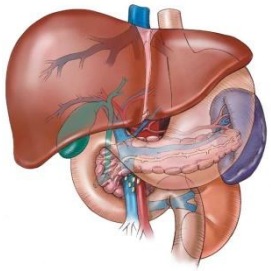


Transformation of HCV Management:
The IFN-free Era

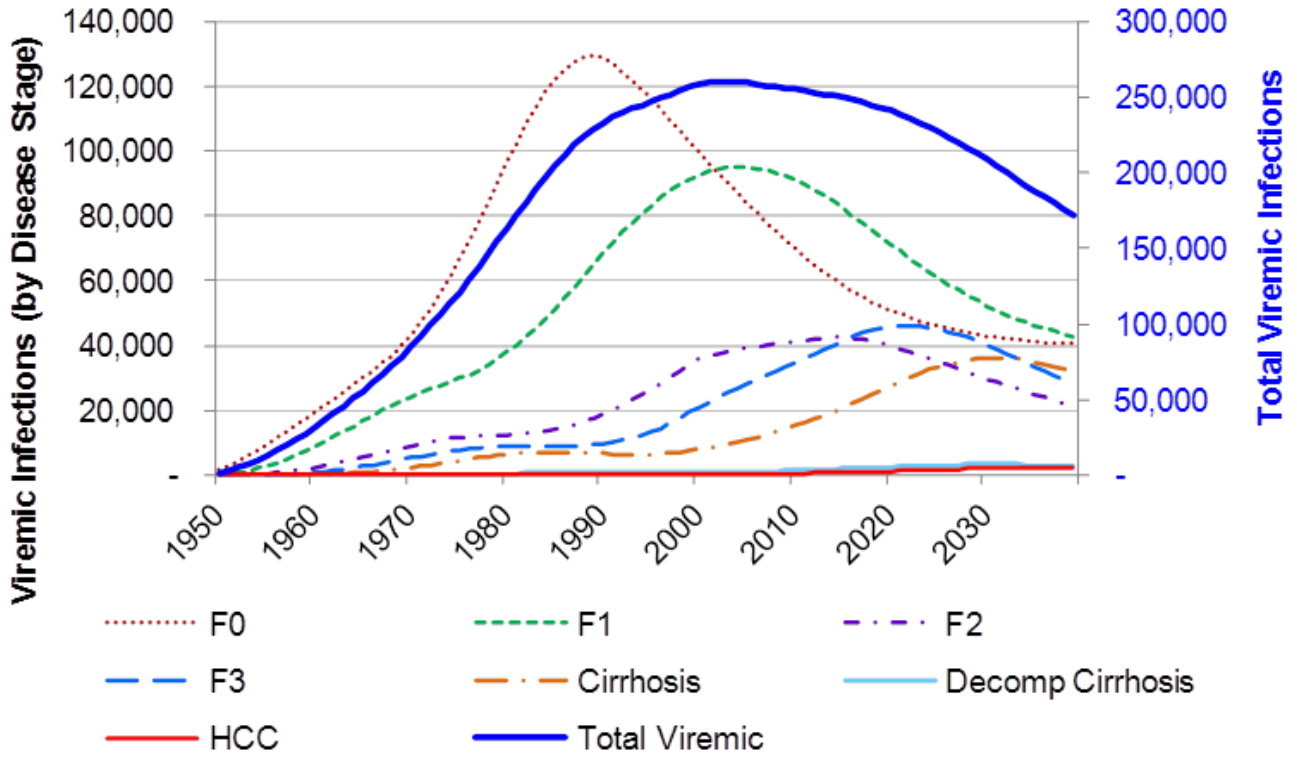
Dr. Paul Marotta

September 8, 2014

London Health Sciences Centre
Multi-Organ Transplant Program

HCV Burden of Disease in Canada:

Significant Increase in Medical Burden Due to Continued Progression of Liver Deterioration



- ***Cirrhosis (+89%)***
- ***Hepatocellular carcinoma (+160%)***
- ***Decompensated Liver Disease (+80%)***
- ***Liver transplantation (+205%)***

Source of graph data: Robert P. Myers, MD, et al. BURDEN OF DISEASE AND COST OF CHRONIC HEPATITIS C VIRUS INFECTION IN CANADA. Canadian Journal of Gastroenterology May 2014, Volume 28 Issue 5: 243-250.

