Novel strategies for Hepatitis C Treatment & Liver Transplantation

- Optimizing Dx & current Tx

서울의대 내과, 간연구소

김 윤 준, MD, PhD

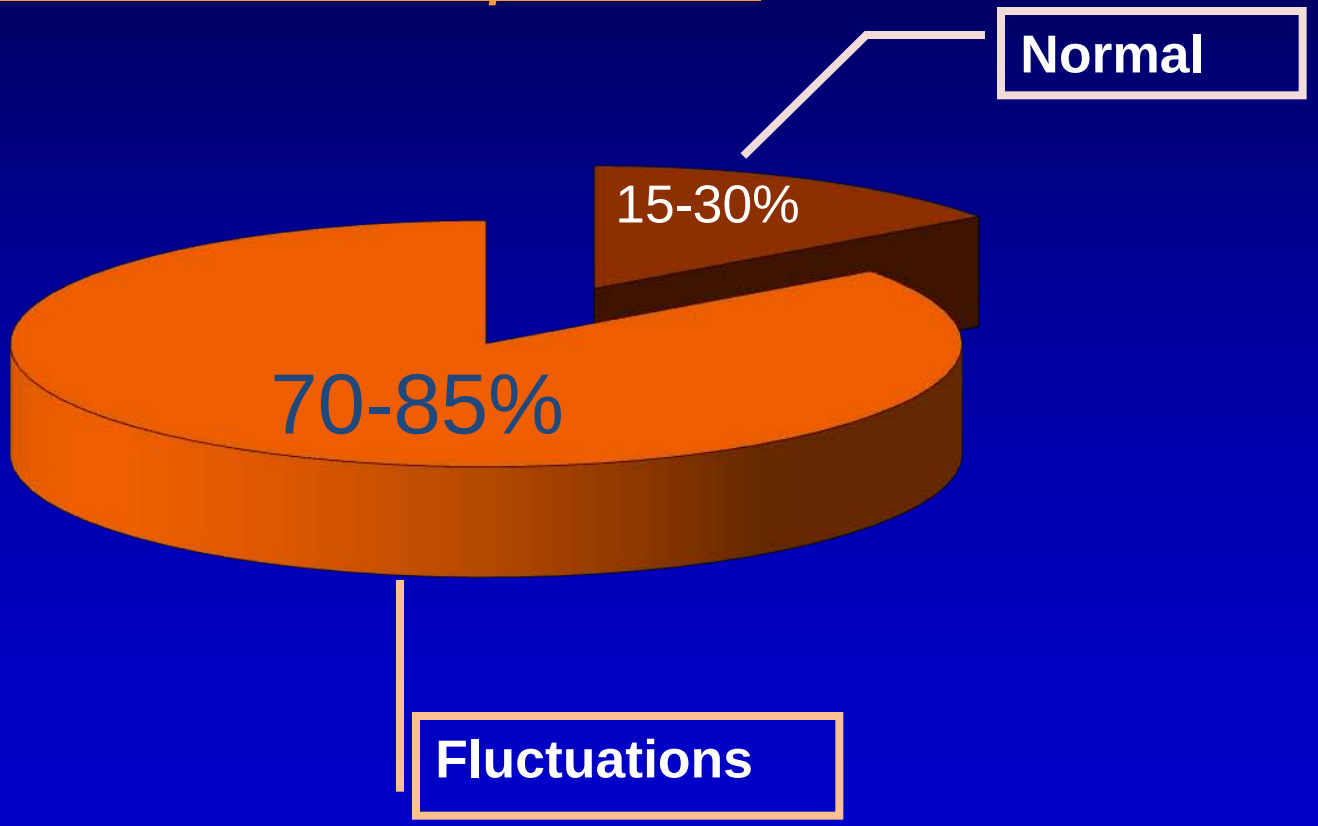
Indication of antiviral treatment

- HCV RNA, *positive*
- Elevated ALT level
- Over stage 2 of Histologic findings in liver biopsy
- No signs of decompensation
  - Hepatic coma, ascites, jaundice

2004, 대한 간학회 Guideline

Characteristics of Hepatitis C Infection

ALT change in chronic hepatitis C



Haber MM *et al., Am J* ***Gastroenterol*** *1995*

권고사항

치료의 대상

- 치료 금기가 없는 모든 C형 간염환자는 치료의 대상으로 고려한다. (A2)

- 치료 여부는 간질환의 중증도, 치료 성공 확률, 심각한 부작용 발생 가능성, 동반 질환유무, 환자의 치료 의지 등을 종합적으로 고려하여 개별화해야 한다. (B1)

치료의 금기증: peginterferon-α and ribavirin

Uncontrolled psychiatric illness or depression

Uncontrolled autoimmune disease

Wait until IFN-free regimen is available

Transplantation of solitary organ except liver

Untreated thyroid illness

Pregnancy or unwilling to comply with adequate contraception

Severe concurrent medical illness such as poorly controlled hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes mellitus, and chronic obstructive pulmonary disease

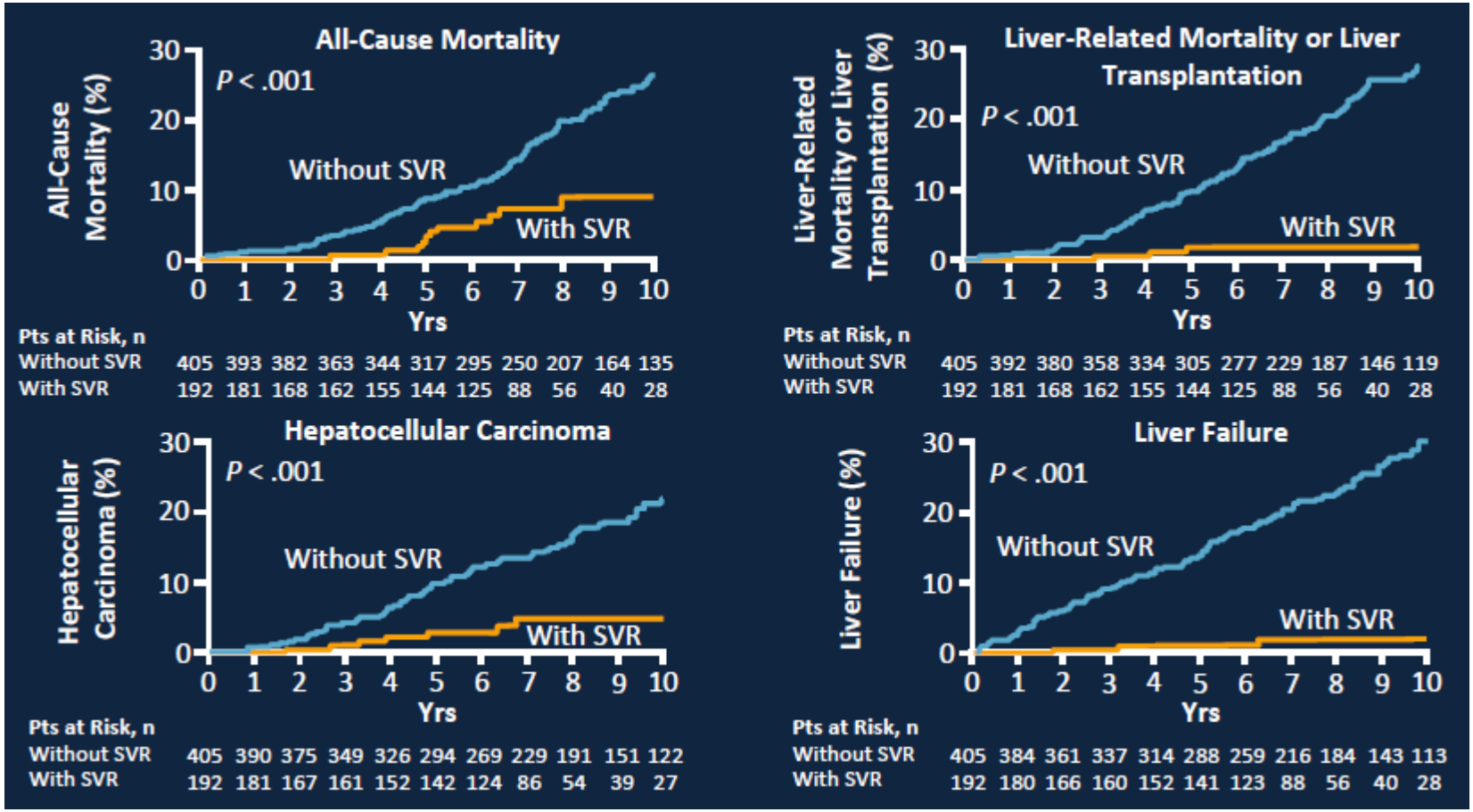
Age ≤ 2 years

Hypersensitivity to peginterferon-alpha or ribavirin

Target of treatment; *Cure*

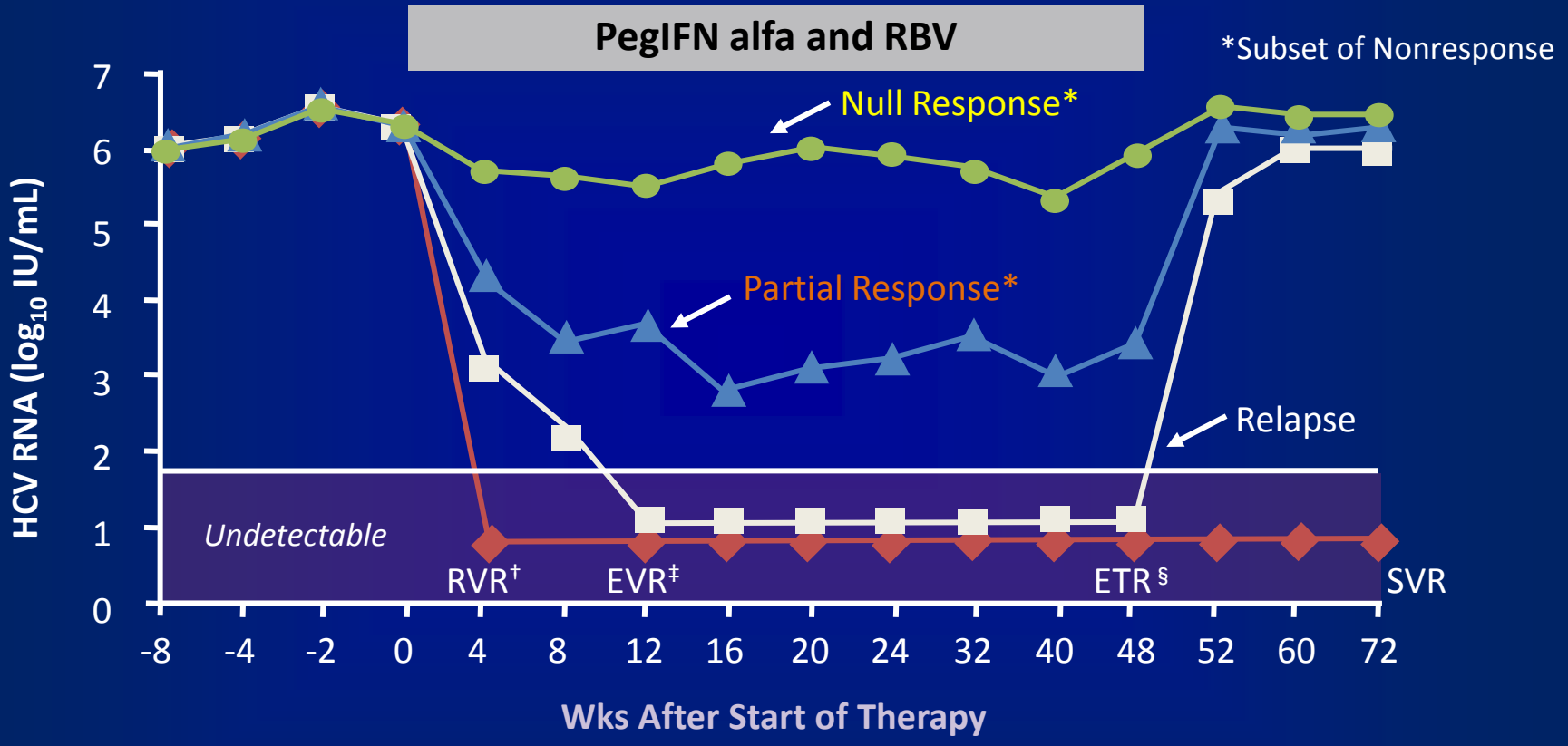
- End of Treatment Response (EOT)
  - End of treatment, HCV RNA(-)
- **Sustained Virologic Response (SVR)**
  - HCV RNA(-), end of treatment & after 6month both
- Relapse
  - End of treatment HCV RNA(-) but HCV RNA(+) during F/U
- Non-respond
  - continue HCV RNA (+) during treatment

Survival outcomes in patients with CHC and advanced fibrosis with/without SVR



Van der Meer AJ, et al. JAMA. 2012;308:2584-2593.7

C형 간염: 바이러스 반응의 패턴



Relapse: reappearance of HCV RNA in serum after discontinuation of therapy ; **Nonresponder**: failure to clear HCV RNA from serum after 24 weeks of therapy ; **Partial nonresponder**: 2 log decrease in HCV RNA but still HCV RNA positive at week 24 ; **Null nonresponder**: failure to decrease HCV RNA by<2 logs after 24 week of therapy

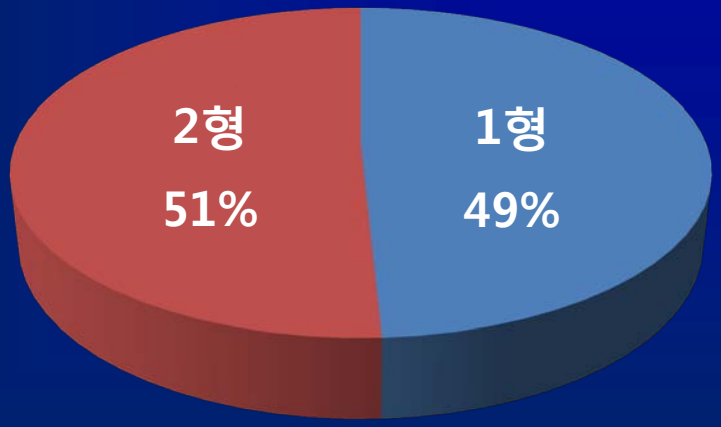
†RVR: Rapid virological response ‡EVR: Early virological response § ETR: End-of-treatment response

Ghany MG, et al. *Hepatology*. 2009;49:1335-1374

C형 간염: HCV 유전자형

- **HCV 유전자형[1]**
  - ✓ 1-6형의 6개의 유전자형으로 구분
  - ✓ 치료 반응을 예측하는 주요 인자로 항바이러스 치료 기간과 약물의 용량 결정에 중요한 정보 제공
  - ✓ 항바이러스 치료 전 HCV 유전자형 검사 반드시 시행

- **한국인의 HCV 유전자형 분포[2]**



HCV: Hepatitis C Virus

1. 2004년 대한간학회 C형 간염 치료 가이드라인. 대한간학회. 2004

2. Kim et al, A nationwide seroepidemiology of hepatitis C virus infection in South Korea. *Liver international* 2013 Apr;33(4):586-94. doi: 10.1111/liv.12108. Epub 2013 Jan 29

Global HCV Prevalence and Genotype Distribution[1]

