT-267 (NS5A) for 16 wks (N = 32)



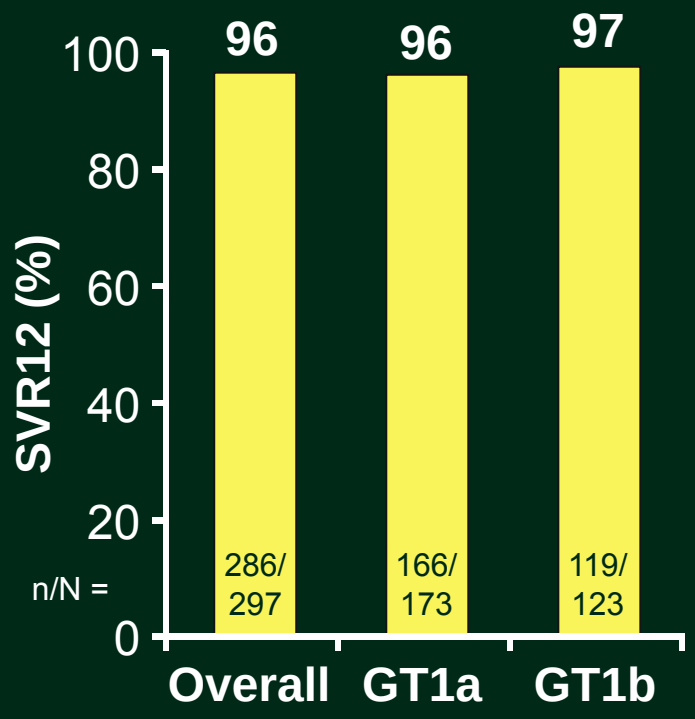
Lawitz E, et al. AASLD 2013. Abstract 75.

SAPPHIRE Phase III Studies: PI Backbone + 2 Other DAAs

SAPPHIRE-1: GT1 treatment-naive noncirrhotic patients: ABT-450/RTV/ABT-267 FDC + ABT-333 + RBV for 12 wks



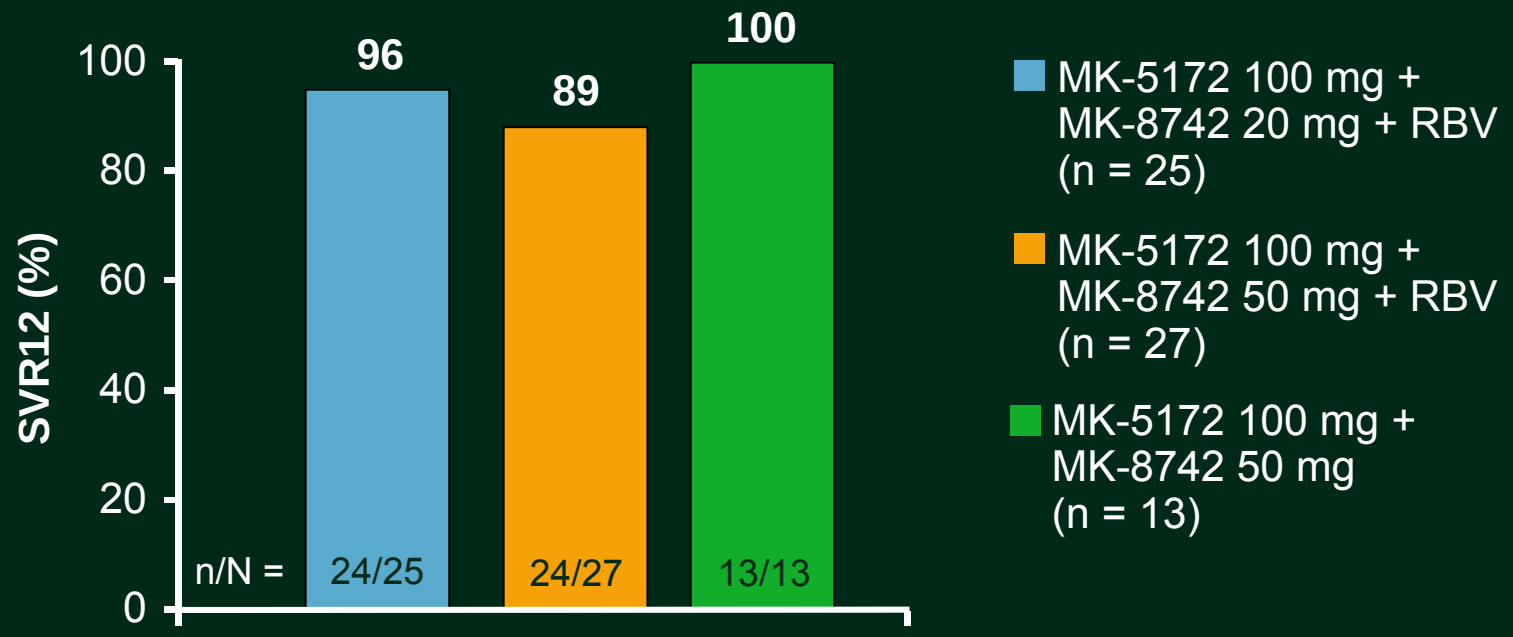
SAPPHIRE-2: GT1 treatment-experienced noncirrhotic patients (49% null responders): ABT-450/RTV/ABT-267 FDC + ABT-333 + RBV for 12 wks



Press release. These data are available in press release format only, have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format before conclusions should be made from these data.

