Sofosbuvir: Going Interferon-Free in Hepatitis C??

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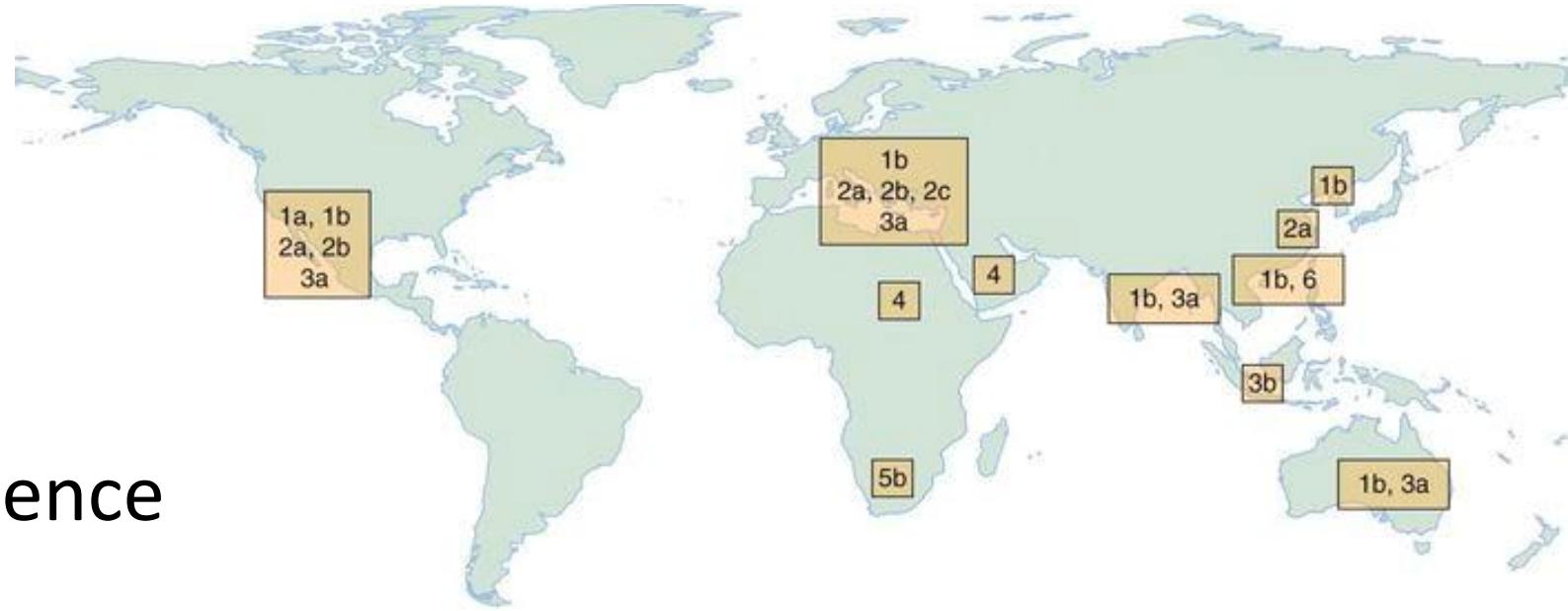
Seminar
April 3, 2014