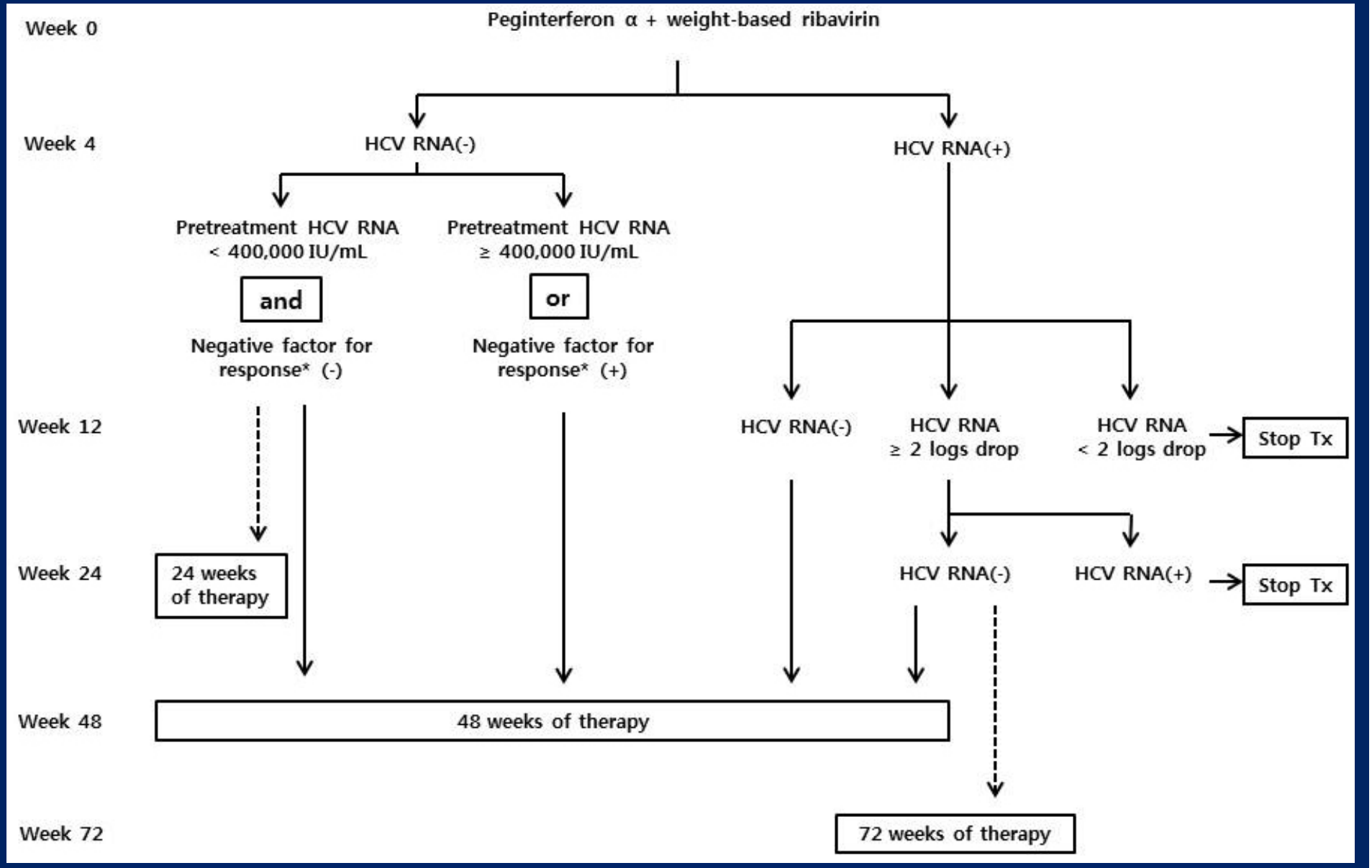
About 150 million people are chronically infected with HCV worldwide[2]

Figure adapted with permission from Center for Disease Analysis (CDA)

HCV = hepatitis C virus.

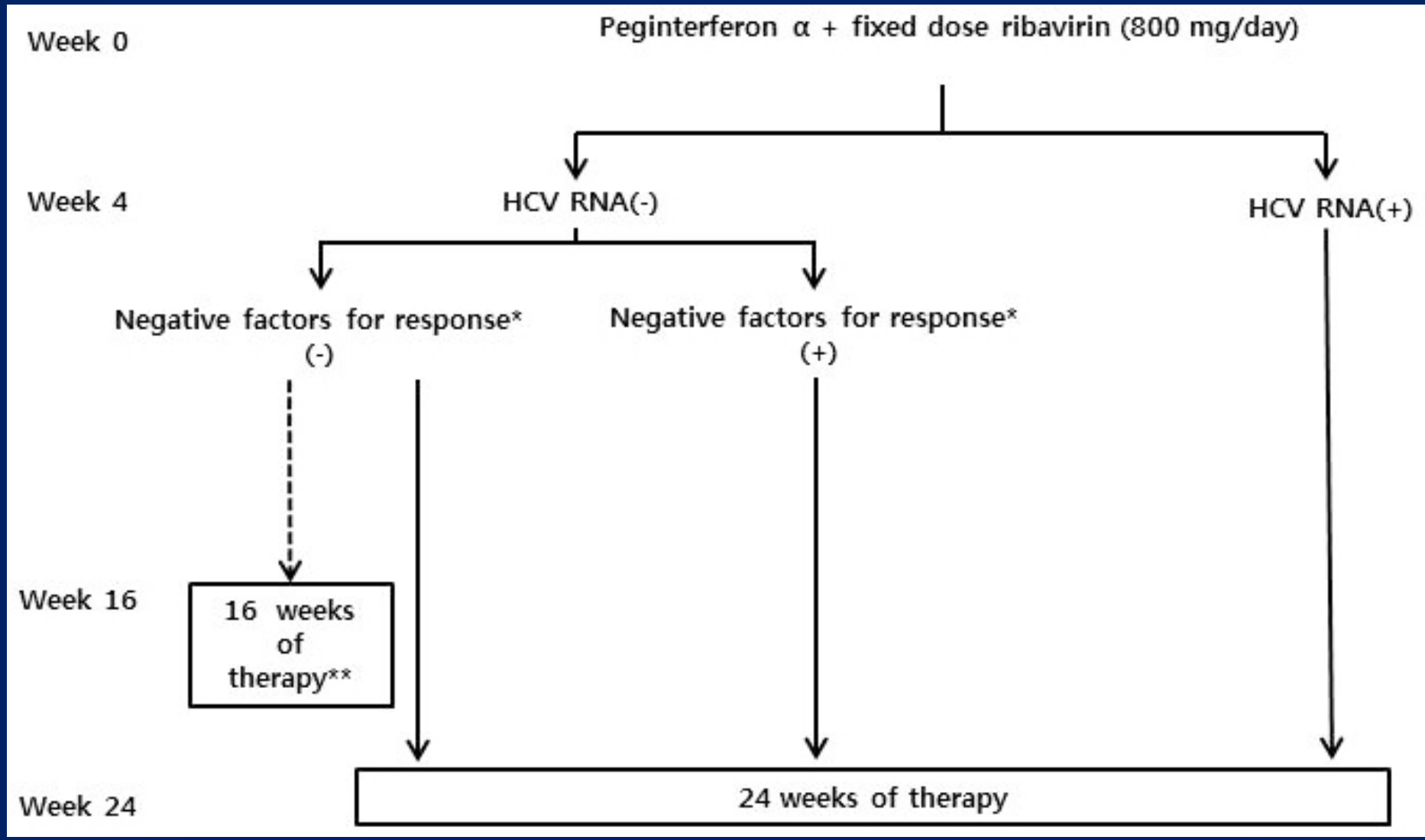
1. Center for Disease Analysis. http://www.c4da.com/Maps/World%20P.jpg. Accessed April 23, 2013. 2. Hepatitis C. World Health Organization Web site. http://www.who.int/mediacentre/factsheets/fs164/en. Accessed April 23, 2013.

2013 대한간학회 C형간염 진료 가이드라인: Treatment algorithm for genotype 1(4)



*Negative factors for response : advanced liver fibrosis or cirrhosis, obesity, insulin resistance

2013 대한간학회 C형간염 진료 가이드라인: Treatment algorithm for genotype 2,3



*Negative factors for response may include advanced fibrosis, cirrhosis and others.
**The shortened therapy may result in higher relapse rate.

Side Effects of IFN Treatment

- **Flu-like symptoms**
  - Headache
  - Fatigue or asthenia
  - Myalgia, arthralgia
  - Fever, chills
- Nausea
- Anorexia
- Diarrhea
- Psychiatric symptoms
  - Depression
  - Insomnia
- Alopecia
- Injection-site reaction
- **Leukopenia**
- Thyroiditis
- Autoimmunity
- Thrombocytopenia

INTRON® A. *PDR*. 56th ed. 2002. ROFERON®-A. *PDR*. 56th ed. 2002.

Side Effects of RBV Treatment

- Hemolytic anemia
- Teratogenicity
- Cough and dyspnea
- Rash and pruritus
- Insomnia
- Anorexia

REBETOL®. *PDR*. 56th ed. 2002. Chutaputti. *J Gastroenterol Hepatol*. 2000 (suppl).

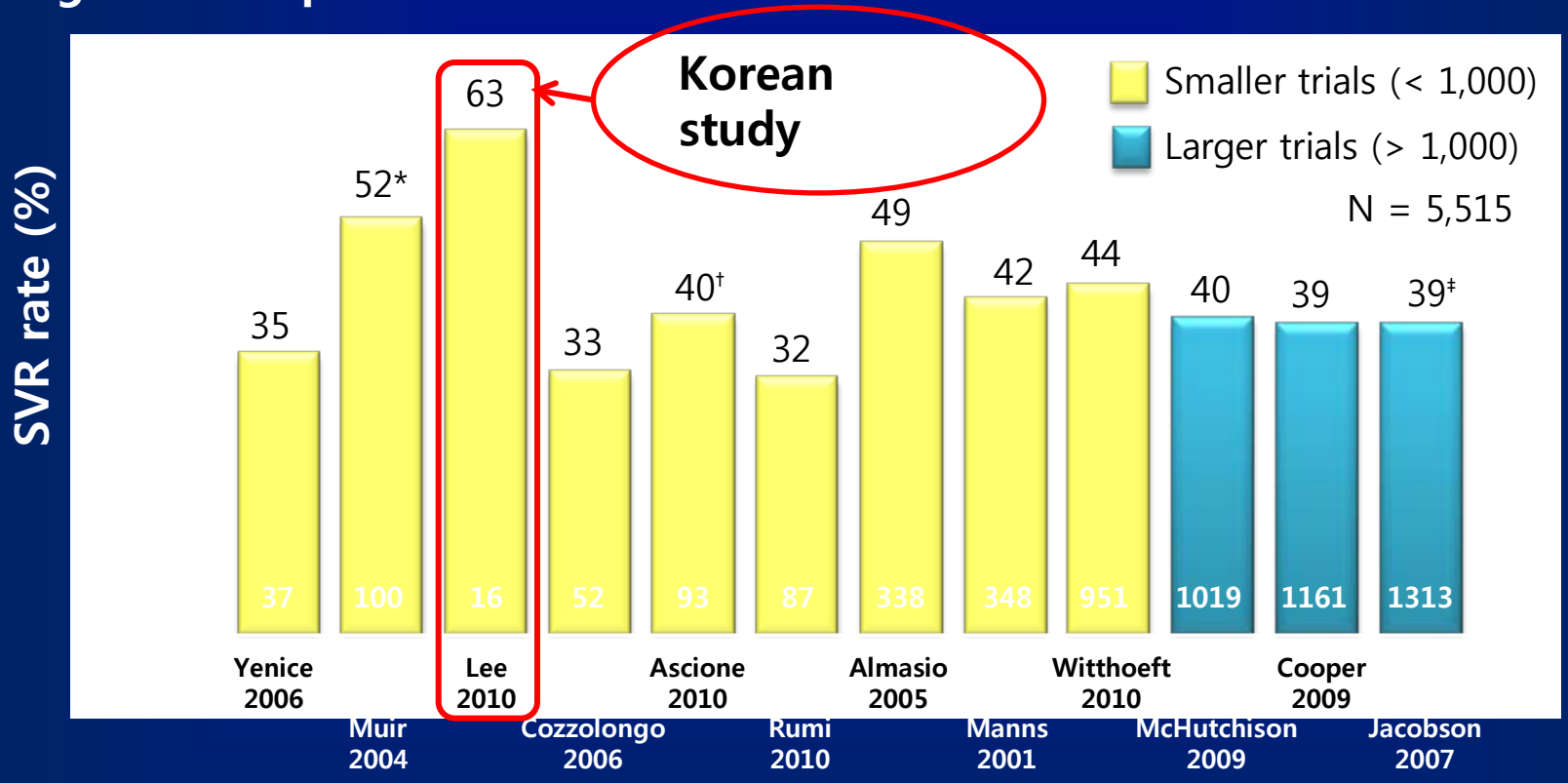
치료 반응 예측 인자

치료 전	치료 중
• HCV 유전자형 • 조직 섬유화 정도 • 숙주의 IL28B 유전적 다형성 • 혈중 HCV RNA 농도 (400,000~800,000 IU/mL) • 기타– 연령, 인종, 체중, 인슐린저항성 등	• RVR • SVR • 치료 순응도

C형 간염: 치료 성적

SVR in HCV-1 patients: 2001–2010

PegIFN α-2b plus RBV



*SVR of non-Hispanic white patient cohort with 98% of them having genotype 1.†99% of patients had HCV-1. ‡Estimated SVR analysis: intended to account for patients with undetectable HCV RNA at the end of treatment and who lacked follow-up data and were considered nonresponders in the primary analysis.

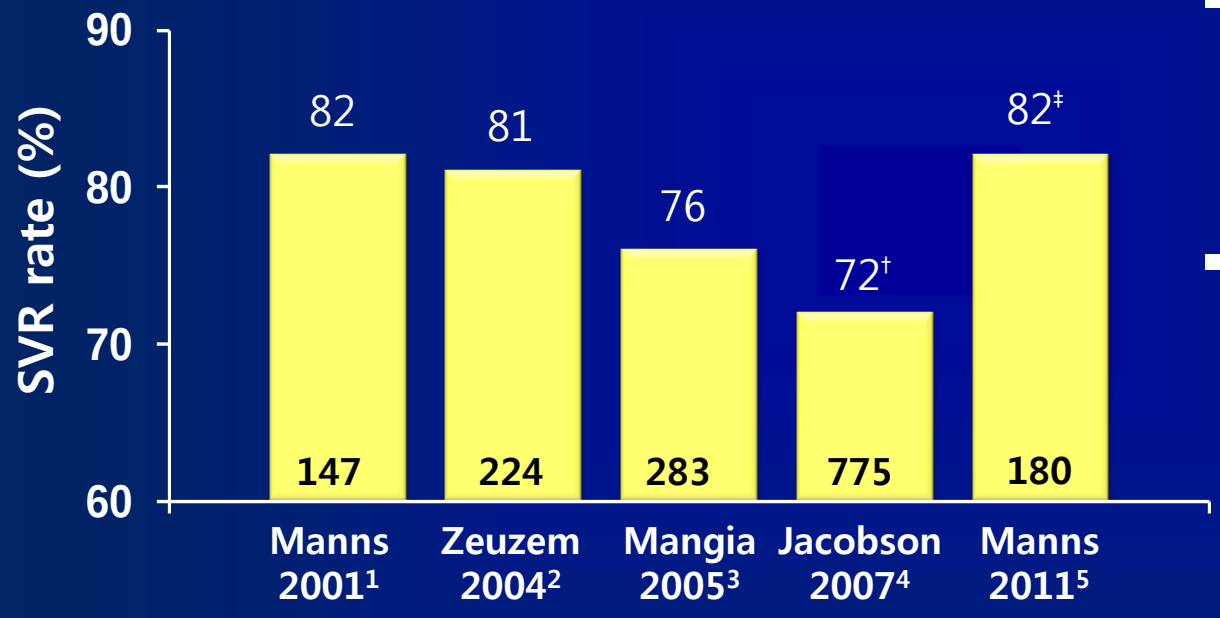
SVR, sustained virologic response, i.e. negative HCV RNA 24 weeks after completion of therapy.

Yenice N, *et al. Turk J Gastroenterol.* 2006;17:94-98; Muir AJ, *et al. N Engl J Med.* 2004;350:2265-2271; Lee S, *et al. Intervirology.* 2010;53:146-153; Cozzolongo R, *et al.* Abstract presented at: 41st Annual EASL; April 26-30, 2006; Vienna, Austria. No. 563; Ascione A, *et al. Gastroenterology.* 2010;138:116-122; Rumi MG *et al. Gastroenterology.* 2010;138:108-115; Almasio PL *et al.* Poster presented at: 56th Annual AASLD; November 11-15, 2005; San Francisco, CA. No. LB03; Manns MP, *et al. Lancet.* 2001;358:958-965; Witthoeft T, *et al. J Viral Hepat.* 2010;17:459-468; McHutchison JG, *et al. N Engl J Med.* 2009;361:580-593; Cooper C, *et al.* Poster presented at: 60th Annual AASLD; October 30-November 3, 2009; Boston, MA. No. 820; Jacobson IM, *et al. Hepatology.* 2007;46:971-981.