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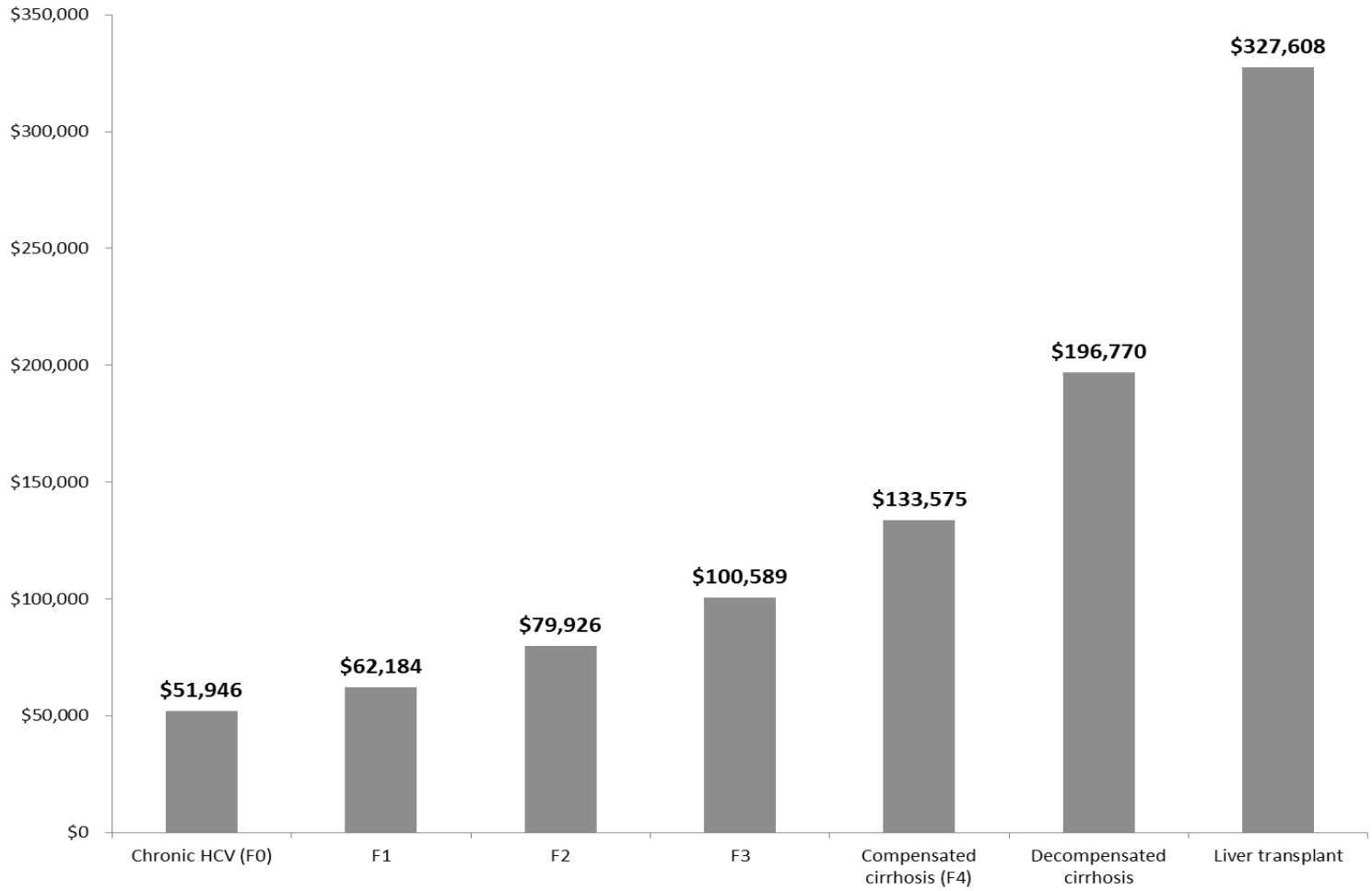
Cost of Untreated HCV Rises Significantly with Advanced Disease



Source of graph data: Robert P. Myers, MD, et al. BURDEN OF DISEASE AND COST OF CHRONIC HEPATITIS C VIRUS INFECTION IN CANADA. Canadian Journal of Gastroenterology May 2014.