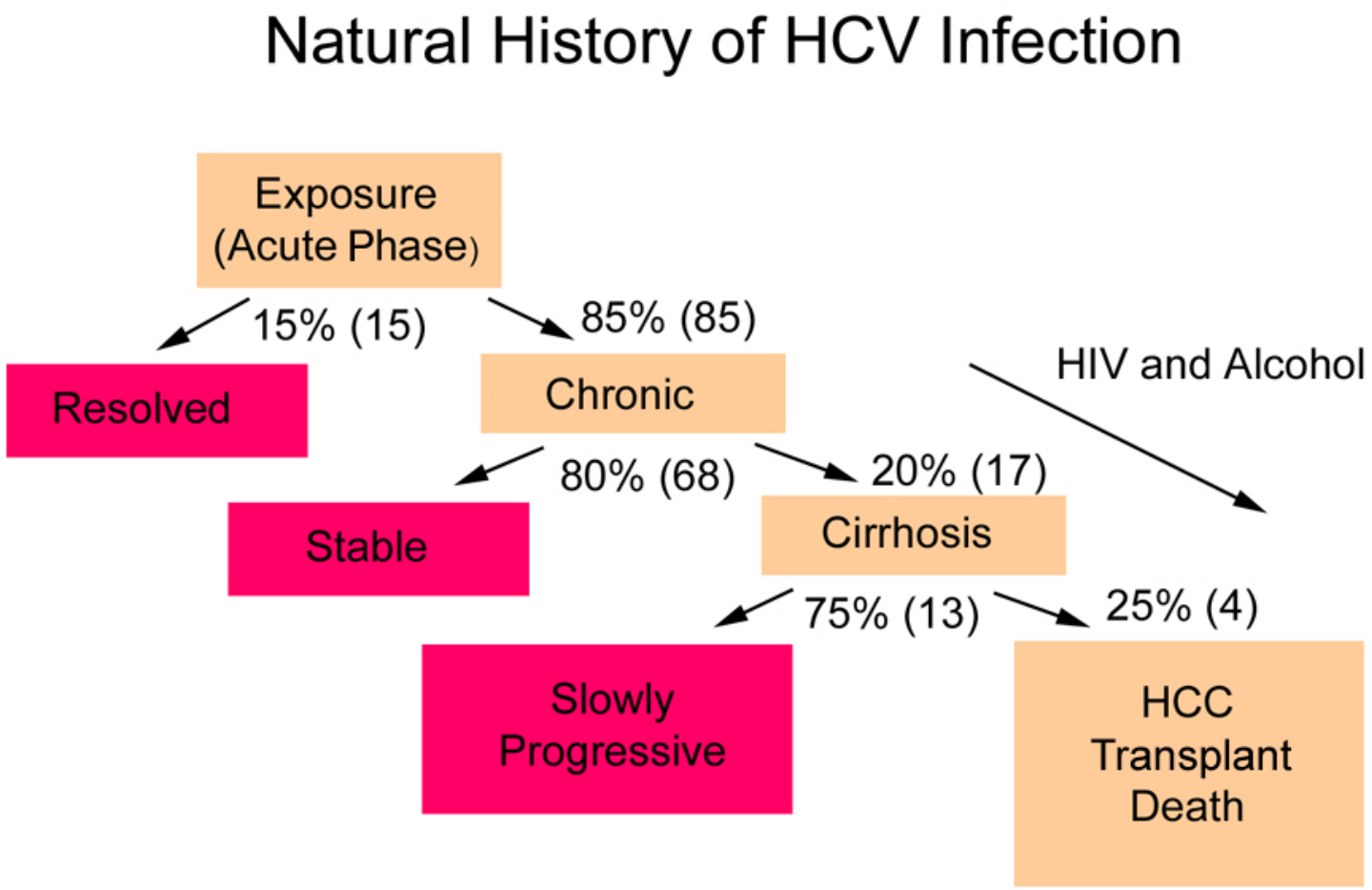
Hepatitis C



- RNA virus
- 0.8% Canadian prevalence
- Genotypes
  - G1 – most common (65%), difficult to treat
  - G2, G3 – second most common (30%), easier to treat
  - G4-6 – least common (<5%), treated like G1
- Transmitted through infected blood
  - 60% IVDU, 20% immigrants, 11% contaminated blood products
- Prevention: blood donor screening, risk behavior modification

Can J Gastroenterol, 2012; (26)

Hepatitis C – Clinical Course



Complications

- Symptoms of liver disease
- Fibrosis →Cirrhosis
  - Portal hypertension, varices, ascites, SBP
  - Hepatic encephalopathy
- Extrahepatic manifestations
  - Cryoglobinemia
  - Small vessel vasculitis
- Decompensation to end stage liver disease
- Liver transplant
- Hepatocellular carcinoma (HCC) – 1-3%
- Death

Goals of Therapy

- **Eradicate the virus**
  - Sustained virologic response (SVR): undetectable serum HCV RNA at 24 weeks post treatment
- **Prevent or slow development of cirrhosis and it's complications**
- **Minimize treatment-related adverse effects**
- **Improve quality of life**