C형 간염: 치료 성적

SVR in Western studies of HCV-2/3 patients

PegIFN α-2b plus RBV



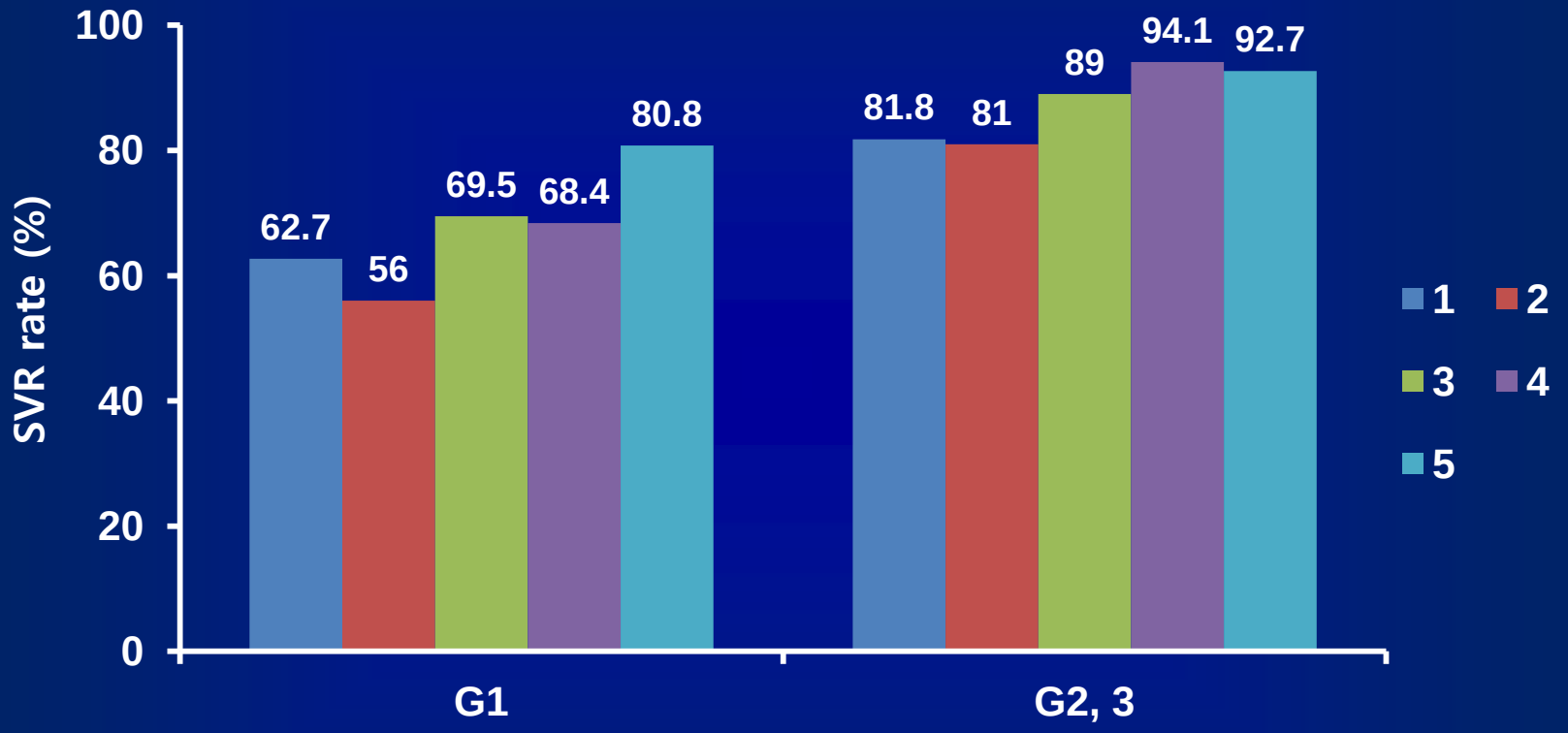
- Patients were treated with pegIFN α-2b (1.5 µg/kg/wk) plus RBV for 48[1] or 24[2–5] weeks.
- Patients with HCV-2/3 often respond more readily to pegIFN α-2b and RBV than do patients with HCV-1.

†Estimated SVR analysis: intended to account for patients with undetectable HCV RNA at the end of treatment and who lacked follow-up data and were considered non-responders in the primary analysis. ‡Completers' analysis, i.e. had both end-of-treatment and 24-week follow-up results.
SVR, sustained virologic response, *i.e.* negative HCV RNA 24 weeks after completion of therapy.

1. Manns MP, *et al. Lancet.* 2001;358:958-965; 2. Zeuzem S, *et al. J Hepatol.* 2004;40:993-999; 3. Mangia A, *et al. N Engl J Med.* 2005;352:2609-2617; 4. Jacobson IM, *et al. Hepatology.* 2007;46:971-981; 5. Manns M, *et al. J Hepatol* 2011;55:554-563.

C형 간염: 치료 성적

SVR in Korean patients



1. N=92, Jeong SW, et al. Korean J Hepatol2009 ;15:338
2. N=92, Kwon JH, et al. Korean J Intern Med 2009;24:203
3. N=192, Kang MJ, et al. Korean J Hepatol 2008;14:318
4. N=86, Lee HJ, et al. Korean J Hepatol 2008;14:46
5. N=343, Song YJ, et al. Korean J Hepatol2010;16(suppl3):S57

C형 간염: 한국인 IL28B 유전자 현황

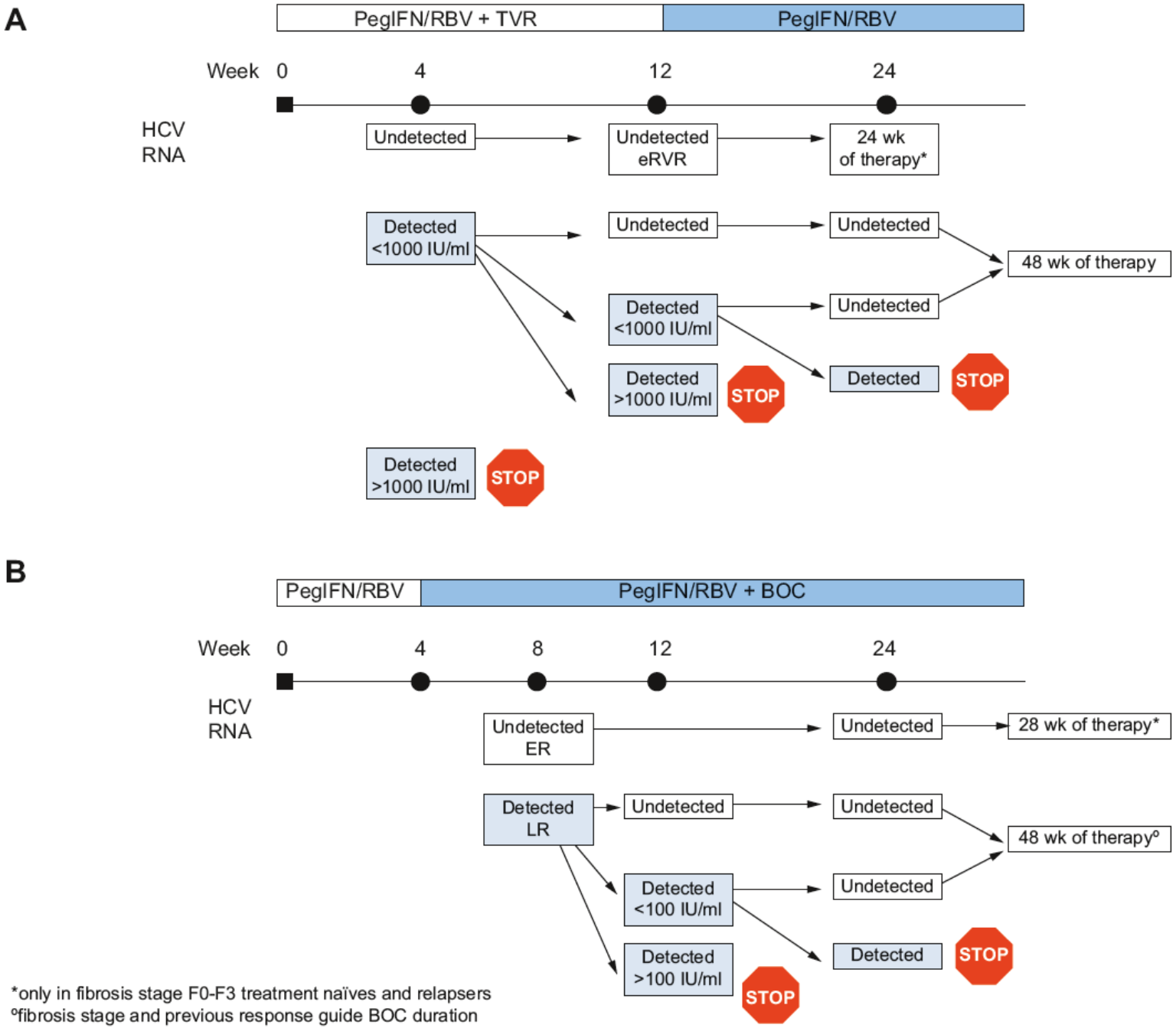
- IL28B polymorphism은 치료 반응 예측에 중요한 factor
- 한국인은 치료 반응이 높은 CC type의 IL28B 유전자 비율이 높음

Genotype frequency (%) of individual SNPs in the Korean and various populations.

Ethnicity	rs12979860			
	CC	CT	TT	*P* value[a]
Caucasians	37.2	50.9	11.9	$3.7X10^{-7}$
African-American	14.0	48.7	37.3	$9.4X10^{-33}$
Hispanic	29.3	48.3	22.4	$7.1X10^{-15}$
Japanese	68.8	29.6	1.4	$2.3X10^{-3}$
Taiwanese	89.9	10.1	0.1	0.579
Korean	87.7	12.7	0	-

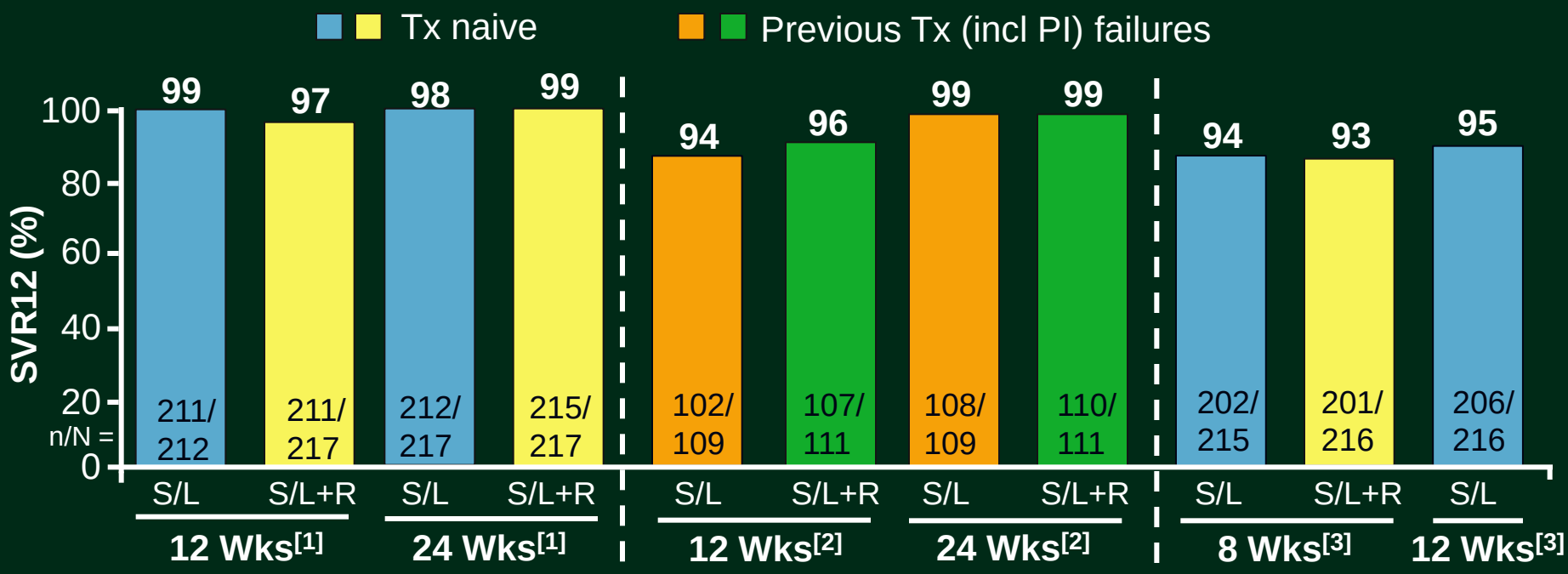
[a] Comparison of genotype frequency (CC and CT + TT for rs12979860) between Korean and other ethnic groups

Lyoo L et al, Polymorphism near the IL28B gene in Korean hepatitis C virus-infected patients treated with peg-interferon plus ribavirin. *J Clin Virol.* 2011 Dec;52(4):363-6. doi: 10.1016/j.jcv.2011.08.006. Epub 2011 Sep 9.



*only in fibrosis stage F0-F3 treatment naïves and relapsers
°fibrosis stage and previous response guide BOC duration

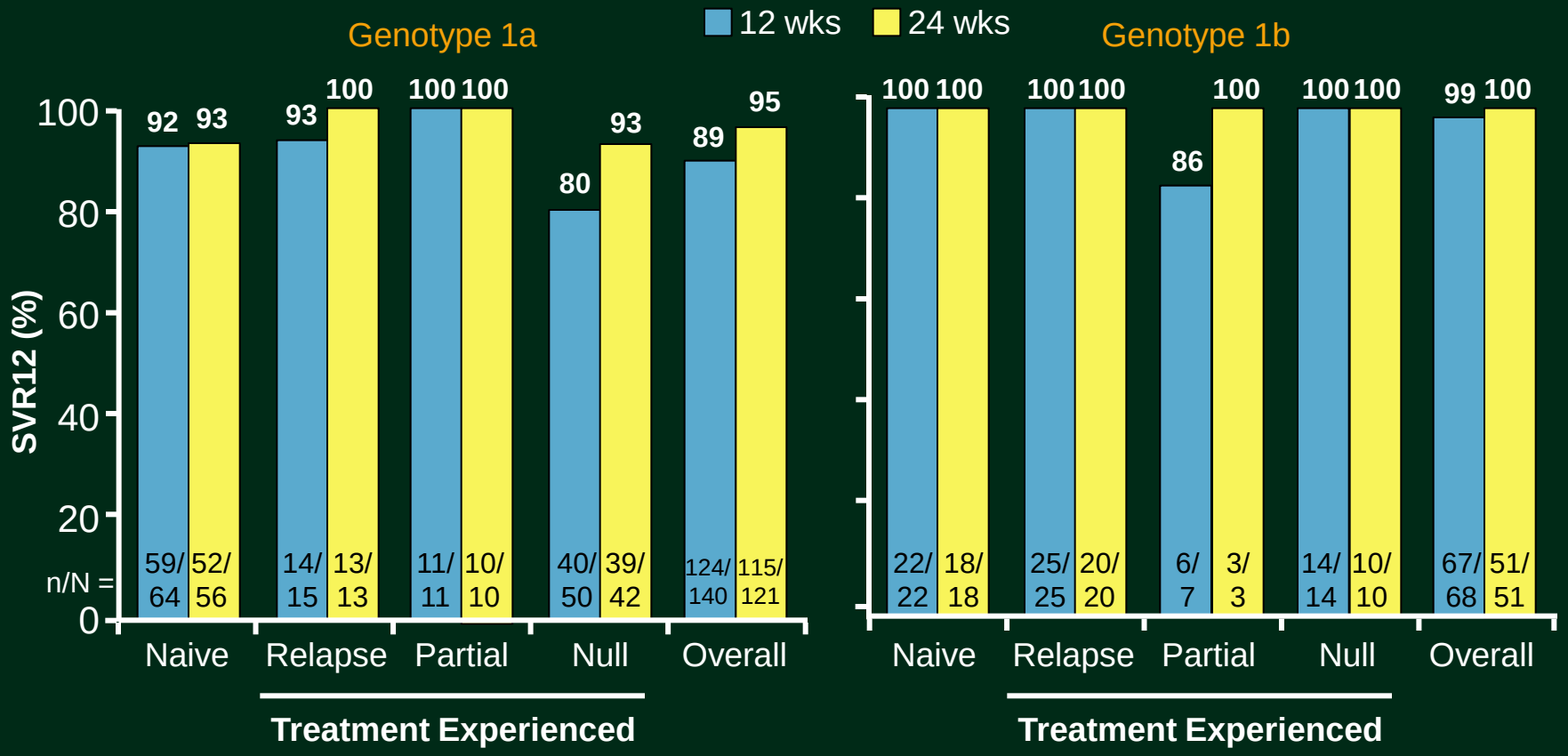
ION 1, 2, and 3: Sofosbuvir/Ledipasvir ± RBV in Tx-Naive Pts and Previous Failures



- 8 wks adequate for noncirrhotic treatment-naive pts
- RBV provides no benefit
- No SOF resistance observed; most virologic failures have LDV resistance