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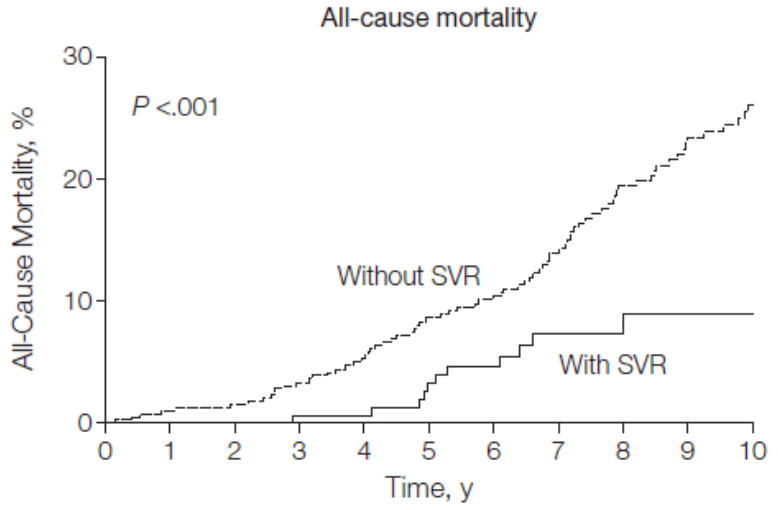
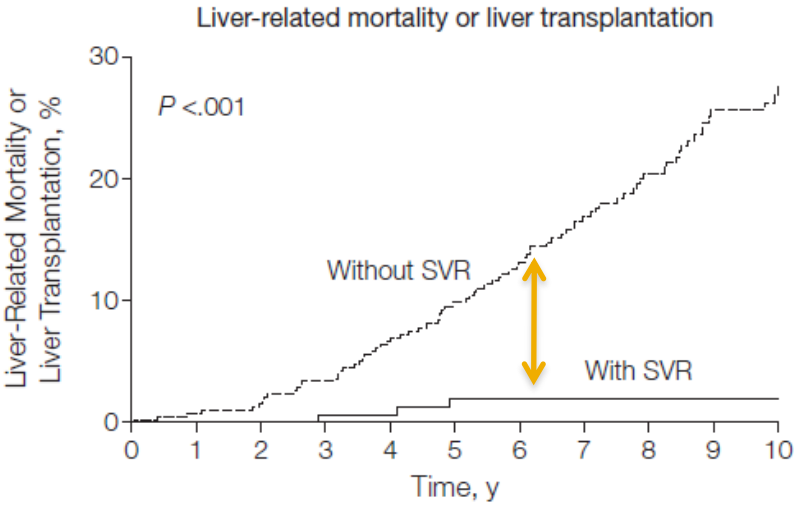
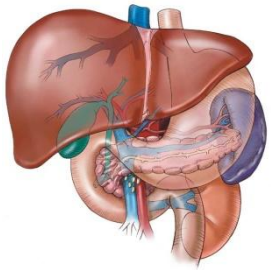
Achieving Sustained Virologic Response (SVR) Effectively Halts HCV-Disease Progression

- **For the patient**
  - Reduced disease sequelae
  - Improved quality of life
  - Prolonged life
- **For the healthcare system**
  - Reduced costs
- **For society**
  - Healthier population
  - More productive population





Source of graph data: Van der Meer AJ *et al*. Association Between Sustained Virological Response and All-Cause Mortality Among Patients With Chronic Hepatitis C and Advanced Hepatic Fibrosis. *JAMA* 2012;308(24):2584-93.

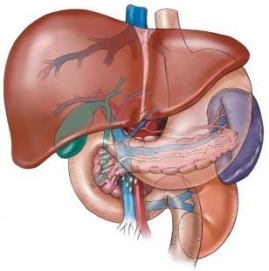


What Does HCV Treatment Look Like *Currently*?

Evolution of Hepatitis C Therapy to Date

	1st Gen PI (BOC/TVR)	2st Gen PI (SMV)	DAA (SOF)
Pill Burden	12 / 6 bid/tid	OD	OD
DDI	Many	Few	Nil
Multi-Genotype	G1 only	G1,(2,4,5,6)	G1,4,5,6,2,3
Resistance Mutations	Yes	Q80K (G1a)	Nil
Duration of Therapy / RGT	24-48 weeks / YES	24/48 weeks / YES	12 weeks / NO
AEs	Many	Few	Fewer
Capacity	Low	Med	High
Adherence	60-80%	24 weeks PEG	12 weeks PEG
Costs / AEs	+30%	Neutral	Trivial
Good for F4s	15-60%	58-65%	80%
SVR	70%	80%	90%