Exception to the Rule: C-WORTHY: PI + NS5A ± RBV in Treatment-Naive GT1 HCV

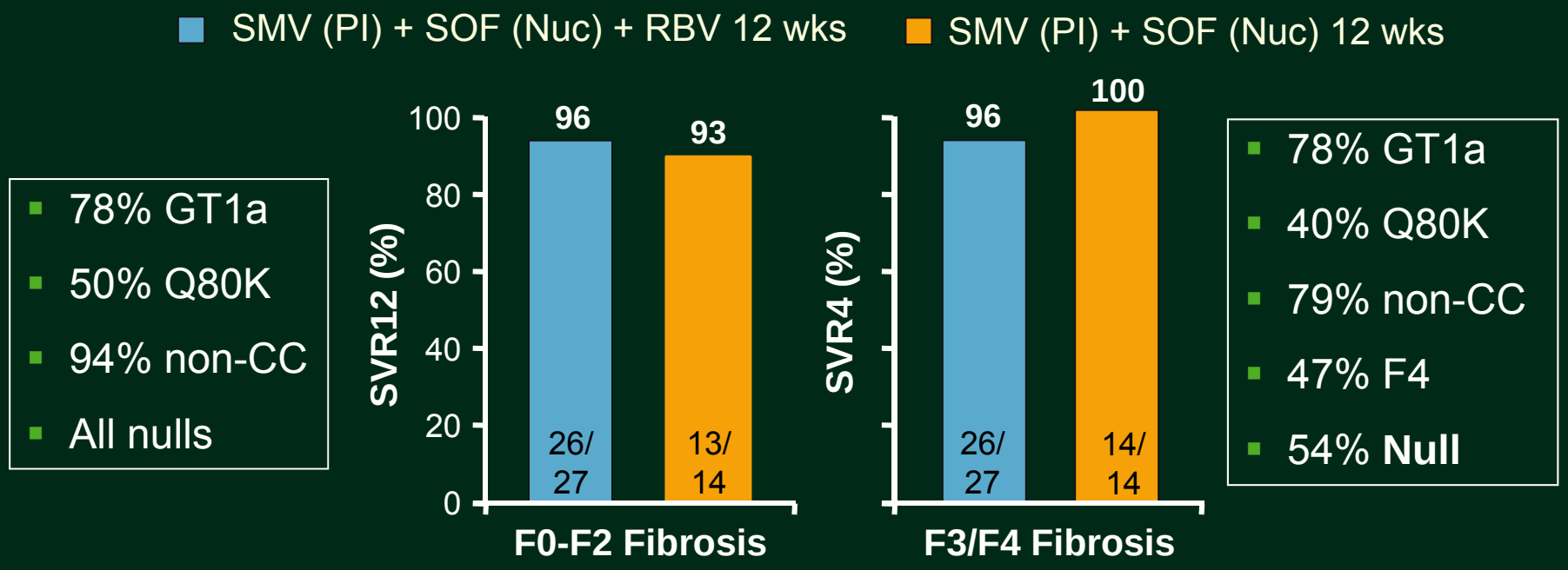
C-WORTHY: MK-5172 (PI) + MK-8742 (NS5A) ± RBV for 12 wks
patients with GT1a randomized 1:1 to RBV arms only;
patients with GT1b randomized 1:1:2 into all 3 arms



Lawitz E, et al. AASLD 2013. Abstract 76.

What About a Nuc Backbone?