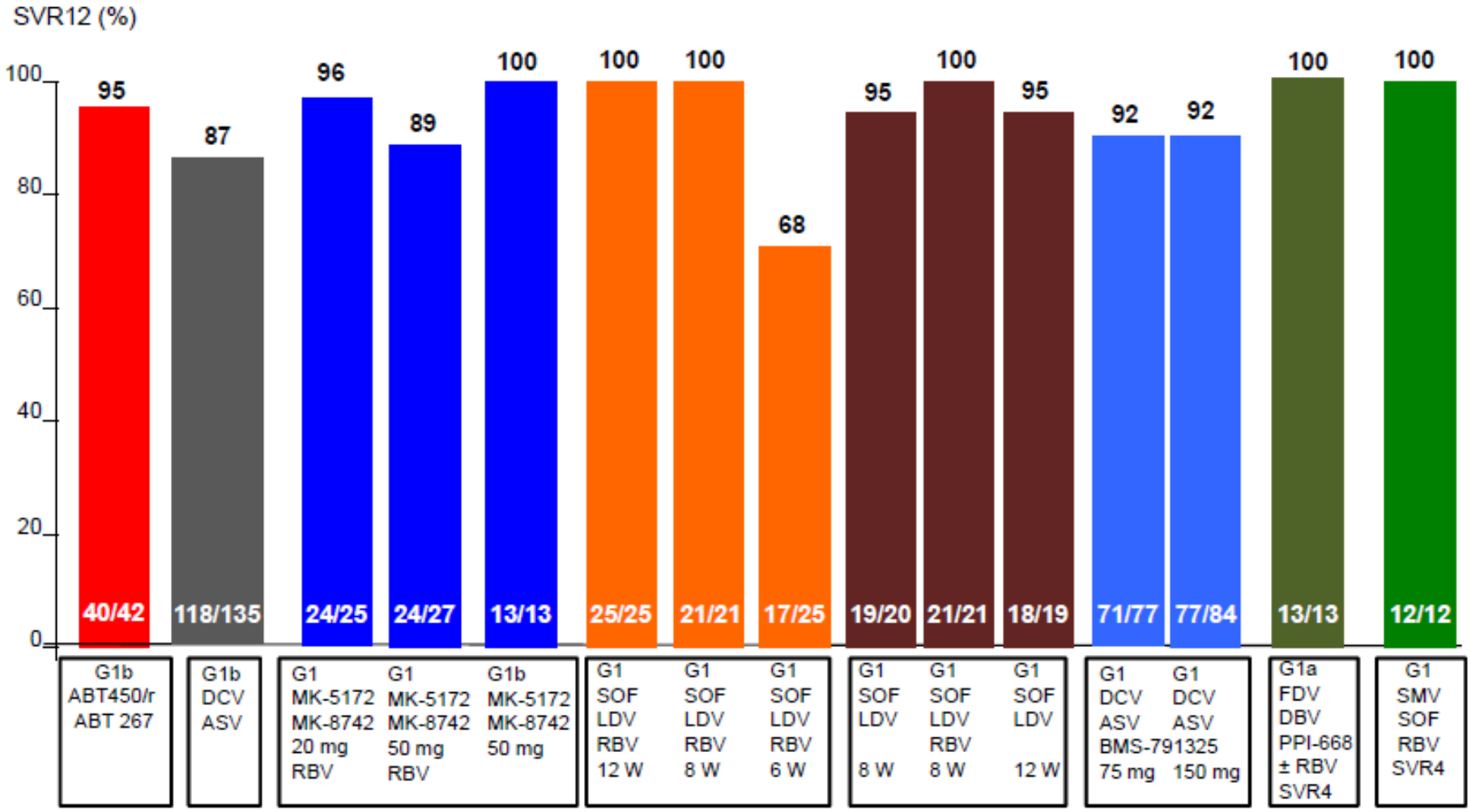
1. Afdhal N, et al. N Engl J Med. 2014;370:1889-1898. 2. Afdhal N, et al. N Engl J Med. 2014;370:1483-1493. 3. Kowdley KV, et al. N Engl J Med. 2014;370:1879-1888.

TURQUOISE II: 12 vs 24 Wks of OMV/PTV/RTV + DSV + RBV in Cirrhotics



Poordad F, et al. EASL 2014. Abstract O163. Poordad F, et al. N Engl J Med. 2014;370:1973-1982. Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

IFN free regimen for G1 Tx-Naive



Pearl-1, ABT450/r + ABT 267; Lawitz et al. AASLD 2013, A75.

Daclatasvir (DCV) + asunaprevir (ASV); Chayama et al. AASLD 2013, A211.

C-Worthy , MK-5172/MK-8742 ± RBV; Lawitz et al. AASLD 2013, A76.

Electron, SOF/ledipasvir (LDV) ± RBV; Gane et al. AASLD 2013, A73

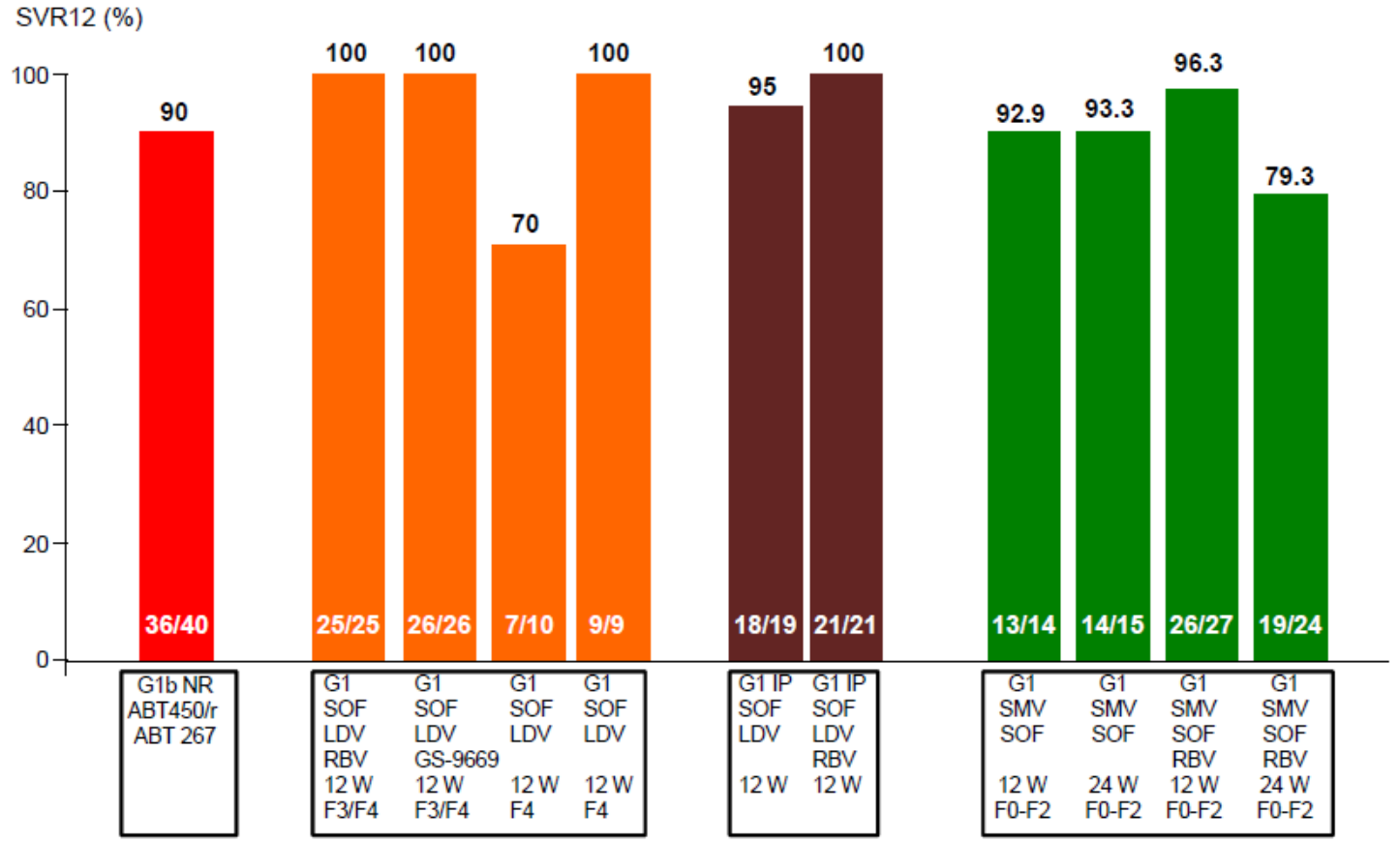
Lonestar : sofosbuvir (SOF)/ledipasvir (LDV) ± RBV; Lawitz et al. AASLD 2013, A215/1844.

Daclatasvir (DCV) + asunaprevir (ASV) + BMS-791325; Everson et al. AASLD 2013, ALB1.

Faldaprevir (FDV), deleobuvir (DBV) +PPI-668; Lalezari et al. AASLD 2013 ALB20.

Cosmos : sofosbuvir (SOF)/simeprevir (SMV) ± RBV; Jacobson et al. AASLD 2013, ALB3.

IFN free regimen for G1 Tx-Experienced



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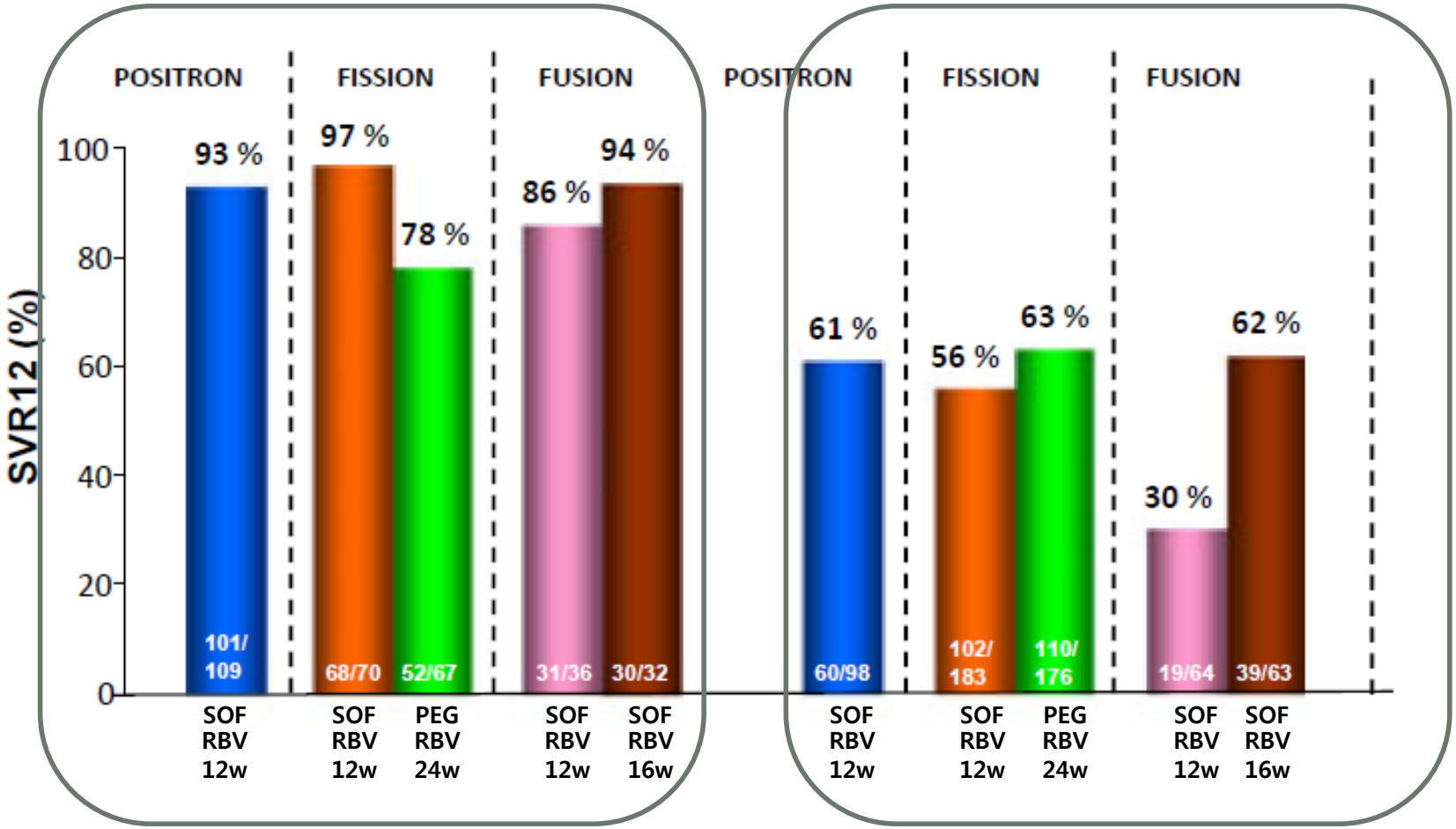
Electron : sofosbuvir (SOF)/ledipasvir (LDV) ± RBV; Gane et al. AASLD 2013, A73.

Lonestar : sofosbuvir (SOF)/ledipasvir (LDV) ± RBV; Lawitz et al. AASLD 2013, A215/1844.

Cosmos : sofosbuvir (SOF)/simeprevir (SMV) ± RBV; Jacobson et al. AASLD 2013, ALB3.

IFN free regimen for non-genotype 1 subject



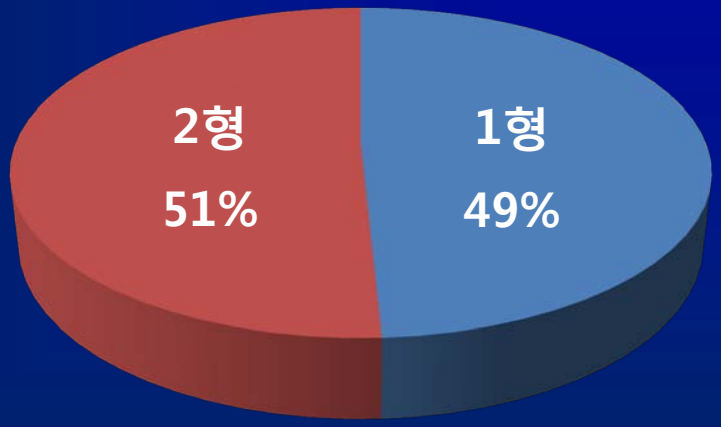
Genotype 2

Genotype 3

C형 간염: HCV 유전자형

- **HCV 유전자형[1]**
  - ✓ 1-6형의 6개의 유전자형으로 구분
  - ✓ 치료 반응을 예측하는 주요 인자로 항바이러스 치료 기간과 약물의 용량 결정에 중요한 정보 제공
  - ✓ 항바이러스 치료 전 HCV 유전자형 검사 반드시 시행