Limitations of PI-Based Therapy

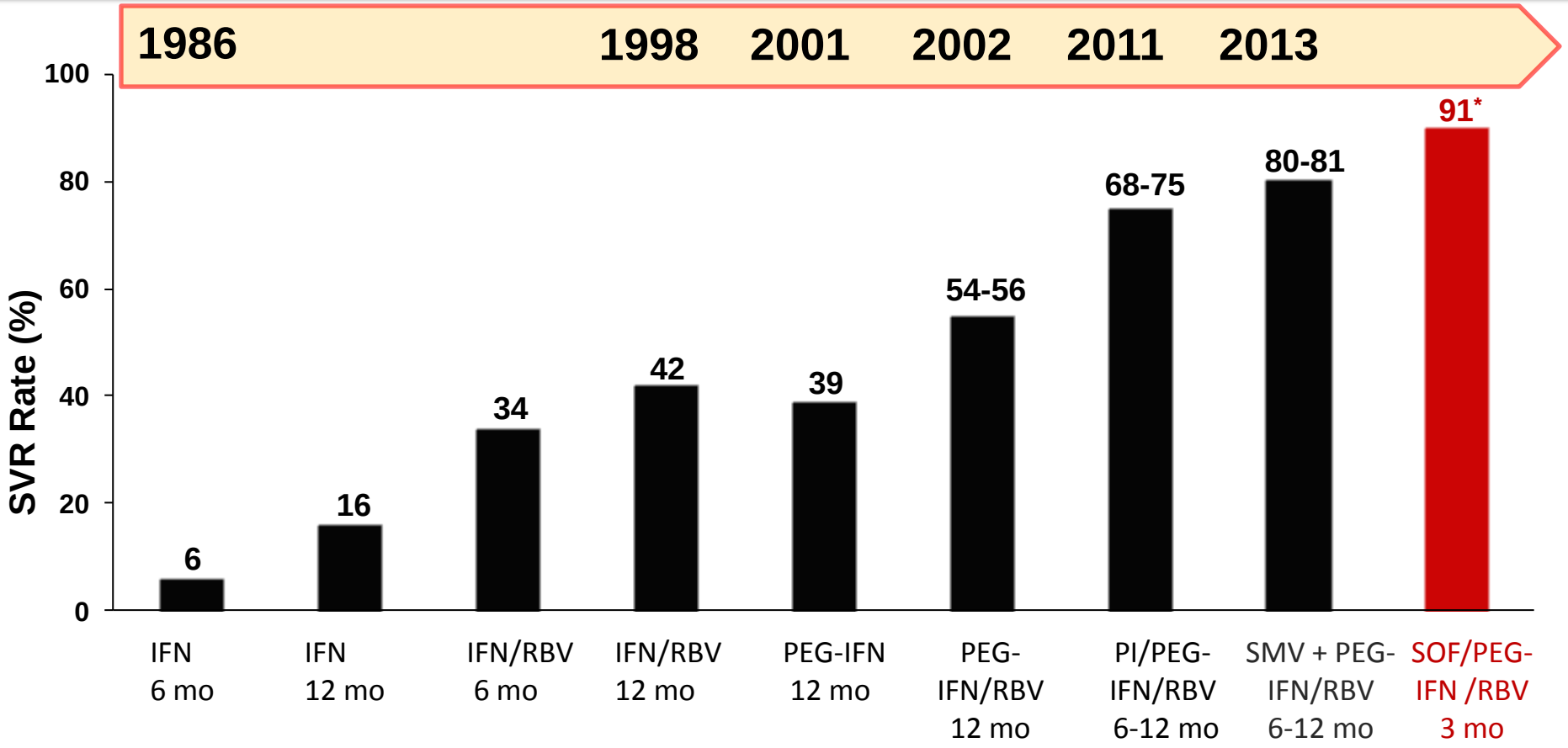


- Limited efficacy, particularly in poor IFN responders
  - Cirrhosis, IL28B non-CC, Black patients
  - Prior non-responders – particularly nulls
- Complicated regimens (RGT), high pill burden and long duration of IFN + RBV = poor adherence
- Toxicity issues, Adverse effects, Duration effects
- Inability to provide therapy in large volume
- Human Resource: Capacity due to AEs, etc.

SOVALDI® (Sofosbuvir):
Approved December 13, 2013

- Sovaldi is a once-daily, direct-acting antiviral agent for the treatment of chronic hepatitis C infection in:
  - Genotypes 1 and 4 in combination with pegylated interferon and ribavirin (12 weeks total)
  - Genotypes 2 and 3 in combination with ribavirin alone (first all-oral treatment regimen)
- In clinical studies, Sovaldi has achieved a cure rate of greater than 90% after only 12 weeks of treatment
- Minimized side effects and well tolerated
- High barrier to resistance

Evolution of SVR Rates in HCV Genotype 1



*SVR12 rate of 90% among GT 1 patients in the Phase 3 NEUTRINO trial (12 weeks of SOF+PEG-IFN+RBV)