Goals of Therapy – SVR as a Surrogate

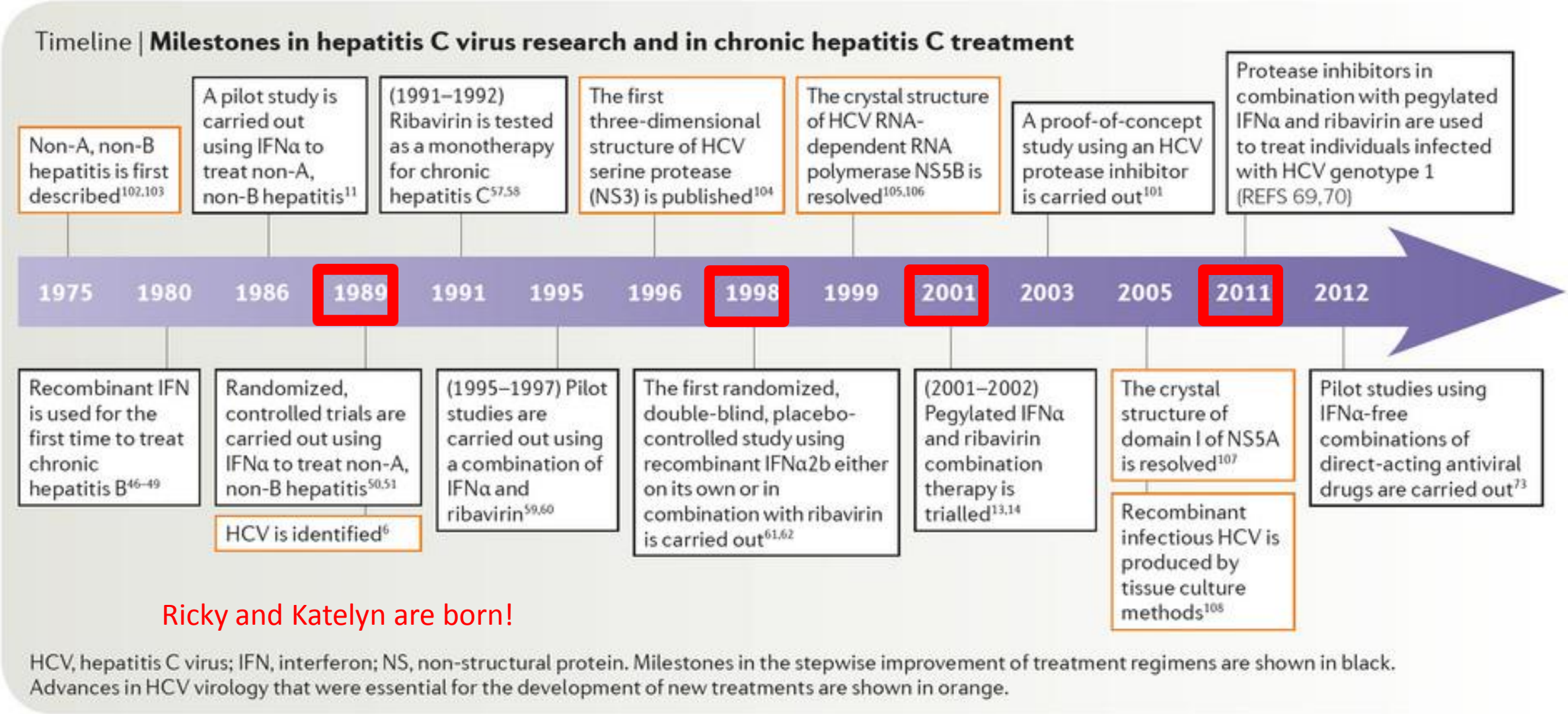
- Best prediction of long-term response
- Late relapses are rare → 92-99% virus free at 5 yrs
- Improvement in:
  - ✓Quality of life
  - ✓Extrahepatic manifestations
  - ✓Regression of fibrosis
  - ✓Morbidity →↓ HCC at 5 yrs
  - ✓Mortality → ↓ liver-related death at 5 yrs

Can J Gastroenterol, 2012; (26)

Ideal Therapy

- ✓Achieve and sustain SVR
- ✓Pan-genotypic
- ✓High barrier to resistance
- ✓Minimal adverse events
- ✓No drug interactions
- ✓Convenient
- ✓Oral
- ✓Affordable

History of Therapy



Nat Rev Immunol, 2013; 13(7):535-42.

Current Therapy

- All Genotypes → **PEGIFN + Ribavirin** x 24 - 48 weeks
- Genotype 1 → **+ Protease Inhibitor** (PI): Telaprevir or Boceprevir