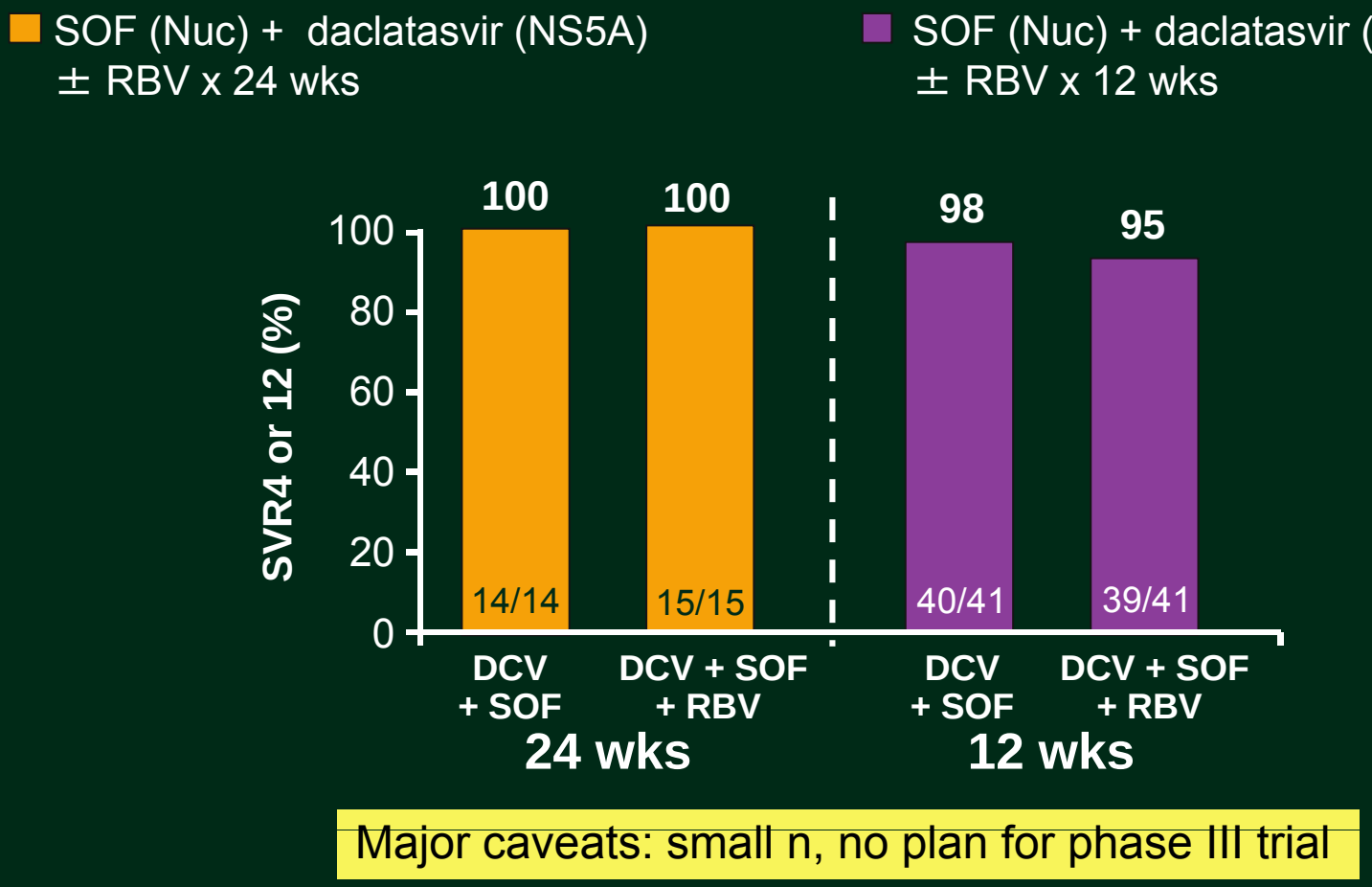
Example of Nuc Backbone + PI in Trt-Naive Pts and Nulls (COSMOS)



- Major caveats: small n, no plan for phase III trial

Jacobson I, et al. AASLD 2013. Abstract LB-3.