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02

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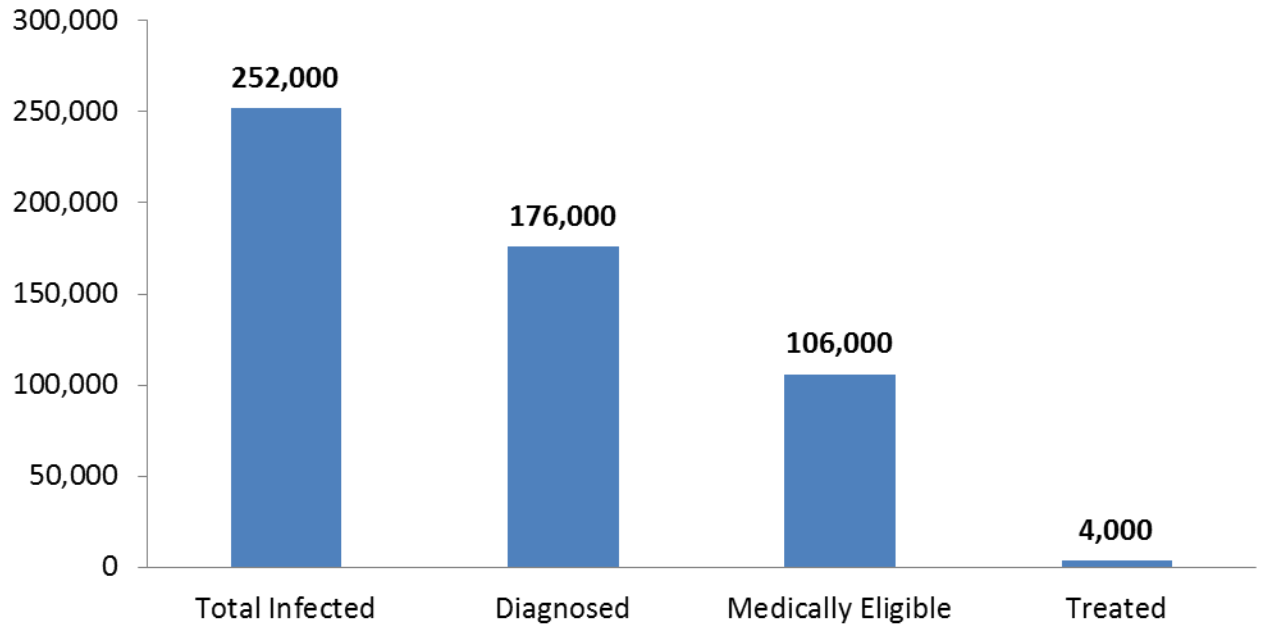
40-50% of CHC Patients are IFN-Ineligible or Intolerant. Despite Potential for Cure, Only 2% of Total Infected Population is Being Treated



Interferon- and RBV-free regimens will offer treatment option for GT1 patients who currently have no other options and expand potential for cure to broader CHC patient population

Source of graph data: Robert P. Myers, MD, et al. BURDEN OF DISEASE AND COST OF CHRONIC HEPATITIS C VIRUS INFECTION IN CANADA. Canadian Journal of Gastroenterology May 2014: Estimates for 2013.

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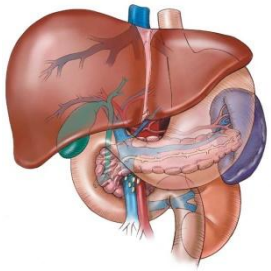

What Does HCV Treatment Look Like in the Near Future?