- **한국인의 HCV 유전자형 분포[2]**

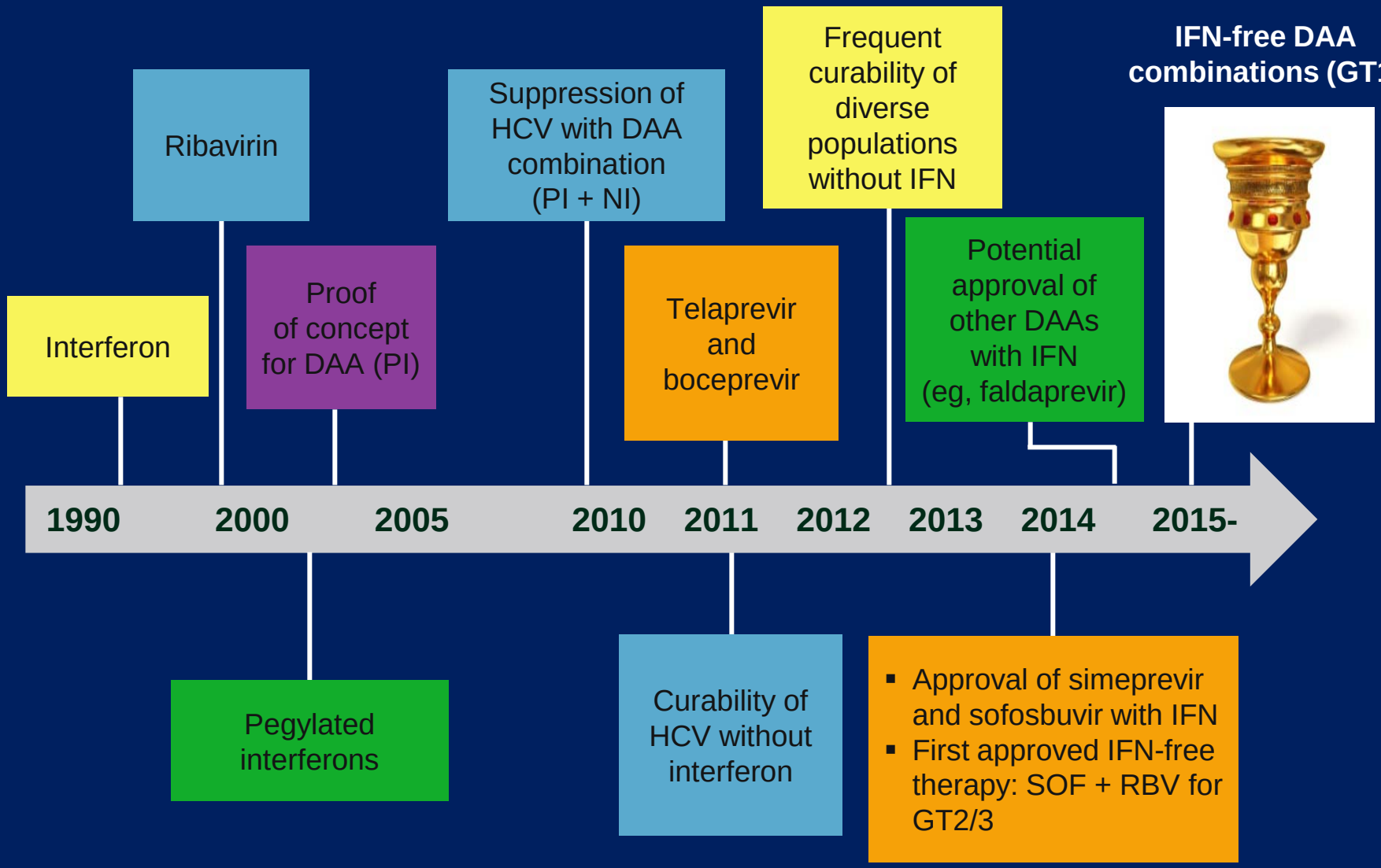


HCV: Hepatitis C Virus

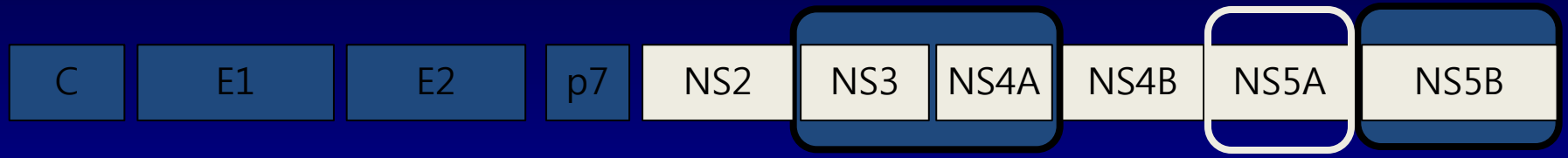
1. 2004년 대한간학회 C형 간염 치료 가이드라인. 대한간학회. 2004

2. Kim et al, A nationwide seroepidemiology of hepatitis C virus infection in South Korea. *Liver international* 2013 Apr;33(4):586-94. doi: 10.1111/liv.12108. Epub 2013 Jan 29

HCV Therapy: Past, Present and Future



Direct-Acting Antiviral Agents: Key Characteristics



NS3/4A Protease Inhibitors (PI)

High potency

Limited genotypic coverage

Low barrier to resistance

NS5B Nucleos(t)ide Inhibitors (NI)

Intermediate potency

Pangenotypic coverage

High barrier to resistance

NS5A Inhibitors

High potency

Multigenotypic coverage

Low barrier to resistance

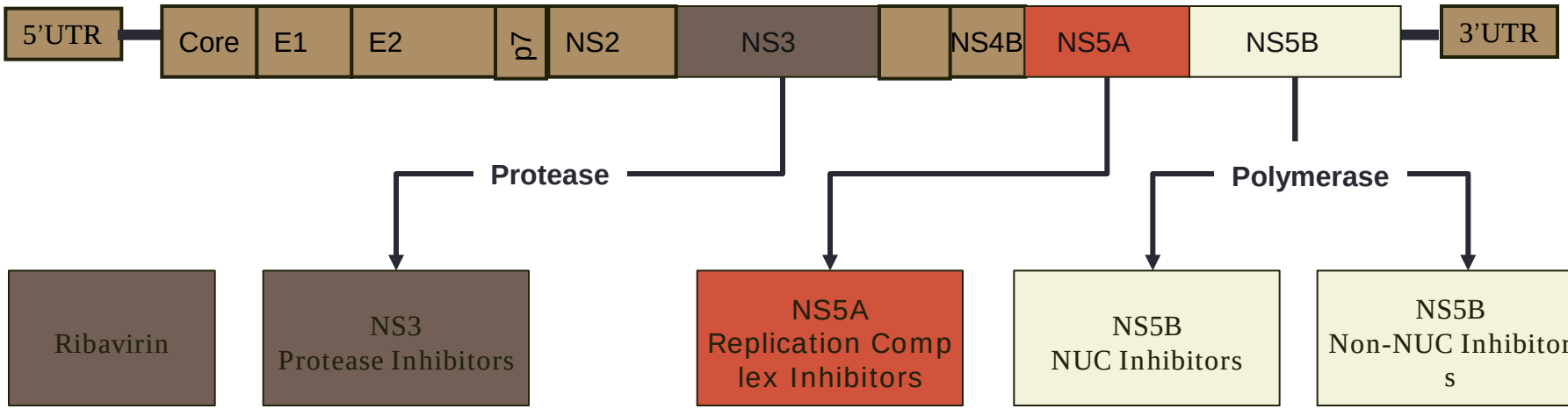
NS5B Nonnucleoside Inhibitors (NNI)

Intermediate potency

Limited genotypic coverage

Low barrier to resistance

Multiple Classes of DAA Agents



Telaprevir
Boceprevir
Simeprevir
Asunaprevir
ABT-450
MK-5172
Faldaprevir
Sovaprevir
ACH-2684

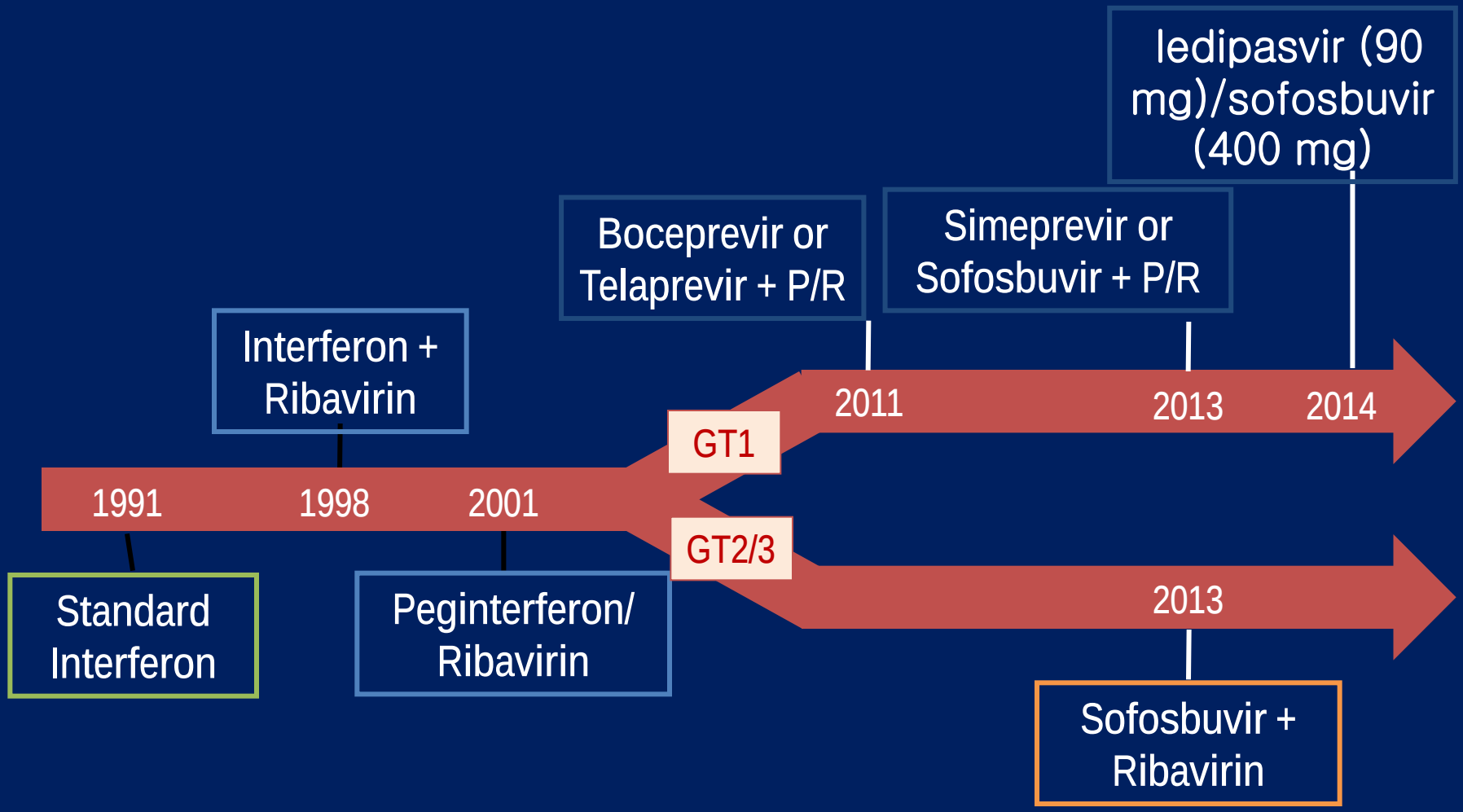
Daclatasvir
Ledipasvir
Ombitasvir
MK-8742
GS-5885
GS-5816
ACH-3102
PPI-668
GSK2336805
Samatasvir

Sofosbuvir
VX-135
IDX21437
ACH-3422

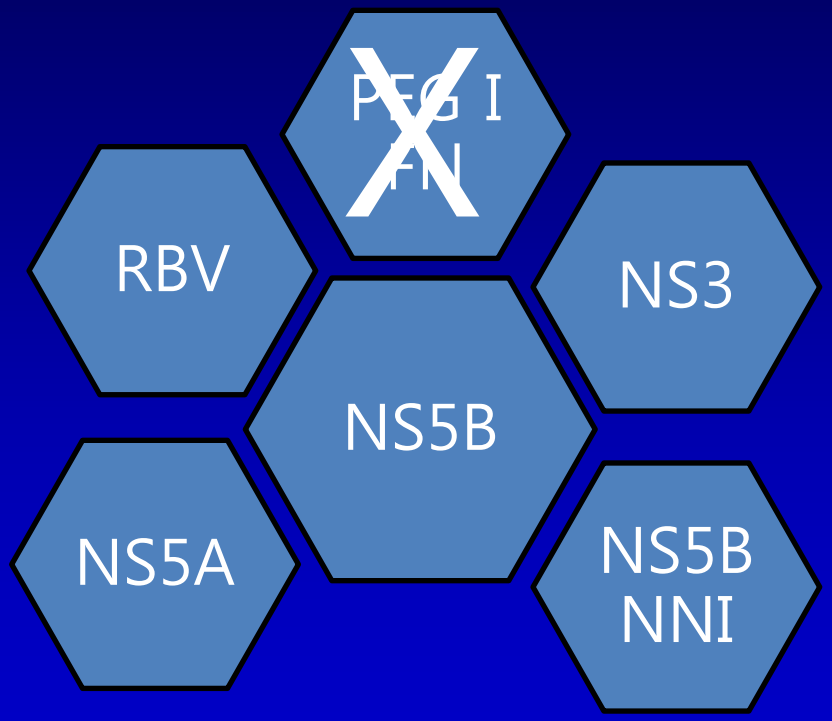
Dasabuvir
BMS-791325
PPI-383
GS-9669
TMC647055

*Representative list; may not be fully inclusive.

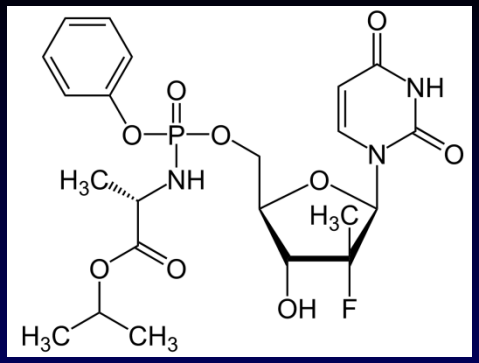
New Standard of Care for HCV in 2015 in USA



The Building Blocks for SVR in HCV Pre– and Post–Liver Transplantation



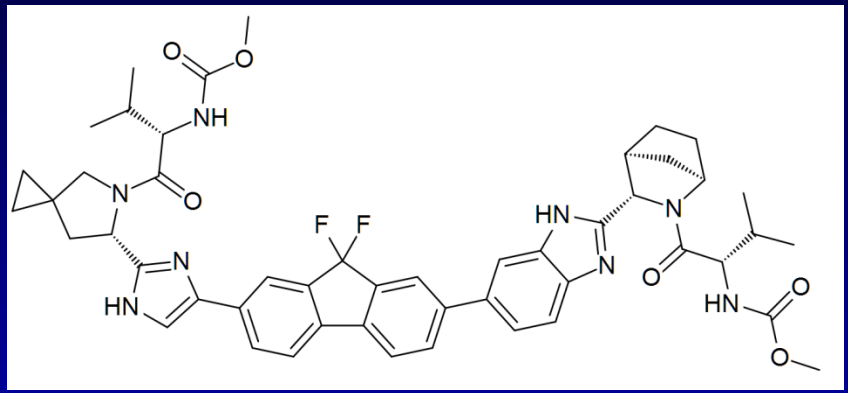
Sofosbuvir



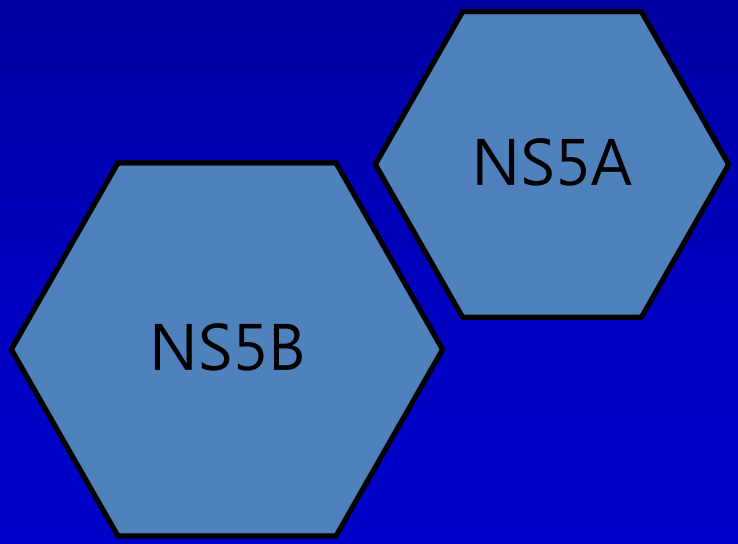
- Oral, once-daily nucleotide NS5B polymerase inhibitor
- Potent antiviral activity; pangenotypic
- High barrier to resistance
- Pharmacology profile
  - No significant drug interactions, including tacrolimus or cyclosporine
- Approved for combination treatment of HCV in following settings
  - Genotypes 1, 2, 3, 4 HCV
  - HCC meeting Milan criteria; awaiting transplantation
  - HIV coinfection

Sofosbuvir/Ledipasvir

- Ledipasvir
  - Picomolar potency against GT1a and 1b HCV[1]
  - Once-daily, oral, 90 mg



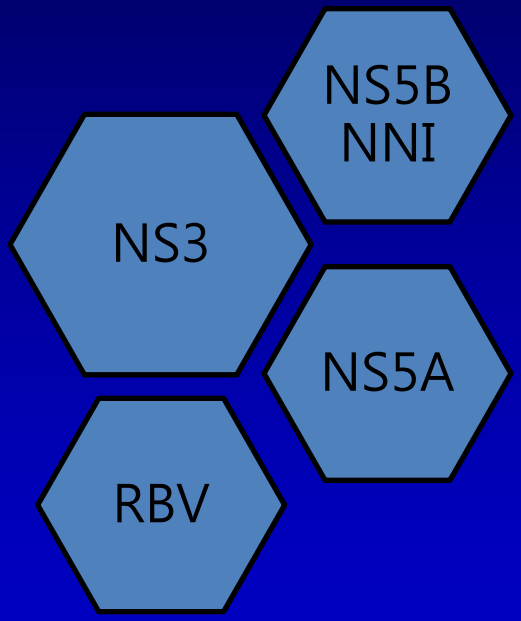
- Ledipasvir/sofosbuvir FDC
  - Once-daily, oral FDC tablet (90/400 mg)



1. Lawitz E, et al. EASL 2011. Abstract 1219.

ABT-450/RTV/Ombitasvir + Dasabuvir

- ABT-450 (paritaprevir): potent NS3/4A protease inhibitor
  - RTV boosting to increase peak, trough, and overall exposures of ABT-450
    - Enables once-daily dosing
- Ombitasvir: potent NS5A inhibitor
  - Coformulated with ABT450/RTV
- Dasabuvir: nonnucleoside NS5B polymerase inhibitor



INITIAL TREATMENT OF HCV INFECTION: GT1a

- ledipasvir (90mg)/sofosbuvir (400 mg) for 12 weeks

- paritaprevir (150mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)

- Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)

INITIAL TREATMENT OF HCV INFECTION: GT1b

- ledipasvir (90mg)/sofosbuvir (400 mg) for 12 weeks

- paritaprevir (150mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks with weight-based RBV (1000mg [<75kg] to 1200 mg [>75 kg]) (cirrhosis)

- Daily sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)

NOT recommended for treatment naive patients with HCV genotype 1

- Daily sofosbuvir (400 mg) and weight-based RBV (1000mg [<75 kg] to 1200 mg [?75 kg]) for 24 weeks
- PEG-IFN and RBV with or without sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 weeks to 48weeks.
- Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Treatment-naive patients with HCV genotype 2

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg[<75 kg] to 1200 mg [>75 kg]) for 12 weeks or 16 weeks (cirrhosis)

NOT recommended for treatment naive patients with HCV genotype 2.