Another Option: Nuc Backbone + NS5A

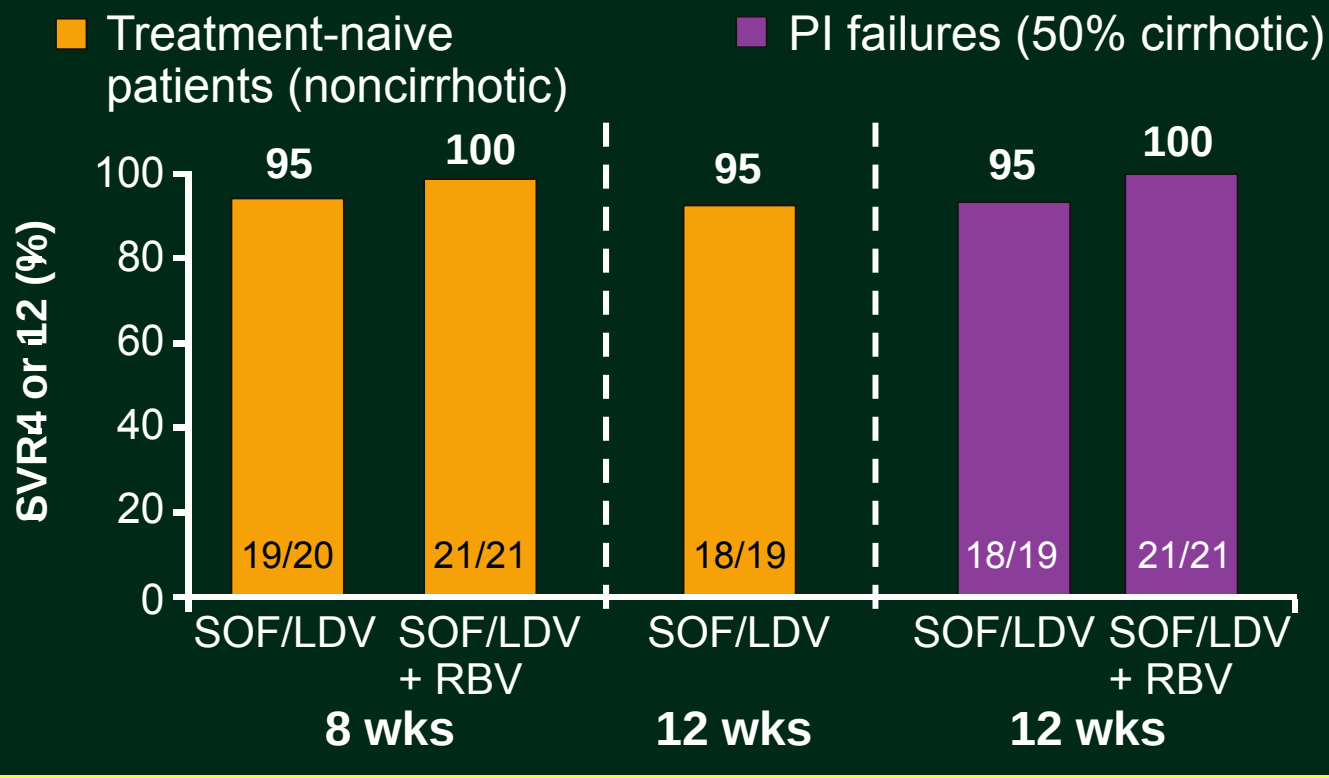


Major caveats: small n, no plan for phase III trial

Sulkowski M, et al. AASLD 2012. Abstract LB-2.

1-Pill Version of Nuc + NS5A

LONESTAR: SOF (Nuc) + ledipasvir (NS5A) FDC ± RBV



- No breakthrough; 2 relapses, both without RBV
- 1 case of resistance – retreated with SOF/LDV + RBV x 24 weeks → SVR

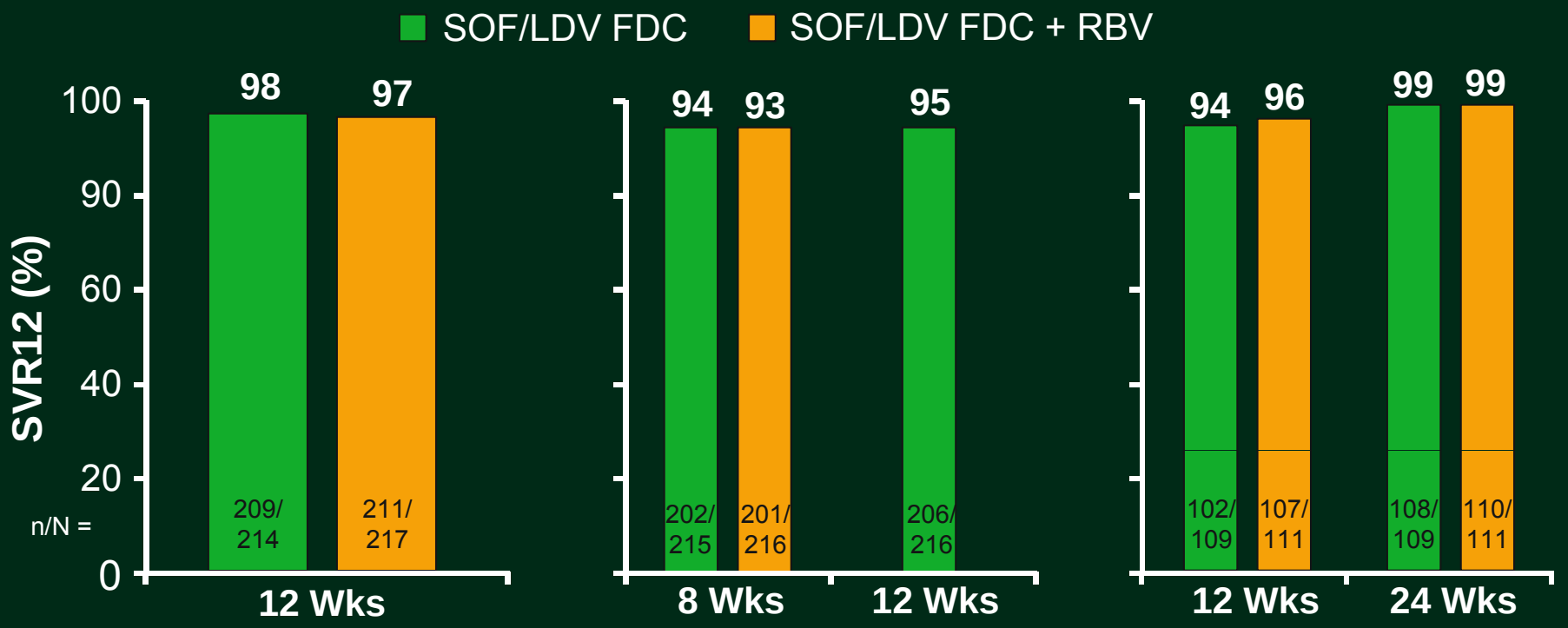
Lawitz E, et al. AASLD 2013. Abstract 215.