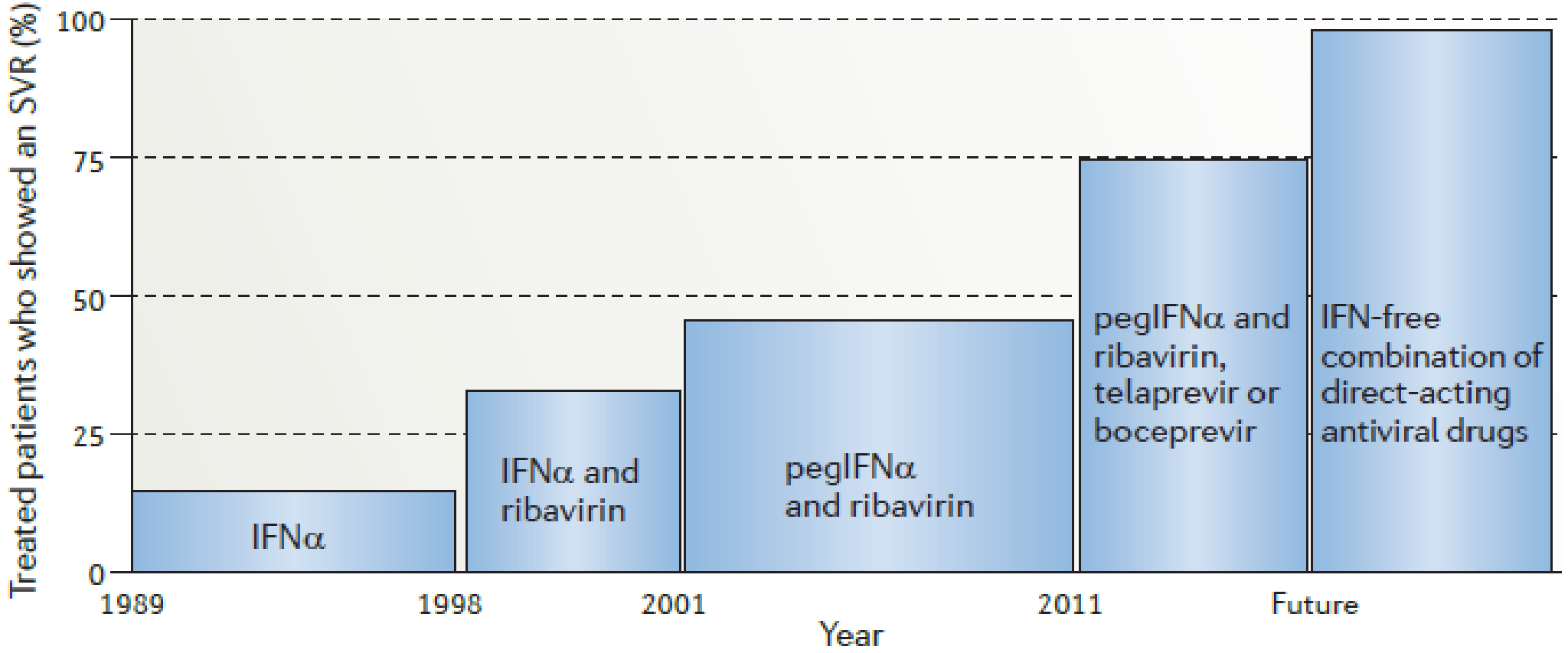


Figure 4 | **The stepwise increase in sustained virological response rates in the past 25 years.**

Nat Rev Immunol, 2013; 13(7):535-42.

Current Therapy – Limitations

Interferon	Ribavirin	Protease Inhibitors
SubQ injection weekly **Side effects:** - Depression/mood – 40% - Flu-like symptoms - >30% - Fatigue - 50% - Neutropenia, thrombocytopenia, anemia - Induction of autoantibodies **Contraindications**: - Hepatic decompensation - Autoimmune disease - Psychiatric illness - Pregnancy	**Side effects**: - Hemolytic anemia - Nausea - Fatigue **Contraindications:** - Pregnancy	• Genotype 1 only • TID dosing with food • Pill burden • Low barrier to resistance • Cross-resistance • Drug interactions – CYP3A4/5, Pgp • **Side Effects**: - TELAPREVIR: anemia, rash, anorectal discomfort - BOCEPRIVER: anemia, neutropenia, altered taste

FDA Approvals > Medscape Medical News

FDA Approves 'Game Changer' Hepatitis C Drug Sofosbuvir

Miriam E. Tucker | Disclosures

December 06, 2013

Health Canada Issues Notice of Compliance for Sovaldi™ (Sofosbuvir) for the Treatment of Chronic Hepatitis C

Gilead's New Hepatitis C Treatment Slated To Surpass Rival Drugs In Prescriptions

"I believe sofosbuvir has the potential to transform HCV treatment in Canada as it addresses many unmet patient needs," said Jordan Feld, MD, MPH, Staff Hepatologist, Toronto Western Hospital, Department of Medicine, Division of Gastroenterology. "The high cure rates, shortened treatment

Gilead's Hepatitis C Pill Works Better, FDA Report Says

Sofosbuvir (Solvaldi®)