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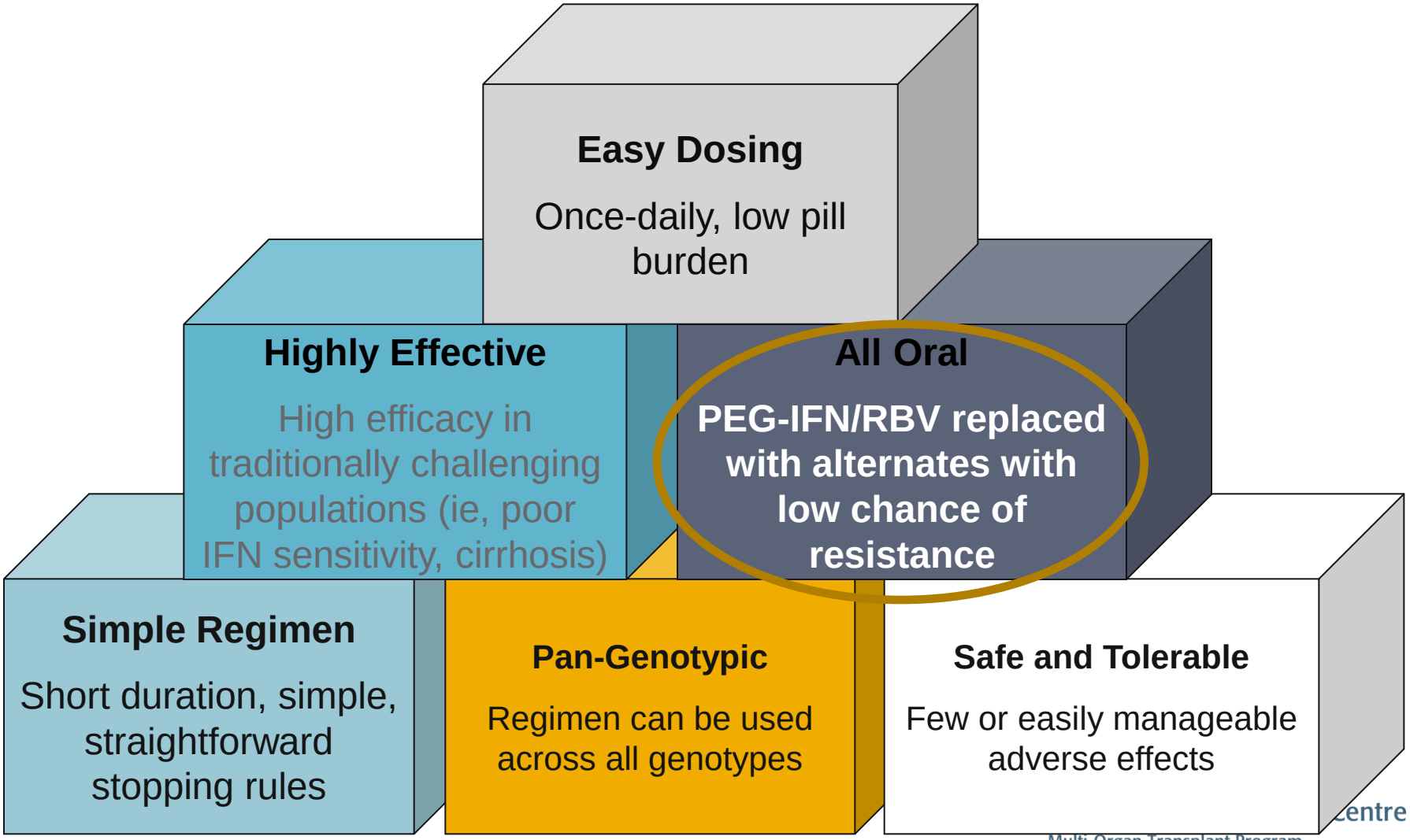
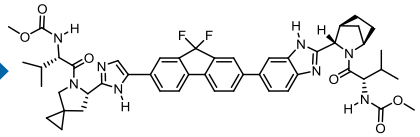
Key Elements of an Ideal HCV Regimen



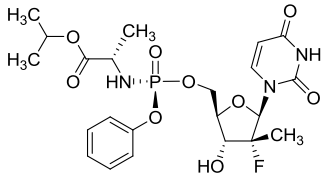
Ledipasvir/Sofosbuvir (LDV/SOF): A Single-Tablet Regimen (STR)

- **Ledipasvir**
  - Picomolar potency against HCV GT 1a and 1b[1]
  - Effective against NS5B RAV S282T[2]
  - Once-daily, oral, 90 mg

LDV NS5A inhibitor



- **Sofosbuvir**
  - Potent antiviral activity against HCV GT 1–6
  - Effective against NS5A RAVs[3]
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet



SOF - NS5B nucleotide polymerase inhibitor

- **Ledipasvir/Sofosbuvir STR**
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet, RBV-free
  - Minimal DDIs, no food effect
  - >2000 patients treated

LDV NS5A inhibitor + **SOF - NS5B nucleotide polymerase inhibitor**

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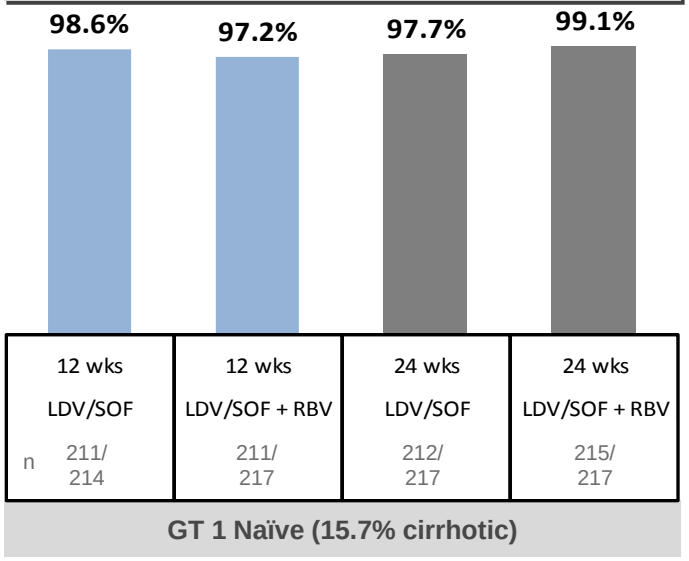
1. Lawitz E, et al. EASL 2011, poster 1219; 2. Cheng G, et al. EASL 2012, poster 1172; 3. SOVALDI® [PI]. Gilead Sciences, Inc. Foster City, CA December 2013