Phase III Studies of Sofosbuvir (Nuc) + Ledipasvir (NS5A) ± RBV in GT1 HCV

ION-1*: GT1 treatment-naive pts (16% cirrhotic): SOF/LDV FDC ± RBV for 12 wks

ION-3: GT1 treatment-naive pts: SOF/LDV FDC ± RBV for 8 or 12 wks

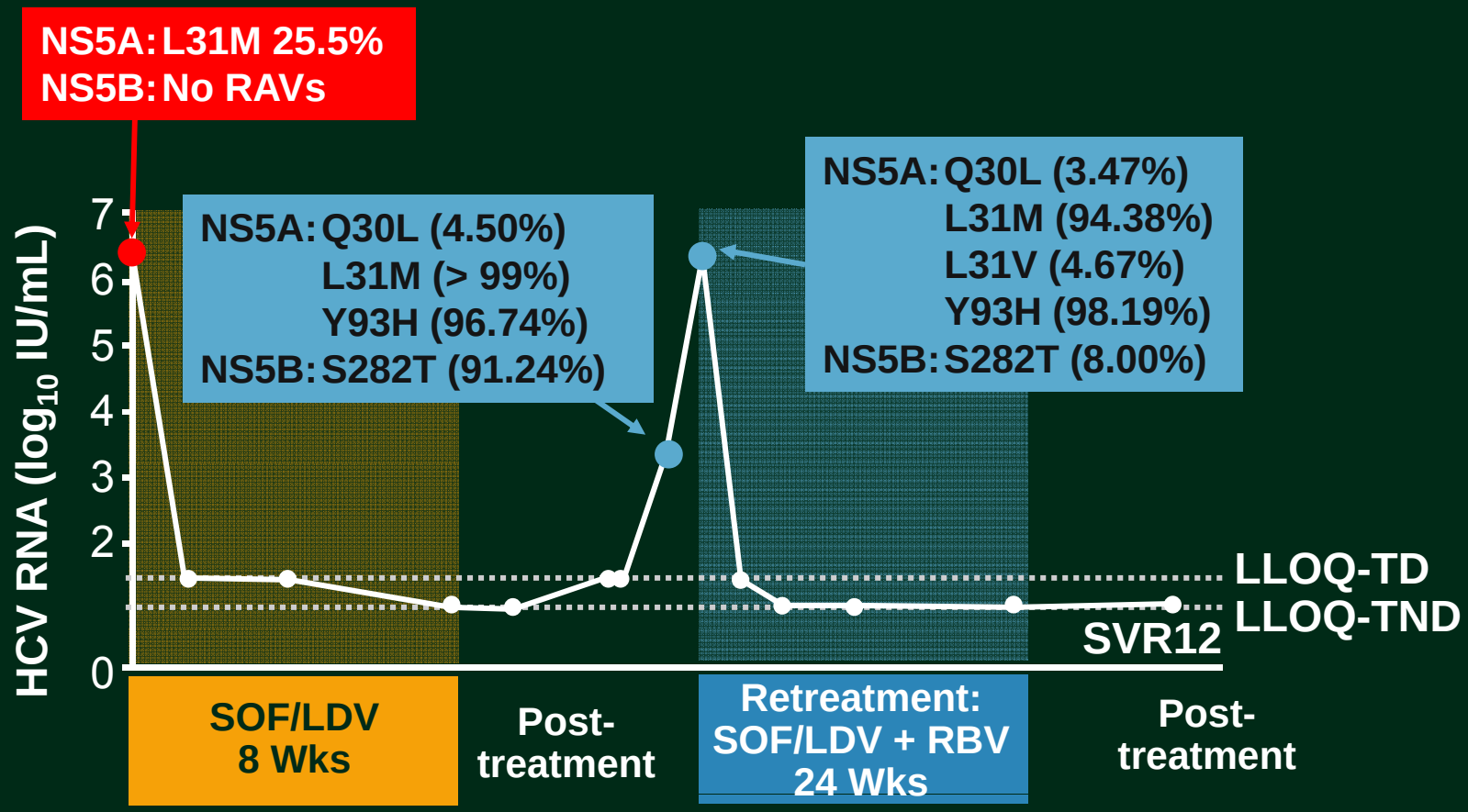
ION-2: GT1 treatment-experienced pts (20% cirrhotic): SOF/LDV FDC ± RBV for 12 or 24 wks



*24-wk arms not yet reported.

Press release. These data are available in press release format only, have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format before conclusions should be made from these data.

What About Resistance?

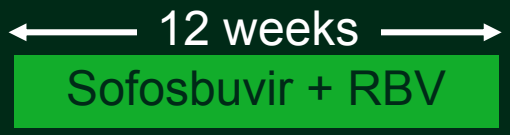


Lawitz E, et al. AASLD 2013. Abstract 215.

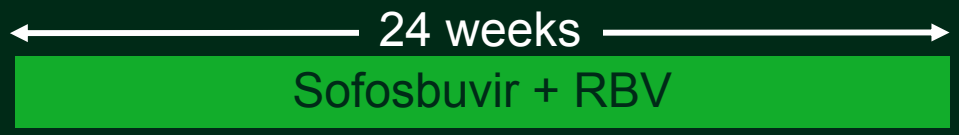
What about GT2 and GT3?