- PEG-IFN and RBV for 24 weeks
- Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral
- Telaprevir-, boceprevir-, or ledipasvir-containing regimens

Mixed Genotypes

- Correct combination or duration: unclear
- Maximize efficacy against each genotype

Drug Interactions With DAA

서울대학교병원 SEOUL NATIONAL UNIVERSITY HOSPITAL

Concomitant Medications	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Acid-reducing agents*	X	X		
Alfuzosin/tamsulosin		X		
Anticonvulsants	X	X	X	X
Antiretrovirals*	Coming Soon	Coming Soon	Coming Soon	tipranavir / ritonavir only
Azole antifungals*		X	X	
Buprenorphine/naloxone		X		
Calcineurin inhibitors*		X	X	
Calcium channel blockers*		X	X	
Cisapride		X	X	
Digoxin	X		X	
Ergot derivatives		X		
Ethinyl estradiol–containing products		X		
Furosemide		X		
Gemfibrozil		X		

Concomitant Medications	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Glucocorticoids		X (inhaled, intranasal	X	
Herbals St. John's wort Milk thistle		X	X X	X
Macrolide antimicrobials*			X	
Other antiarrythmics*		X	X	
Phosphodiesterase type 5 inhibitors*		X	X	
Pimozide		X		
Rifamycin antimicrobials*	X	X	X	X
Salmeterol		X		
Sedatives*		X	X	
Simeprevir	X			
Statins*	X	X	X	

ReTx after PR: *HCV genotype 1b without LC*

- ledipasvir (90mg)/sofosbuvir (400 mg) for 12 weeks
- paritaprevir (150mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks
- Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks

ReTx after PR: *HCV GT1a or 1b with compensated LC*

- ledipasvir (90mg)/sofosbuvir (400 mg) for 24 weeks
- ledipasvir (90mg)/sofosbuvir (400 mg) plus weight-based RBV (1000 mg[<75 kg] to 1200 mg [>75 kg]) for 12 weeks
- paritaprevir (150mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-dailydosed dasabuvir (250 mg) and weight-based RBV (1000 mg[<75 kg] to 1200 mg [>75 kg]) for 24 weeks with 1a and for 12 weeks with 1b
- sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks

Ssofosbuvir-containing regimen failure: GT1

- *Advanced Fibrosis –*
  - clinical trial
- *Advanced Fibrosis +*
  - ledipasvir (90mg)/sofosbuvir (400 mg) with or without weight-based RBV(1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks

PEG-IFN, RBV & PI failure: GT1

- LC (-)
  - ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks
- LC(+):
  - ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks
  - ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200mg [>75 kg]) for 12 weeks

PR failure GT2

- sofosbuvir (400 mg) and weight-based RBV (1000 mg[<75 kg] to 1200 mg [>75 kg]) for 12 weeks to 16 weeks

- daily sofosbuvir (400 mg) and weight based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG-IFN for 12 weeks

DECOMPENSATED LC: GT1 & 4

- Refer to *liver transplant center*
- ledipasvir (90 mg)/sofosbuvir(400 mg) & RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks
- Anemia: ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks
- Sof failure: ledipasvir (90 mg)/sofosbuvir (400 mg) and RBV (initial dose of 600 mg, increased as tolerated) for 24 weeks

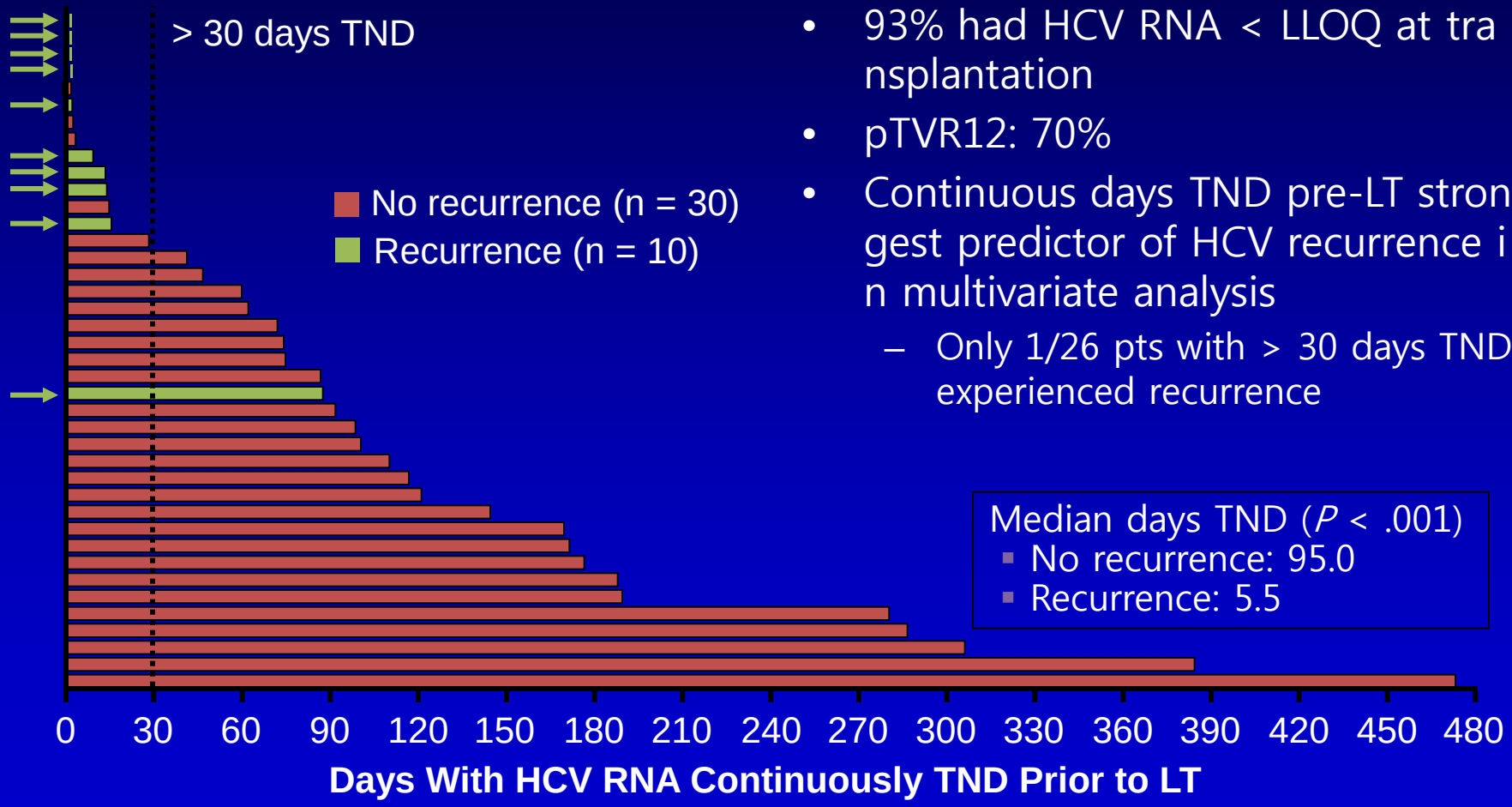
DECOMPENSATED LC: GT 2 & 3

- Refer to *liver transplant center*

- sofosbuvir (400 mg) and weight-based RBV (1000 mg[<75 kg] to 1200 mg [>75 kg]) for up to 48 weeks

Interferon-Free, All-Oral Regimens Available for Transplantation Patients

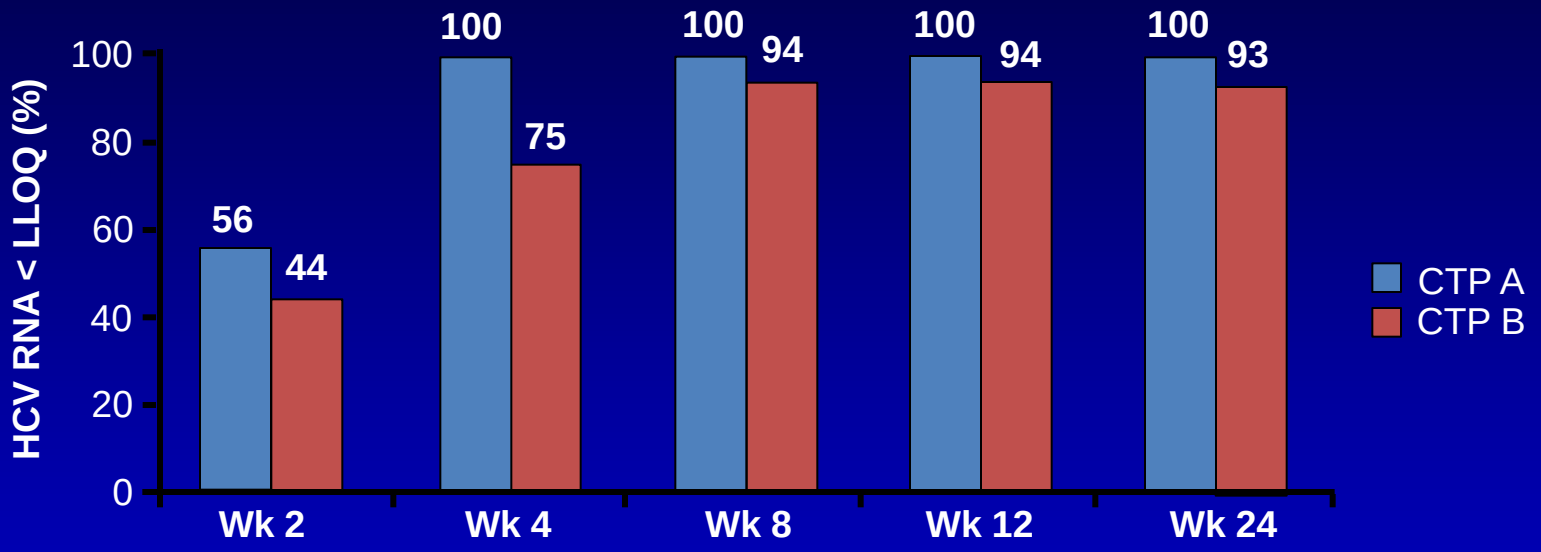
Duration of Undetectable HCV RNA Before Transplant Predicted Lack of Recurrence



- 93% had HCV RNA < LLOQ at transplantation
- pTVR12: 70%
- Continuous days TND pre-LT strongest predictor of HCV recurrence in multivariate analysis
  - Only 1/26 pts with > 30 days TND experienced recurrence

Curry MP, et al. ILTS 2014. Abstract O-137.

On-Treatment Virologic Response to SOF + RBV in Patients With Portal Hypertension



Clinical Events, n	Ascites		Hepatic Encephalopathy	
	SOF + RBV (n = 25)	Observation (n = 25)	SOF + RBV (n = 25)	Observation (n = 25)
Baseline	6	9	5	2
Wk 12	5	8	3	3
Wk 24	0	7	0	4

Afdhal N, et al. EASL 2014. Abstract O68.

RECURRENT HCV INFECTION POST–LT

- GT 1 & 4 including compensated LC
  - ledipasvir (90mg)/sofosbuvir (400 mg) with weight-based RBV (1000 mg[<75 kg] to 1200 mg [>75 kg]) for 12 weeks
  - ledipasvir (90mg)/sofosbuvir (400 mg) for 24 weeks
  - GT1: sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [> 75 kg]) for 12 weeks

Tx-naive and -experienced including compensated cirrhosis after LT

- *GT 2:* sofosbuvir (400 mg) and weight-based RBV (1000 mg[<75 kg] to 1200 mg [>75 kg]) for 24 weeks

- GT3: sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks

Tx-naive &-experienced with decompensated LC after LT

- GT 1 or 4: ledipasvir (90mg)/sofosbuvir (400 mg) with a low initial dose of RBV (600mg, increasing as tolerated) for 12 weeks
- GT2: sofosbuvir (400 mg) and RBV (initial dose 600 mg/day,increased monthly by 200 mg/day as tolerated to 1000 mg [<75 kg] to 1200 mg [>75 kg] mg) for 24 weeks
- GT3: sofosbuvir (400 mg) and low initial dose of RBV (600mg, increasing as tolerated) for 24 weeks

Mild to moderate renal impairment (CrCl>30 mL/min)

- No dosage adjustment using sofosbuvir, simeprevir, fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg)

- CrCl < 30 mL/min: not known

Renal Impairment	eGFR / CrCl level (mL/min)	IFN	RBV	Sofosbuvir	Ledipasvir	Ombitasvir	Dasabuvir	Paritaprevir	Simeprevir
Mild	50-80	180 ug PEG-IFN (2a); PEG-IFN (2b) 1.5 ug/Kg	Standard	Standard	Standard	Standard	Standard	Standard	Standard
Moderate	30-50	180ug PEG-IFN (2a); PEG-IFN (2b) 1 ug/kg (25% reduction)	Alternating doses 200 mg and 400 mg every other day	Standard	Standard	Standard	Standard	Standard	Standard
Severe	<30	135 ug PEG-IFN (2a); PEG-IFN (2b) 1 ug/kg (50% reduction)	200 mg/d	Data not available	Data not available	Data not available	Data not available	Data not available	Standard
ESRD/HD		PEG-IFN (2a) 135 µg/wk or PEG-IFN (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk	200 mg/d	Data not available	Data not available	Data not available	Data not available	Data not available	Data not available

MONITORING PATIENTS

- Assessment of potential drug-drug interactions
- CBC, Cr, PT, LFT, GFR, hCG (RBV)
- TSH (if IFN) q 12 weeks
- HCV genotype and subtype
- Quantitative HCV viral load: 0, 4 weeks, ET, 12 (24) weeks after Tx