- Uridine nucleotide analogue – NS5B RNA Polymerase Inhibitor
- 400 mg po daily

✓ No significant drug interactions

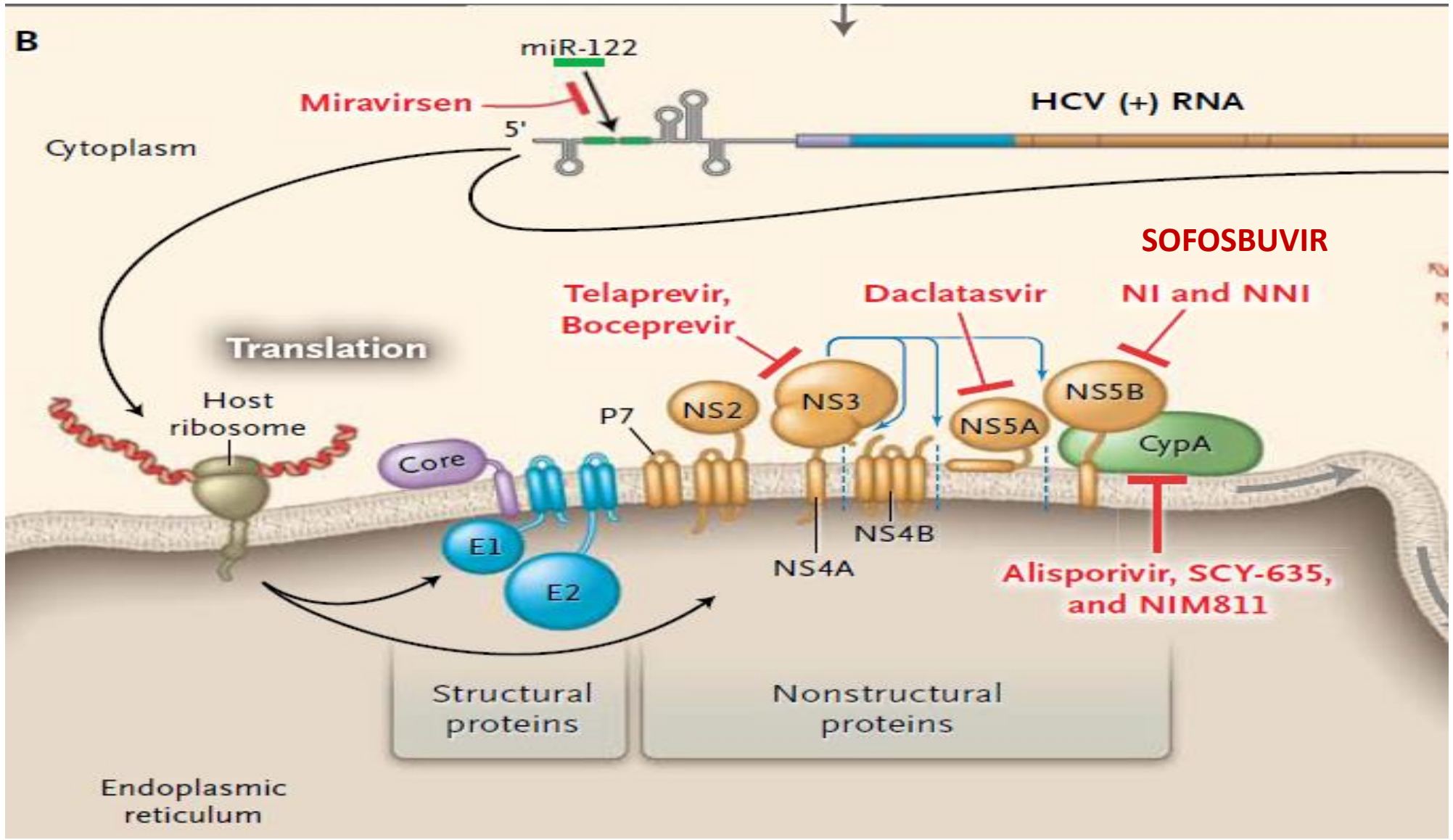
✓ Low incidence of adverse events

✓ Lack of drug resistance

- PEGIFN + ribavirin + sofosbuvir x 12 wks = 89% SVR in G1 (NEUTRINO)

→ ***Potential Ideal Interferon-Free Treatment for Hepatitis C ???***

New HCV Targets



NEJM 2013; 368:1907-17

Clinical Question

P	Adult patients with chronic hepatitis C, genotype 1, treatment-naive
I	sofosbuvir as part of an interferon-free regimen
C	“standard of care”
O	<u>Primary:</u> Mortality Morbidity Sustained virological response <u>Secondary</u>: Adverse events, discontinuation due to adverse events

Search Strategy

Databases	PubMed, EMBASE, Google Scholar, IPA, WHO ICTRP
Search terms	hepatitis C, hepatitis C treatment, sofosbuvir, chemical name =GS-7977
Limits	Adults, Human, English language
Exclusion	Commentaries, Reviews

Search Results

Systematic Review or Meta-Analysis	None
Randomized Trials	Lawtiz et al. J Viral Hepat 2013 – 14 day proof of concept Oisnusi et al. JAMA 2013 – unfavorable characteristics Lalezari et al. J Hepatol 2013 – stopped early **Gane et al. NEJM 2013** **Lawitz et al. Lancet 2014** **Sulkowski et al. 2014** Jacobson et al. Hepatol 2013 – Prelim Results of COSMO trial
Observational	Fontana et al. Am J Transplant 2013 - case report post liver tx
Ongoing trials	55 trials!!!

Gane et al. 2013 (ELECTRON)

ORIGINAL ARTICLE

Nucleotide Polymerase Inhibitor Sofosbuvir plus Ribavirin for Hepatitis C

Edward J. Gane, M.D., Catherine A. Stedman, M.B., Ch.B., Ph.D.,
Robert H. Hyland, D.Phil., Xiao Ding, Ph.D., Evguenia Svarovskaia, Ph.D.,
William T. Symonds, Pharm.D., Robert G. Hindes, M.D.,
and M. Michelle Berrey, M.D., M.P.H.

NEJM 2013;368-34-44

Gane et al. 2013 (ELECTRON)

- **Rationale:**
  - Limitations of current therapy
  - Development of an all oral regimen ideal
  - High SVR achieved with sofosbuvir + PEGIFN + ribavirin in G1-3

- **Objective:**
  - Test safety and efficacy of sofosbuvir + ribavirin in various PEGIFN sparing regimens in G1-3

NEJM 2013;368:34-44

Gane et al. 2013 (ELECTRON)

D	2 part Phase II study, 2 centres in New Zealand, December 2010 – 2011 Randomized (G2-3), open-label
P	Adults with chronic Hep C infection G1-3 without cirrhosis Excluded Hep B and HIV coinfections
I	**Genotype 1: Sofosbuvir 400 mg/d + ribavirin 1000-1200 mg x 12 weeks**
C	No comparator
O	**Virologic response**: serum HCV RNA levels throughout and post treatment Resistance monitoring **Adverse events**
Stats	Not designed to evaluate statistical hypotheses, descriptive statistics
Sponsor	Gilead Sciences