Sofosbuvir + RBV for GT2 and GT3 HCV: Approved Indications

- All GT2 patients receive same regimen, regardless of previous treatment history or fibrosis level



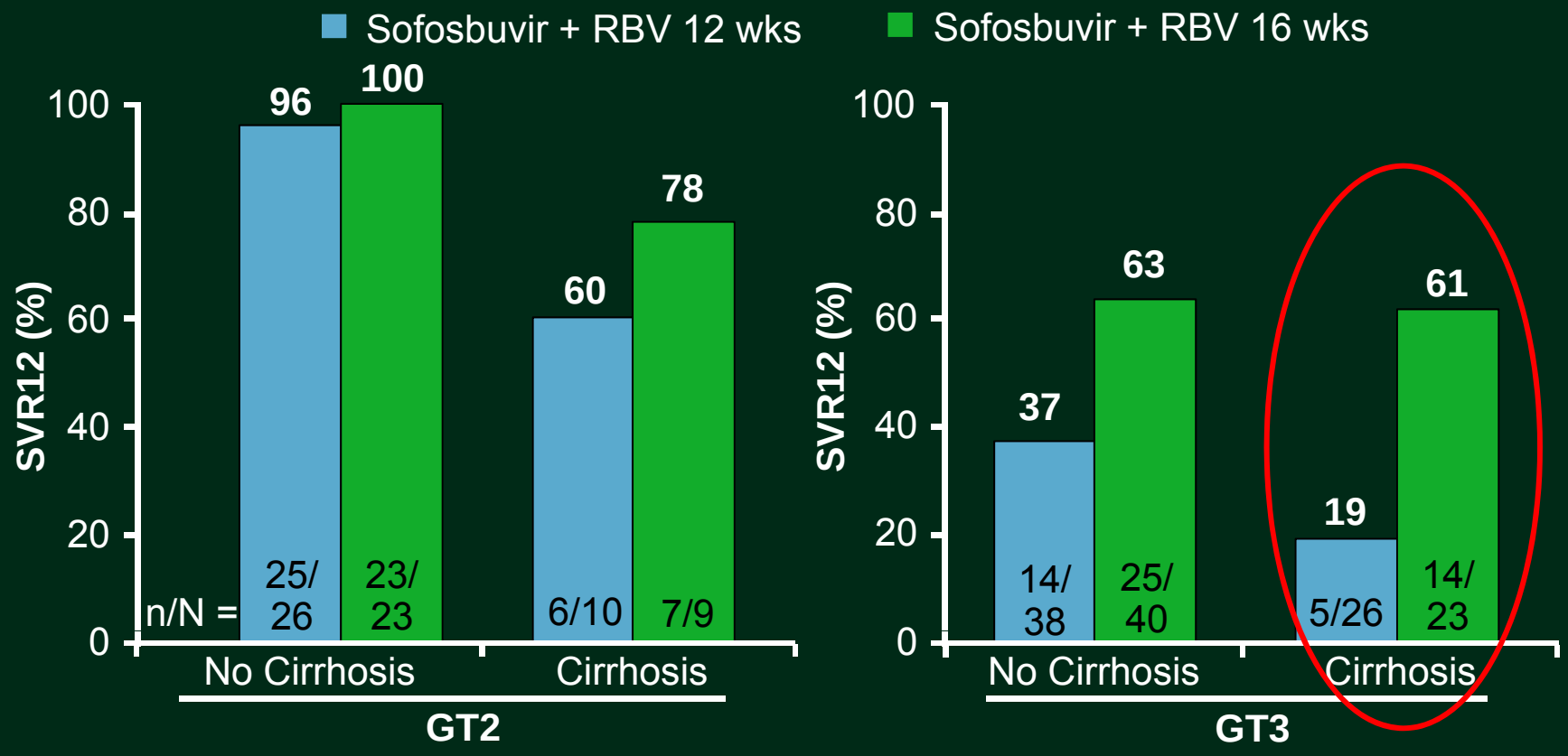
- All GT3 patients receive same regimen, regardless of previous treatment history or fibrosis level



- If drugs combined with sofosbuvir must be permanently discontinued, sofosbuvir should also be discontinued

Sofosbuvir [package insert]. December 2013.