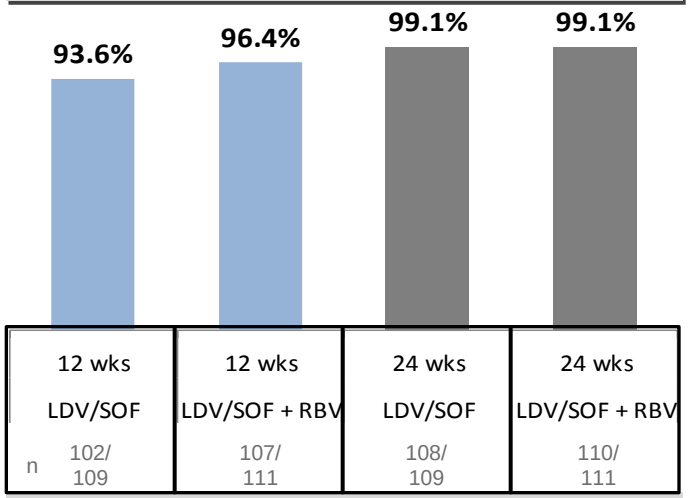
STR of LDV/SOF Phase 3 Results

ION-1



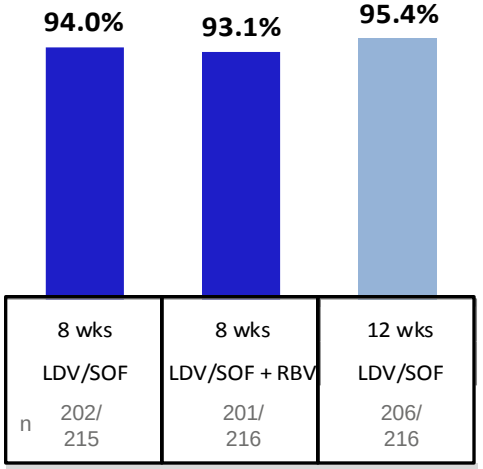
GT 1 Naïve (15.7% cirrhotic)

ION-2



GT 1 Experienced (20.0% cirrhotic)

ION-3



GT 1 Naïve (non-cirrhotic)

97% overall SVR 12 rate

Percentages represent SVR12 rates.

Afdhal N, et al. N Engl J Med 2014; 370: 1889-98; Afdhal N, et al. N Engl J Med 2014; 370: 1483-93; Kowdley K, et al. N Engl J Med 2014; 370: 1879-88