NEJM 2013;368-34-44

Gane et al. 2013 (ELECTRON)

Genotype 1		
N, (%)	**No response to prior therapy (n=10)**	**Treatment naïve (n=25)**
Male	7 (70)	15 (60)
White	9 (90)	20 (80)
Age, mean (SD)	48 (30-58)	49 (22-69)
HCV RNA log10, median	7.0	6.2
Virologic response (undetectable HCV RNA)		
Week 12 & 24 post treatment, n (%)	1 (10)	21 (84)

NEJM 2013;368:34-44

Gane et al. 2013 (ELECTRON)

- Reported adverse events >10%:
  - Headache
  - Fatigue
  - Insomnia
  - Nausea
  - Rash
  - Anemia
  - Diarrhea
  - URTI

NEJM 2013;368:34-44

Gane et al. 2013 (ELECTRON)

- **Limitations:**
  - Small sample
  - No comparator
  - Open-label
  - No standardized reporting of adverse effects
- **Take-away:**
  - Sofosbuvir + ribavirin x 12 wks achieved SVR 84% in untreated G1 without cirrhosis
  - Sofosbuvir + ribavirin has low efficacy in G1 with prior non-response

NEJM 2013;368:34-44

Sulkowski et al. 2014

ORIGINAL ARTICLE

Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection

Mark S. Sulkowski, M.D., David F. Gardiner, M.D., Maribel Rodriguez-Torres, M.D., K. Rajender Reddy, M.D., Tarek Hassanein, M.D., Ira Jacobson, M.D., Eric Lawitz, M.D., Anna S. Lok, M.D., Federico Hinestrosa, M.D., Paul J. Thuluvath, M.D., Howard Schwartz, M.D., David R. Nelson, M.D., Gregory T. Everson, M.D., Timothy Eley, Ph.D., Megan Wind-Rotolo, Ph.D., Shu-Pang Huang, Ph.D., Min Gao, Ph.D., Dennis Hernandez, Ph.D., Fiona McPhee, Ph.D., Diane Sherman, M.S., Robert Hindes, M.D., William Symonds, Pharm.D., Claudio Pasquinelli, M.D., Ph.D., and Dennis M. Grasela, Pharm.D., Ph.D., for the AI444040 Study Group

NEJM 2014;370:211-21

Sulkowski et al. 2014

- **Rationale:**
  - Daclatasivr and sofosbuvir shown efficacy in G1-3 combined with PEGIFN and ribavirin
  - Sofosbuvir + ribavirin shown efficacy in G1-3 without PEGIFN

- **Objective:**
  - Evaluate daclatasvir + sofosbuvir +/- ribavirin in untreated G1-3 and G1 without response to previous treatment with protease inhibitors

NEJM 2014;370:211-21

Sulkowski et al. 2014

D	Open-label, randomized, multi-centered in USA, June 2011- November 2012
P	Adults with chronic Hep C infection G1-3 without cirrhosis Excluded Hep B and HIV coinfections
I	**Sofosbuvir 400mg + daclatasivir 60mg x 12 or 24 weeks**
C	**Sofosbuvir 400mg + daclatasvir 60mg + ribavirin 800-1200mg x 12 or 24 weeks**
O	**1◦ Outcome – Proportion of patients with SVR at week 12 after end of treatment** **2◦ Outcome – SVR at week 4 and 24 after treatment** **Adverse events at scheduled visits**
Stats	Sample size calculation, modified ITT, data missing recorded as not having a response
Sponsor	Gilead Sciences

NEJM 2013;368-34-44

Sulkowski et al. 2014

GENOTYPE 1 – Treatment Naïve					
	S + D x 23wks (n=15)	**S + D x 24wks (n=14)**	**S + D + R x 24wks (n=15)**	**S + D x 12wks (n=41)**	**S + D + R x 12wks (n=41)**
Median age, yr	56	54	54	55	54
Male sex, n	7	9	7	20	21
White, n	11	11	12	33	33
HCV RNA, log10	6.5	6.6	6.7	6.2	6.4
Virologic Response (undetectable HCV RNA)					
Week 12 post treatment, n (%)	15 (100)	14 (100)	15 (100)	41 (100)	39 (95)

NEJM 2013;368:34-44

Sulkowski et al. 2014

- Most common side effects >25%:
  - Fatigue
  - Headache
  - Nausea
  - 2 patients discontinued therapy
  - 5 patients required ribavirin dose reduction for anemia

NEJM 2013;368:34-44

Sulkowski et al. 2014

- **Limitations:**
  - Small sample size
  - Open-label
  - Methods of randomization, allocation concealment not described

- **Take Away:**
  - Sofosbuvir + daclatasvir attained high SVR rates in untreated G1
  - Ribavirin may not be required when combining 2 direct anti-viral agents
  - Well tolerated