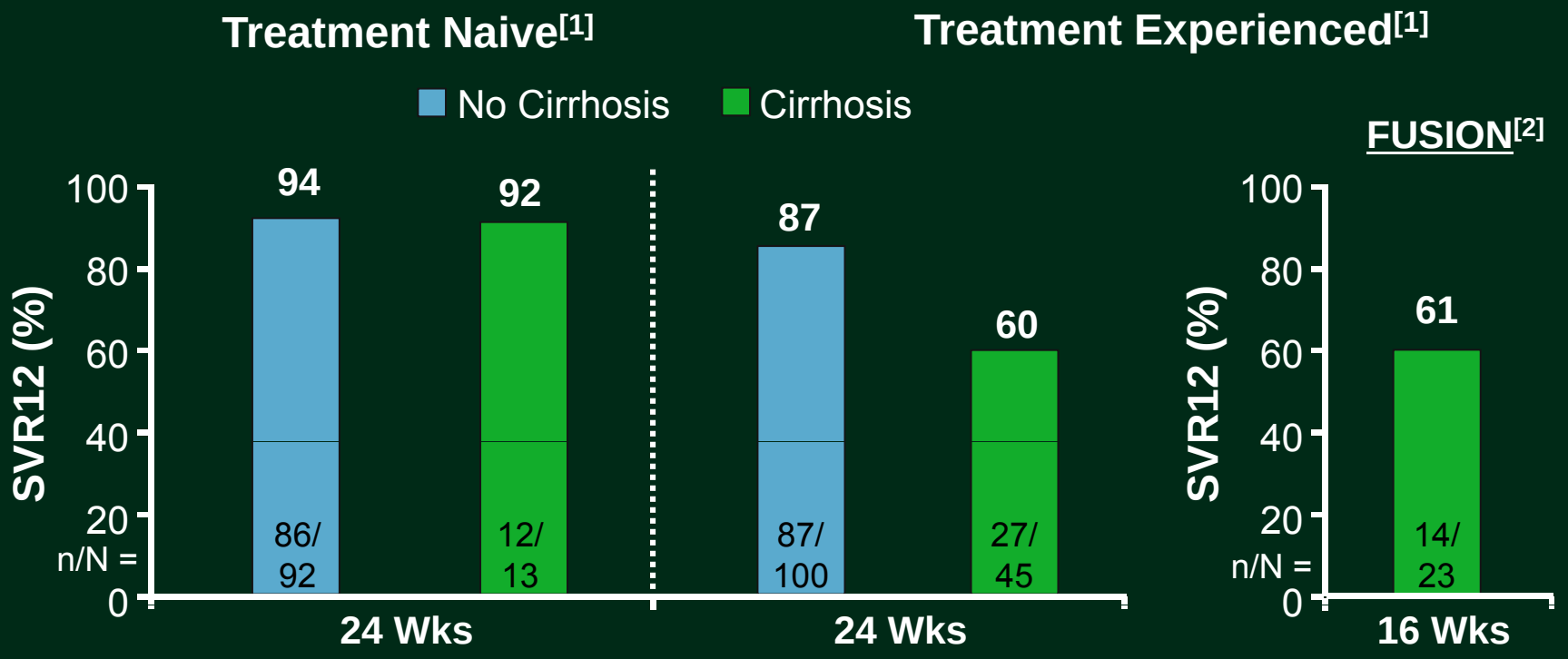
FUSION: SVR by GT and Cirrhosis in Treatment-Experienced Patients



- 12 weeks sufficient for GT2
- 16 weeks better than 12 weeks for GT3… so what about 24 weeks?

Jacobson IM, et al. N Engl J Med. 2013;368:1867-1877.

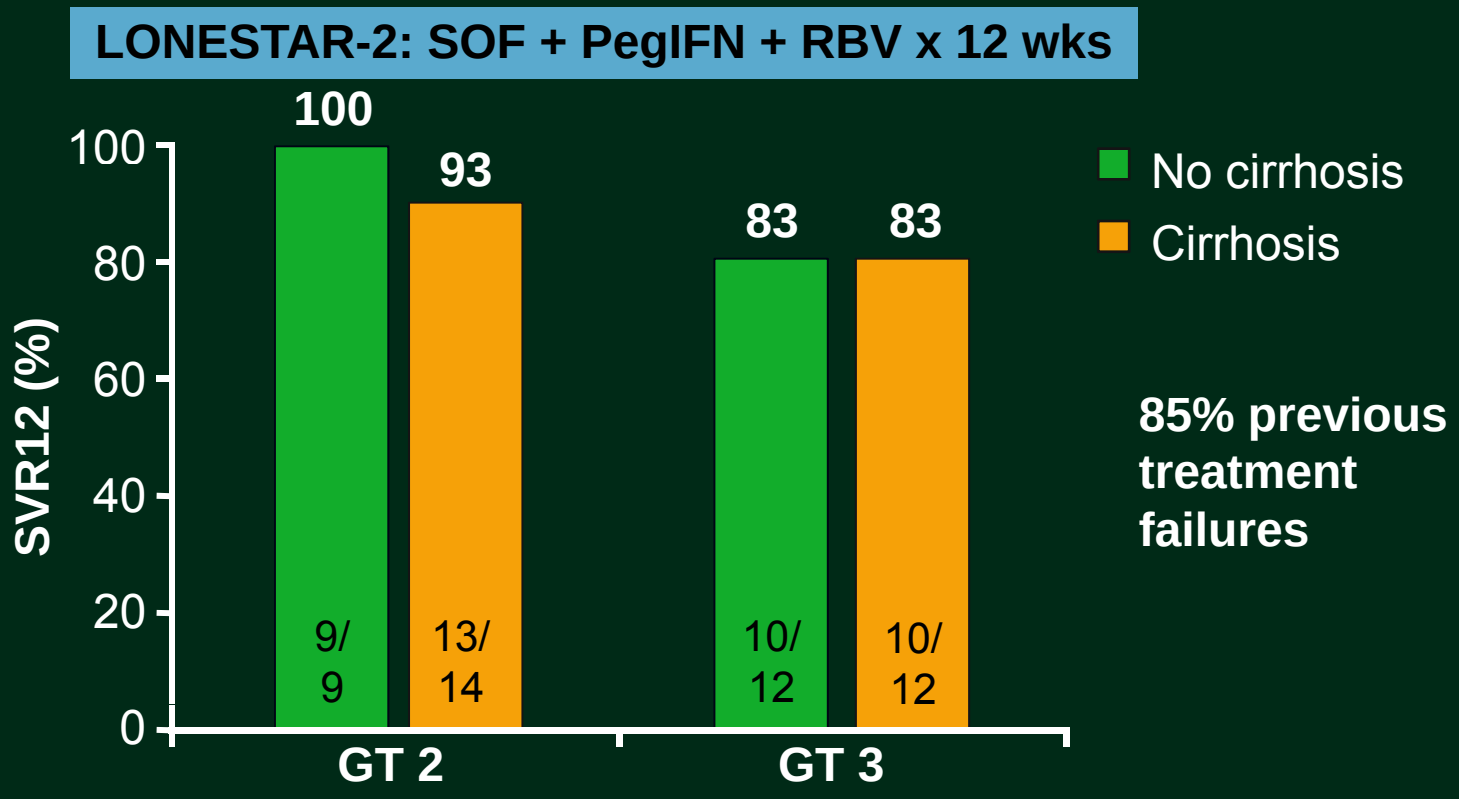
VALENCE: Efficacy With 24-Week Sofosbuvir Plus Ribavirin in GT3 Patients