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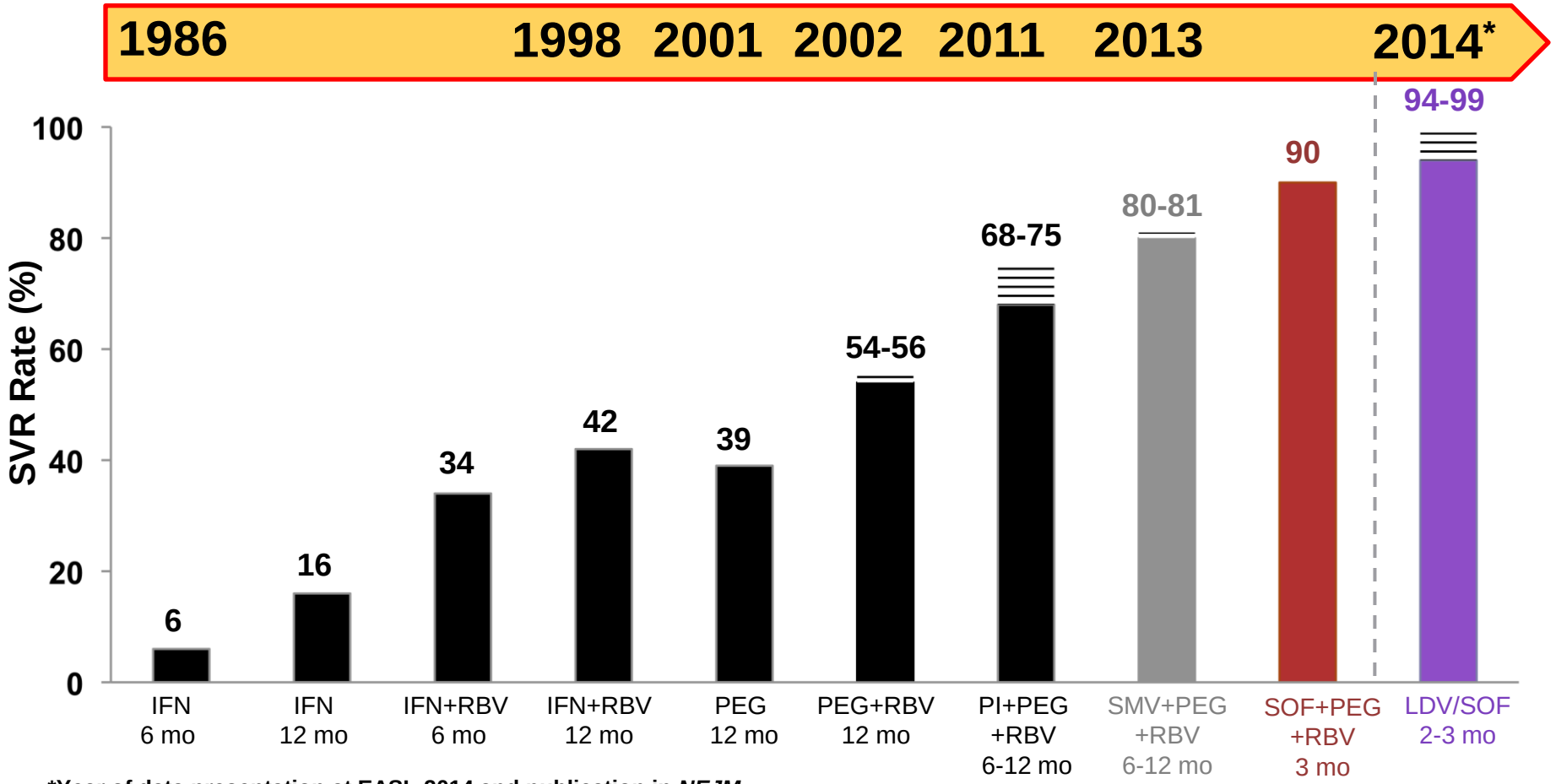
Sofosbuvir as the Backbone for a Simple Single-Tablet Regimen

SVR Rates in HCV Genotype 1:

Treatment-Naïve Patients



Year of data presentation at EASL 2014 and publication in *NEJM

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02; Afdhal N, et al. N Engl J Med 2014; 2014 Apr 12 [Epub ahead of print]; Kowdley K, et al. N Engl J Med 2014; 2014 Apr 11 [Epub ahead of print]

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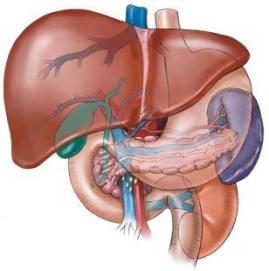
Hepatitis C Therapy

	1st Gen PI (BOC/TVR)	2st Gen PI (SMV)	DAA (SOF)	STR (LDV/SOF)
Pill Burden	12 / 6 bid/tid	OD	OD	OD
DDI	Many	Few	Nil	Nil
Resistance Mutations	Yes	Q80K (G1a)	Nil	Few
Duration of Therapy / RGT	24-48 weeks / YES	24/48 weeks / YES	12 weeks / NO	8-12 weeks/ No
AEs	Many	Few	Fewer	Fewest
Capacity	Low	Med	High	Highest
Adherence	60-80%	24 weeks PEG	12 weeks PEG	No PEG No RBV
Costs / AEs	+30%	Neutral	Trivial	Minuscule
Good for F4s	15-60%	58-65%	80%	≥90%
SVR	70%	80%	90%	97%

Ledipasvir/Sofosbuvir - Summary



- LDV/SOF combines the novel NS5A inhibitor Ledipasvir with guideline-preferred NS5B inhibitor Sofosbuvir
  - To provide a simple, once-daily, oral, single-tablet regimen for genotype 1 CHC infection
- Delivers consistently high efficacy (SVR ≥94%) in GT1 patients despite-
  - Presence of Cirrhosis
  - Prior poor response to IFN
  - Prior combination PI + IFN + RBV failures
- Favourable safety and tolerability profile
  - Absence of any clinically relevant safety signals with <1.0% of patients discontinuing due to AEs
  - Reduces or eliminates adverse events and laboratory abnormalities typically associated with IFN and RBV (e.g. anemia, rash, depression, fatigue, flu-like symptoms and gastrointestinal symptoms)