NEJM 2013;368:34-44

Lawitz et al. 2014 (LONESTAR)

Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial

Eric Lawitz, Fred F Poordad, Phillip S Pang, Robert H Hyland, Xiao Ding, Hongmei Mo, William T Symonds, John G McHutchison, Fernando E Membreno

Lancet 2014; 383:515-23

Lawitz et al. 2014 (LONESTAR)

- **Rationale:**
  - Limitations of current therapy, including protease inhibitors
  - Ledipasvir is a novel agent and active vs variants with reduced susceptibility to sofosbuvir

- **Objectives:**
  - Assess efficacy of fixed-dose single-tablet combination of sofosbuvir and ledipasvir +/- ribavirin in treatment-naïve and previously-treated G1 patients

Lancet 2014; 383:515-23

Lawitz et al. 2014 (LONESTAR)

D	Open-label, randomized Texas, USA, November 2012 – December 2012
P	Adults with chronic Hep C infection G1 without cirrhosis Excluded Hep B and HIV coinfections, hepatic decompensation, BMI <18
I/C	**Sofosbuvir 400mg + ledipasvir x 8 weeks** **Sofosbuvir 400mg + ledipasvir + ribavirin 1000-1200 mg x 8 weeks** **Sofosbuvir 400 mg + ledipasvir x 12 weeks**
O	**1◦ Outcome – Proportion of patients with SVR at week 12 after end of treatment**
Stats	ITT analysis, exploratory, not powered to compare among groups, no statistical hypothesis testing
Sponsor	Gilead Sciences

Lancet 2014; 383:515-23

Lawitz et al. 2014 (LONESTAR)

	Cohort A: treatment-naive patients		
	Sofosbuvir plus ledipasvir for 8 weeks (n=20)	Sofosbuvir plus ledipasvir with ribavirin for 8 weeks (n=21)	Sofosbuvir plus ledipasvir for 12 weeks (n=19)
Age (years)	48 (10·7)	50 (11·1)	46 (11·6)
Men	14 (70%)	12 (57%)	11 (58%)
Race			
Black	4 (20%)	0	1 (5%)
Non-black	16 (80%)	21 (100%)	18 (95%)
Ethnic origin			
Hispanic or Latino	3 (15%)	12 (57%)	9 (47%)
Non-Hispanic	17 (85%)	9 (43%)	10 (53%)
Body-mass index (kg/m^2)	28·7 (6·9)	29·8 (5·5)	28·1 (5·8)
Log_{10} HCV RNA (IU/mL)	6·1 (0·8)	6·0 (0·8)	6·1 (0·8)

Lancet 2014; 383:515-23

Lawitz et al. 2014 (LONESTAR)

GENOTYPE 1 – Treatment Naïve			
	S + L x 8wks (n=20)	**S + L + R x 8wks (n=21)**	**S + L x 12wks (n=19)**
Virologic Response (undetectable HCV RNA)			
Week 12 post treatment, n (%)	19 (95)	21 (100)	18 (95)
Adverse Events, n (%)			
Anemia	0	2 (10)	0
Nausea	2 (10)	2 (10)	1 (5)
Headache	2 (10)	3 (14)	0

Lancet 2014; 383:515-23

Lawitz et al. 2014 (LONESTAR)

- **Limitations:**
  - Open-label, no allocation concealment
  - Excluded cirrhosis, Hepatitis B and HIV coinfections

- **Take-Away:**
  - Sofosbuvir + ledipasvir for 8 or 12 weeks attained similar SVR
  - Well tolerated, no anemia if ribavirin excluded
  - Ribavirin may not be required