Discontinuation of treatment

- Detectable at week 4 & increase >1 log10 IU/mL at week 6

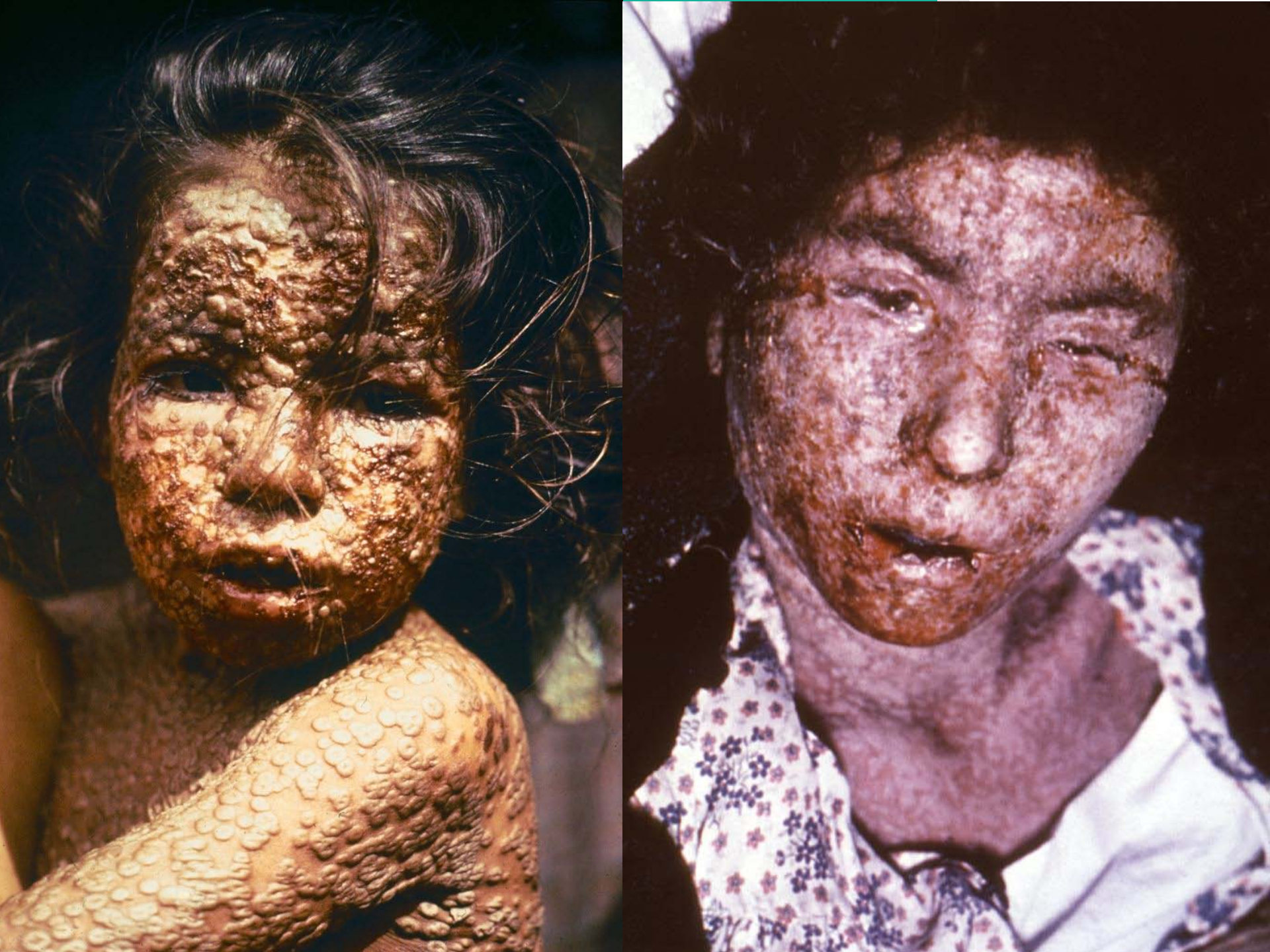
- Detectable at week 4 & lower at week 6 or 8
  - Unknown
  - Do not stop or extend Tx

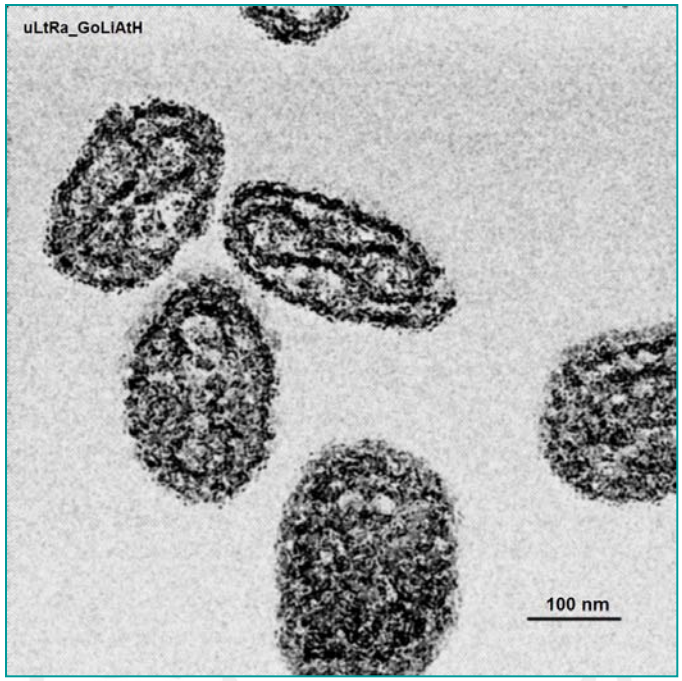
After Tx

- SVR –
  - CBC, PT, LFT q 6 – 12 months
  - Metavir stage F3 or F4: USG q 6 months
  - Varix surveillance
- SVR +
  - Metavir stage F0-F2: normal
  - Metavir stage F3 or F4: USG q 6 months, varix surveillance

요 약

- PR로 완치가능, 비교적 높은 치료성공률. Vs. 부작용
- Boceprevir, Telaprevir: little role
- 현재 경구약제 치료로 완치율 90%이상 가능
  - Cirrhosis, 과거 치료 여부에 따라
- 이식 전 vs. 이식 후 치료
- Drug-drug interaction
- 얼마나 비용이 들 것인가? -가장 비용효과적인 치료는?
- 치료 후에도 진행된 간섬유화 환자들에서는 간암발생 위험 상존

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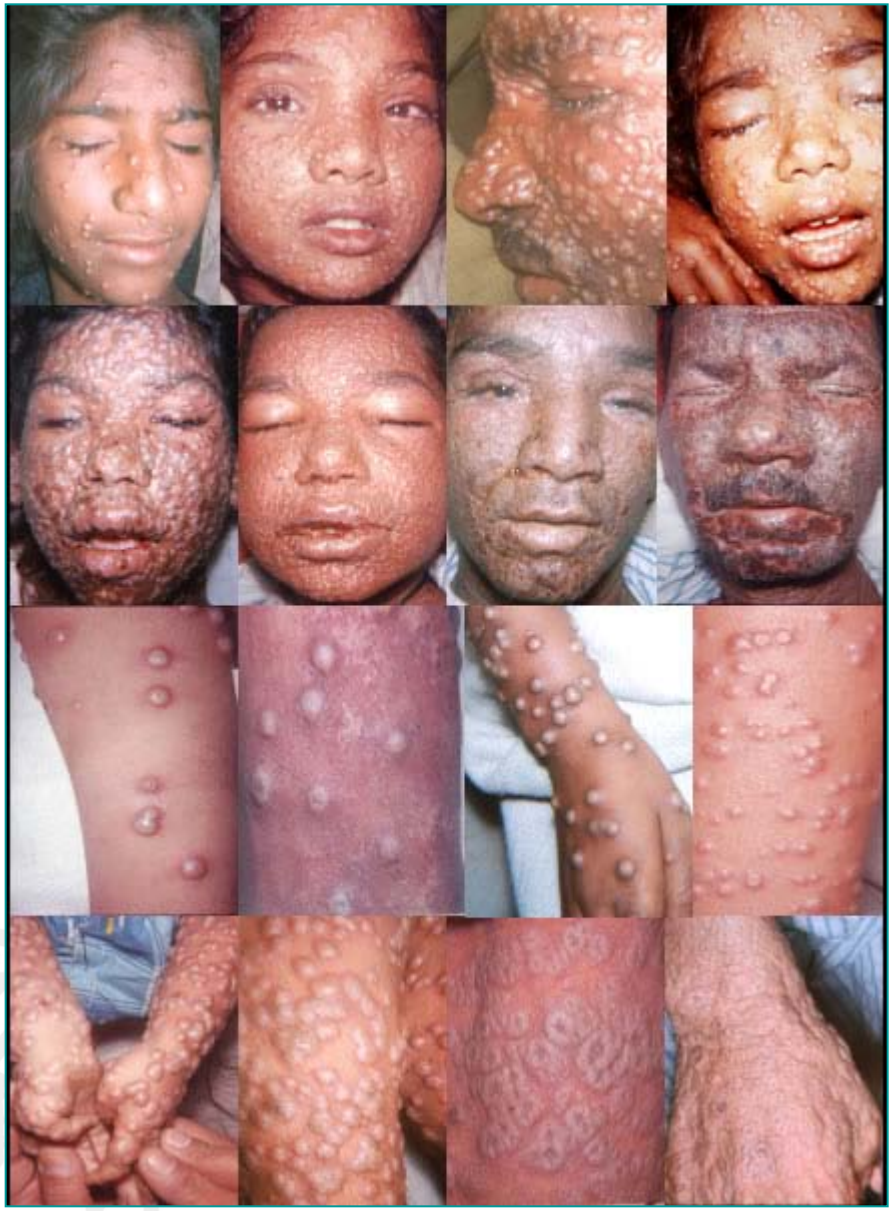
100 nm

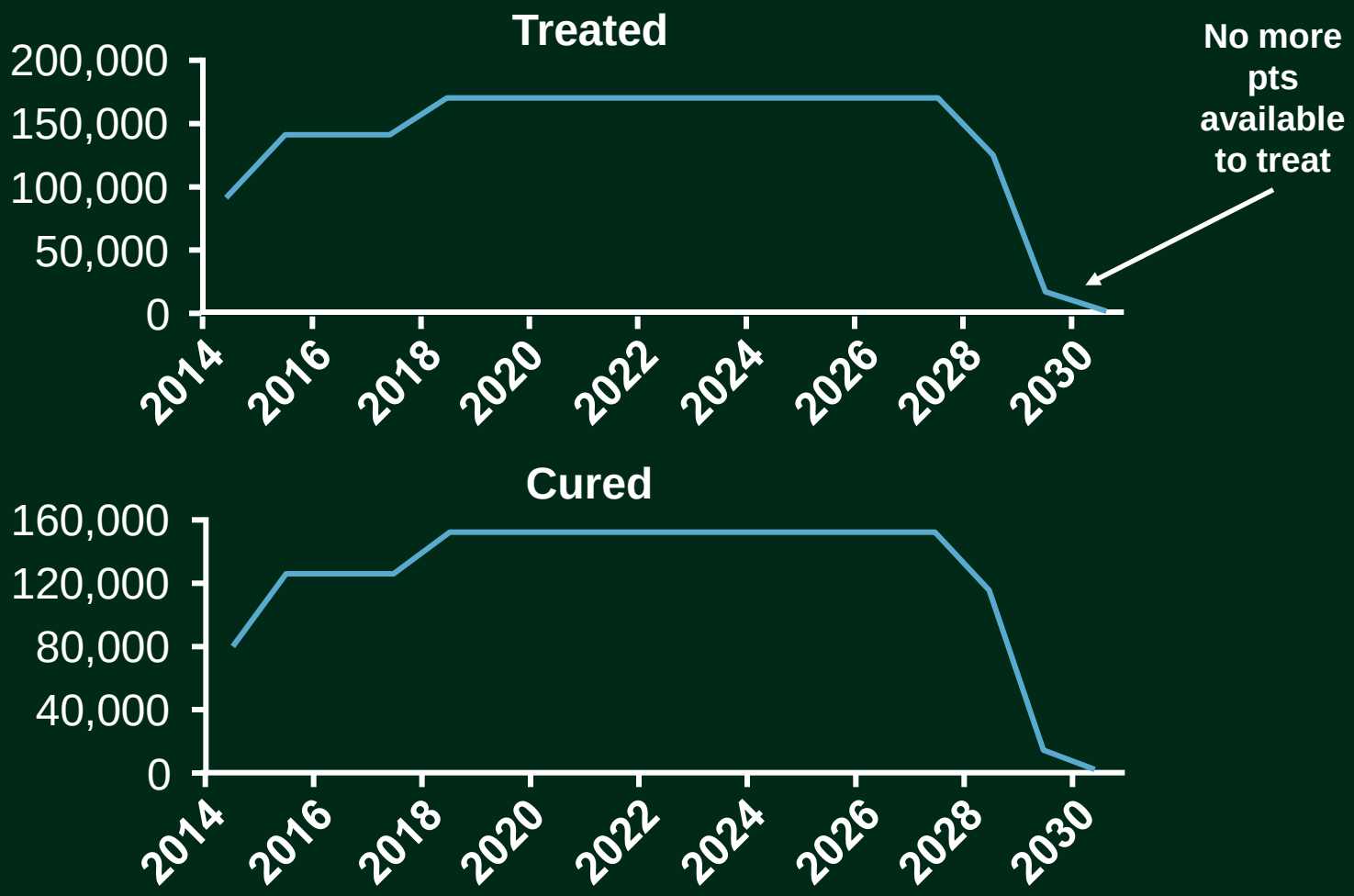


Edward Jenner 1749-1823

14 May 1796 James Phipps

WHO Global eradication of small pox 1980

Increasing Use of High SVR Therapy (~ 90%) Will Eliminate HCV in the US by 2029



Razavir H, et al. Hepatology. 2013;57:2164-2170.

Recommended Regimens for GT1

- Options listed alphabetically, not by order of preference
- LDV/SOF (QD) ± RBV for 12-24 wks
- OMV/PTV/RTV (QD) + DSV (BID) ± RBV for 12-24 wks
  - Not recommended for pts with prior PI failure
- SMV (QD) + SOF (QD) ± RBV for 12-24 wks
  - Not recommended for pts with prior SOF or PI failure
- Regimens no longer recommended for GT1
  - SOF + RBV, pegIFN, boceprevir, telaprevir

AASLD/IDSA HCV Guidelines.

Recommended Regimens for Tx-Naive GT1 HCV Pts

Subtype	Noncirrhotic		Compensated Cirrhotic	
	Regimen	Duration, Wks	Regimen	Duration, Wks
GT1a or 1b	LDV/SOF	12*	LDV/SOF	12
GT1a	OMV/PTV/RTV + DSV + RBV	12	OMV/PTV/RTV + DSV + RBV	24
GT1b	OMV/PTV/RTV + DSV	12	OMV/PTV/RTV + DSV + RBV	12
GT1a	SMV + SOF ± RBV	12	SMV + SOF ± RBV	24
GT1b	SMV + SOF	12	SMV + SOF	24

*Shorter course can be considered in pts with pretreatment HCV RNA < 6 million IU/mL at provider's discretion but should be done with caution.

AASLD/IDSA HCV Guidelines.

Recommended Regimens for Tx-Experienced GT1 HCV Pts

Population	Noncirrhotic		Compensated Cirrhotic	
	Regimen	Duration, Wks	Regimen	Duration, Wks
Prior PegIFN/RBV				
▪ GT1a or 1b	LDV/SOF	12	LDV/SOF	24
▪ GT1a or 1b			LDV/SOF + RBV	12
▪ GT1a	OMV/PTV/RTV + DSV + RBV	12	OMV/PTV/RTV + DSV + RBV	24
▪ GT1b	OMV/PTV/RTV + DSV	12	OMV/PTV/RTV + DSV + RBV	12
▪ GT1a or 1b	SMV + SOF ± RBV	12	SMV + SOF ± RBV	24
Prior SOF				
▪ GT1a or 1b	Defer therapy*		LDV/SOF ± RBV	24
Prior PI				
▪ GT1a or 1b	LDV/SOF	12	LDV/SOF	24
▪ GT1a or 1b			LDV/SOF + RBV	12

*Based on limited available data, pts without advanced fibrosis and without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider clinical trial.

AASLD/IDSA HCV Guidelines.

Recommended Regimens for GT4

- Recognizing that data are limited, AASLD/IDSA guidance makes these recommendations
  - LDV/SOF for 12 wks
  - OMV/PTV/RTV + RBV for 12 wks
  - SOF + RBV for 24 wks
    - Recommended in treatment-experienced and as alternative for treatment-naive pts: SOF + RBV + pegIFN for 12 wks
    - Alternative for treatment-naive pts: SOF + SMV ± RBV for 12 wks

AASLD/IDSA HCV Guidelines.

Guidance for HCV/HIV Coinfection

- Same recommendations as in HCV-monoinfected pts
- Consider drug–drug interactions
  - Need to adjust or withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    - Avoid LDV if CrCl < 60 mL/min or if receiving tenofovir with RTV-boosted PI
  - Do not interrupt antiretroviral therapy
  - Other interactions at aidsinfo.nih.gov/guidelines, hiv-druginteractions.org
- Do not use OMV/PTV/RTV ± DSV in coinfected pts not taking ant iretroviral therapy

AASLD/IDSA HCV Guidelines.

Guidance for Renal Impairment

- If CrCl > 30 mL/min, no dosage adjustment needed with
  - LDV/SOF
  - OMV/PTV/RTV + DSV
  - SMV
  - SOF
- If CrCl < 30 mL/min, consult with expert—limited safety and efficacy data available

AASLD/IDSA HCV Guidelines.