- 24 weeks better for treatment-naive patients
- Not ideal for cirrhotic treatment failures

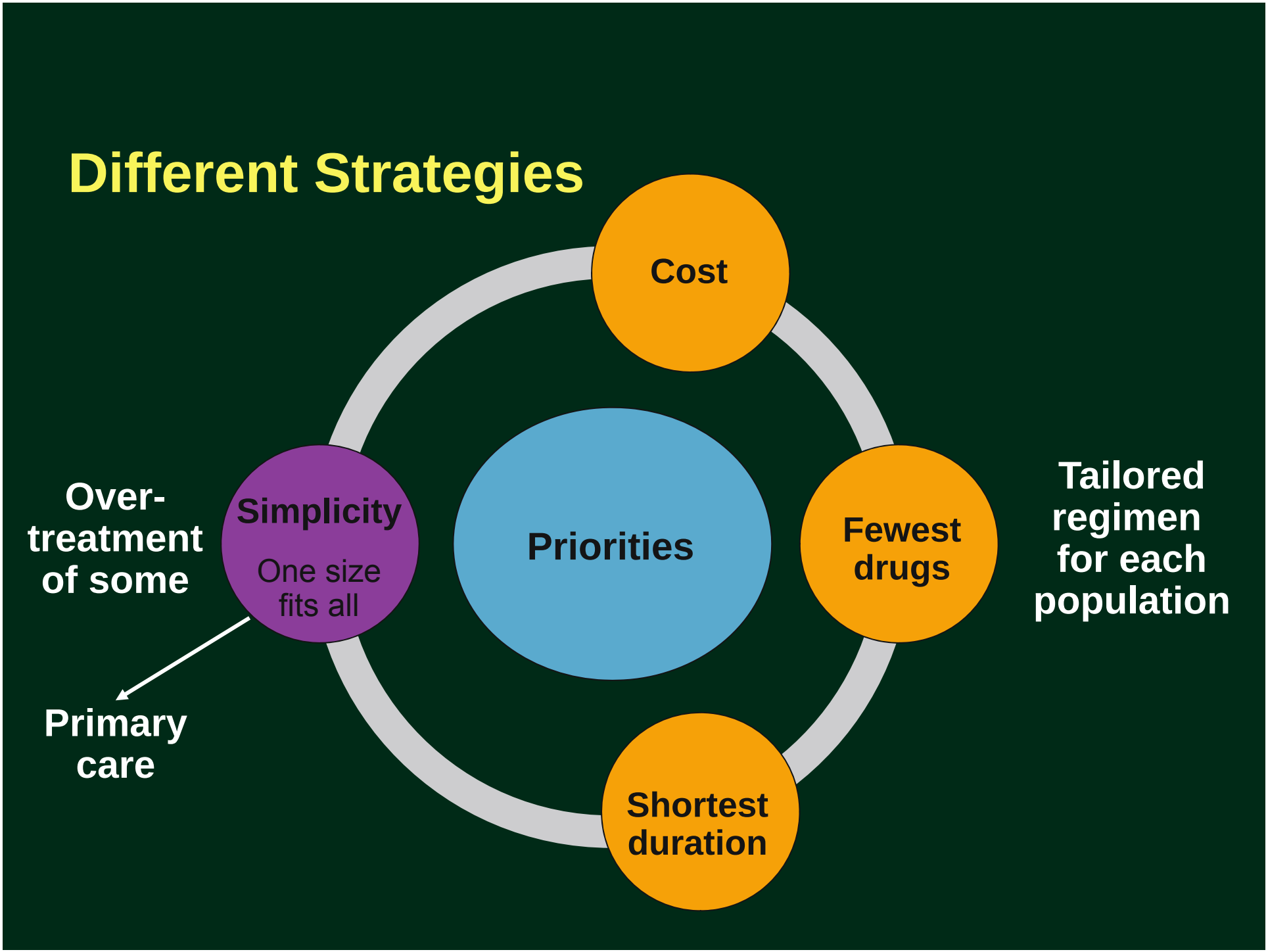
1. Zeuzem S, et al. AASLD 2013. Abstract 1085. 2. Jacobson IM, et al. N Engl J Med. 2013;368:1867-1877.

Do We Still Need IFN for GT3?



- Small single-center study but looks promising. . .
- IFN is not dead yet!

Lawitz E, et al. AASLD 2013. Abstract LB-4.


Different Strategies
Cost
Simplicity
One size fits all
Priorities
Fewest drugs
Shortest duration
Over-treatment of some
Primary care
Tailored regimen for each population