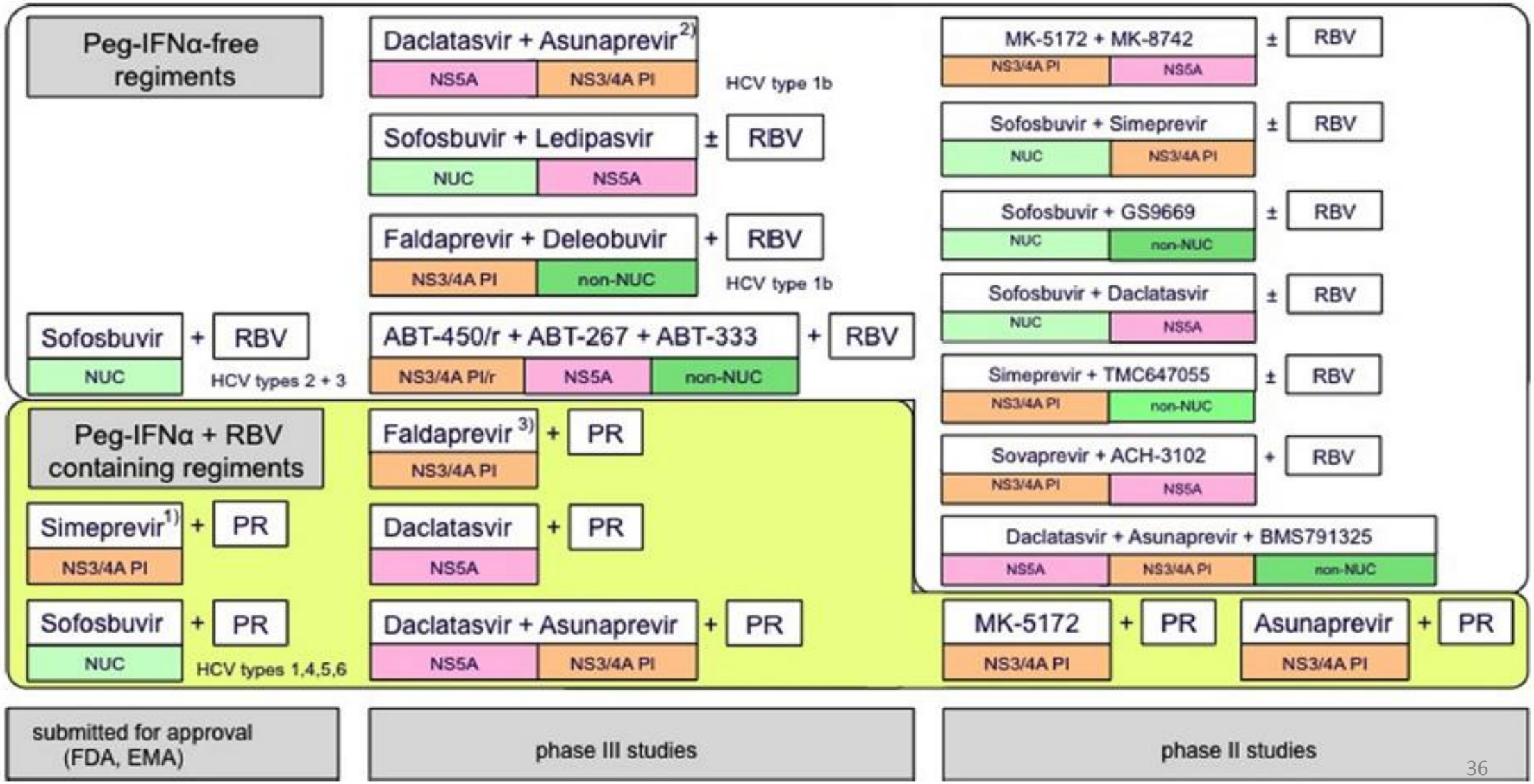
Lancet 2014; 383:515-23

Summary & Conclusions

- **Trial limitations**
  - Small samples, exclusion of cirrhosis, Hepatitis B, HIV coinfections
  - ? long-term data for efficacy or safety (+ small numbers)
  - ? comparison to PEGIFN + ribavirin + PI
  - Significant sponsorship

- **Conclusions – Treatment naïve G1**
  - Sofosbuvir containing regimens attain high SVR
  - 8 - 12 week treatment duration optimistic
  - Well-tolerated
  - Next step – longer term phase III trials, CEA, budget impact analysis

Just the beginning……



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Supplementary Slides

Genotype	Treatment	Response (SVR)
Genotype 1 Treatment naïve	IFN PEGIFN+ ribavirin PEGIFN+ ribavirin + telaprevir PEGIFN+ ribavirin + boceprevir	10% 41-55% 69-88% 59-68%
Genotype 1 Previous null-responders	PEGIFN + ribavirin PEGIFN + ribavirin + PI	10% 30-40%
Genotypes 2, 3 Treatment naïve	PEGIFN + ribavirin	65-85%
Genotypes 4,5,6 Treatment naïve	PEGIFN + ribavirin	60%

Definitions

Early virologic response (EVR)	Patient who experiences at least a 2-log reduction in viral load by the 12th week of treatment
End-of-treatment response (ETR)	Patient with no detectable viral load at the end of treatment
Sustained virologic response (SVR)	Patient with no detectable viral load at the conclusion of therapy and 6 months later
Relapser	Patient who responds to therapy but whose viral load becomes detectable at the conclusion of therapy
Nonresponder	Patient with a stable viral load during the course of therapy
Partial Responder	Patient with at least a 2-log reduction in viral load but who never has undetectable viral levels

Pharmacokinetics

Absorption	Prodrug, Tmax=1 hr
Distribution	PPB=61-65%
Metabolism	Hepatically to active metabolite Not CYP mediated
Elimination	Median t1/2=0.6h Active metabolite t1/2 =9 h Renal elimination 80%, no info for CrCl <30 mL/min

Cost-Effectiveness

- NICE - under review
- CADTH - under review
- $1000/pill → $84000 per 12 week treatment course
- PEGIFN/Ribavirin = ~$20000
- PEGIFN/Ribavirin + PI = ~ $40-50000
- A cost-effectiveness analysis suggests drug costs of an oral regimen would need to be <$75 000 to stay below $50000/QALY (US dollars)
- Gilead Sciences Canada has developed the Momentum Support Program

J Viral Hepatitis, 2013; 20:847-857