Guidance for Decompensated LC

- Refer to experienced HCV practitioner (ideally liver TPL center)
- Avoid IFN, TVR, BOC, SMV, OMV/PTV/RTV + DSV
- GT1/4 HCV infection
  - LDV/SOF + RBV* for 12 wks
    - Consider 24 wks for prior SOF failure
  - LDV/SOF for 24 wks in pts with anemia or RBV intolerance
- GT2/3 HCV infection
  - SOF + RBV† for up to 48 wks

*Initial dose of 600 mg daily, increased as tolerated.
†1000-1200 mg daily based on weight, with consideration for pt's CrCl and hemoglobin.

AASLD/IDSA HCV Guidelines.

Guidance for Recurrent HCV Post Liver Transplantation

- For pts with GT1 infection
  - Recommended
    - LDV/SOF + RBV for 12 wks
  - Alternative
    - SOF + SMV ± RBV for 12 wks
    - For F0-F2: OMV/PTV/RTV + DSV + RBV for 24 wks
    - For treatment naive: LDV/SOF for 24 wks

AASLD/IDSA HCV Guidelines.

Management of Acute HCV Infection

- If Tx delay acceptable, monitor for spontaneous clearance for 6-12 mos
  - Monitor HCV RNA every 4-8 wks
- If Tx initiated during acute infection phase
  - Monitor for spontaneous clearance at least 12-16 wks before treatment
  - Recommended regimens are the same as for chronic HCV infection
  - Alternative regimen for IFN eligible acute HCV: pegIFN ± RBV for 16 wks (GT2 or 3 with rapid viral response) to 24 wks (GT1)

AASLD/IDSA HCV Guidelines.

Key Monitoring Guidance

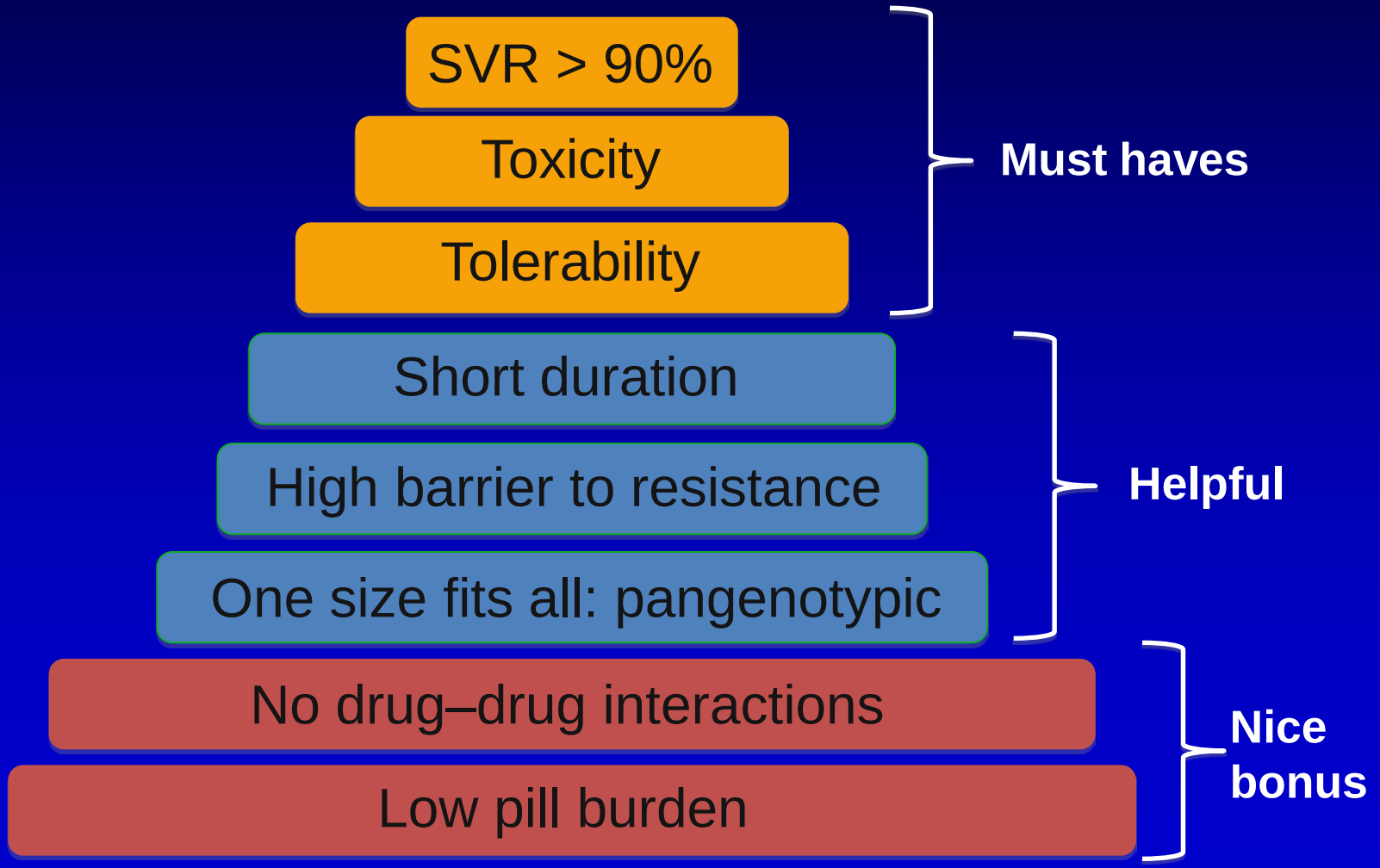
- Before treatment
  - Degree of hepatic fibrosis by noninvasive testing or by biopsy
  - Potential drug–drug interactions (hep-druginteractions.org)
- Before and during Tx
  - HCV RNA before treatment and at Wk 4
    - If detectable at Wk 4, assess again at Wk 6 only
  - ALT before treatment and at Wk 4
    - If elevated at Wk 4, assess again at Wk 6 and Wk 8
- After treatment
  - If pretreatment Metavir ≥ F3, ultrasound for HCC every 6 mos

AASLD/IDSA HCV Guidelines.

Summary

- PegIFN no longer recommended for first-line Tx of any pt
- 3 FDA-approved pegIFN-free regimens f or GT1
- No differences in treatment recommenda tions for HCV monoinfected vs HCV/HIV-coinfected pts
  - Consider drug–drug interactions

Requirements for HCV Therapy

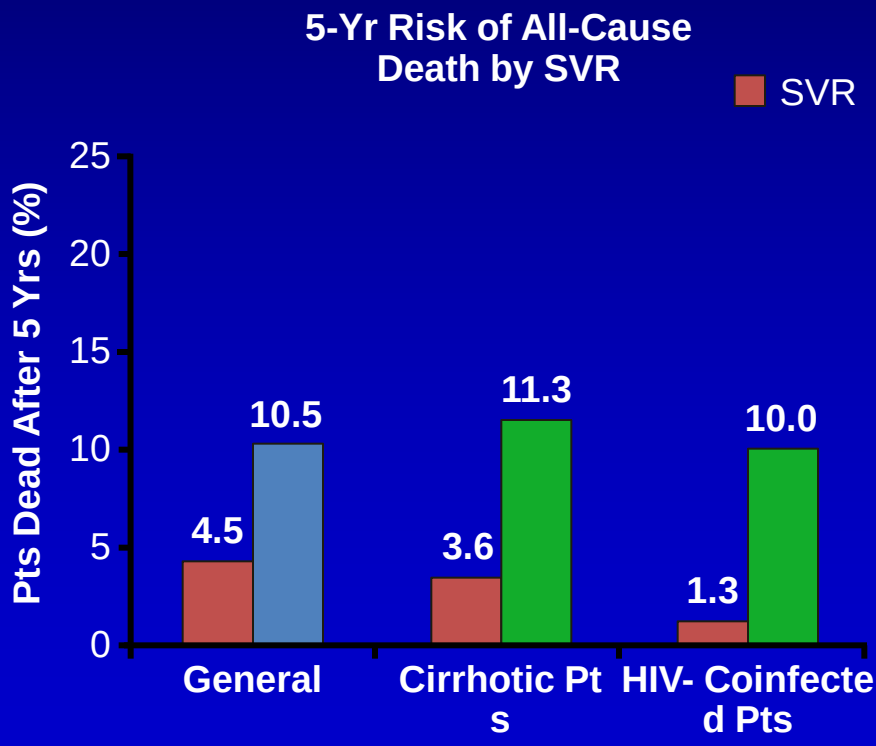


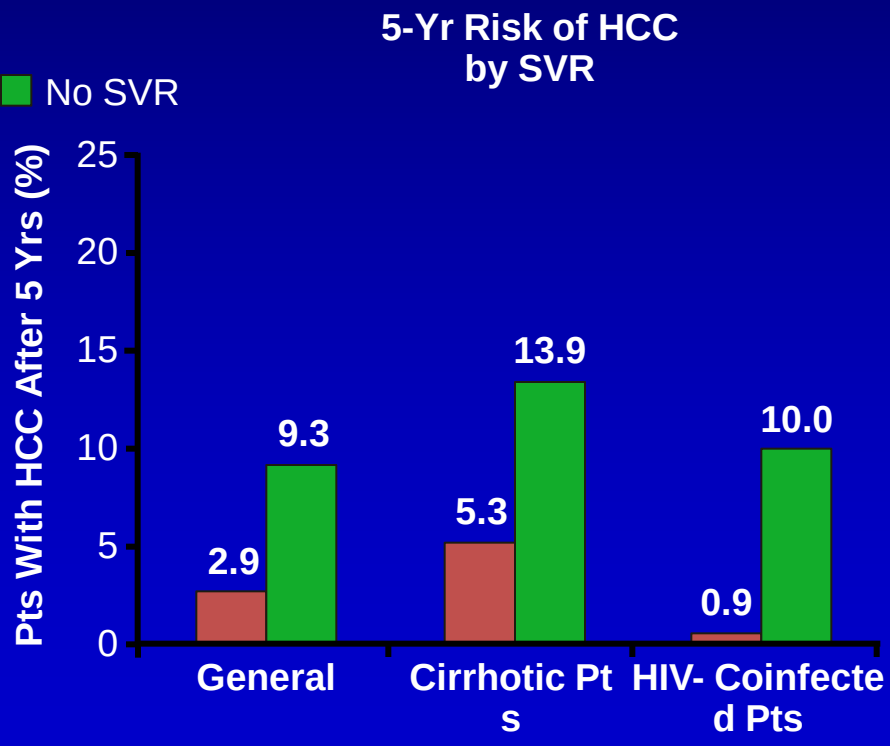
Historically "Hard-to-Treat" Pts and Special Populations

- Cirrhosis pts
  - Compensated
  - Decompensated
  - Cirrhosis with HCC
- Treatment failure pts with GT3 HCV (pegIFN/RBV ± DAA)
- Posttransplant HCV
- HCV/HIV-coinfected individuals

SVR Associated With Reduced 5-Yr Risk of Death and HCC in All Populations

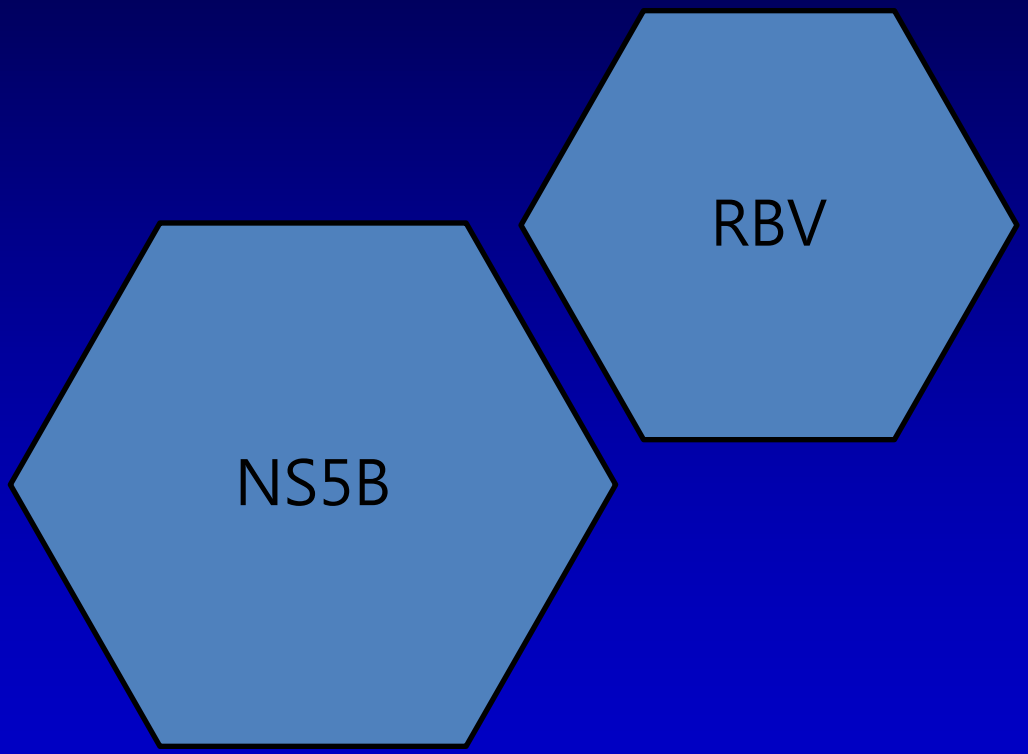
- SVR on IFN-based therapy was associated with substantial benefit vs no SVR
  - 62% to 84% reduction in all-cause mortality, 90% reduction in liver transplantation, 68% to 79% reduction in HCC





Hill AM, et al. AASLD 2014. Abstract 44.

Sofosbuvir + Ribavirin in Transplantation Patients

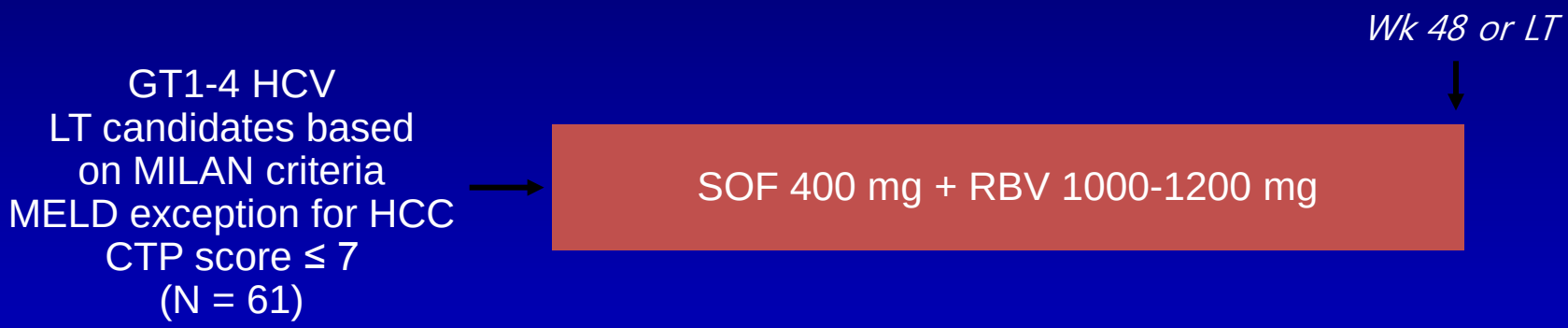


Sofosbuvir

- Oral, once-daily nucleotide NS5B polymerase inhibitor
- Potent antiviral activity; pangenotypic
- High barrier to resistance
- Pharmacology profile
  - No significant drug interactions, including tacrolimus or cyclosporine
- Approved for combination treatment of HCV in following settings
  - Genotypes 1, 2, 3, 4 HCV
  - HCC meeting Milan criteria; awaiting transplantation
  - HIV coinfection

Sofosbuvir + Ribavirin to Prevent Posttransplantation HCV

Single-arm, open-label phase II study from 16 liver transplantation sites across 8 UNOS regions and 2 international sites



- Excluded decompensated cirrhosis, renal impairment, living donor LT
- Original protocol: 24 wks of treatment or until LT; amended to extend treatment duration to 48 wks or LT

Curry MP, et al. ILTS 2014. Abstract O-137.

Opportunities and Challenges Prior to Transplant

- We now have pre-OLT therapy that can prevent reinfection of graft
- No dose adjustment of SOF required
- Anemia with RBV more problematic in more advanced liver disease
- Data thus far only in Childs A/B with CTP 7, MELD < 22, HCC within Milan criteria
  - Unknown: MELD > 22, CTP > 7
- Duration of therapy 24-48 wks can make timing of transplant difficu lt for some centers
  - SVR (SOF/SIM) may be a more cost-effective goal than suppression (SO F/RBV)
  - Elimination of RBV also more effective
- Additional data required in those with more advanced disease
  - Ascites and encephalopathy may improve
  - Especially with Share 35