Meeting the Current and Future Challenges of HCV

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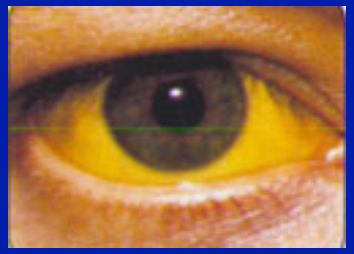
Learning Objectives

- To know the currently recommended therapy for chronic HCV infection by genotype
- To be aware of simpler PegIFN + RBV containing triple therapies for HCV genotype 1 that are expected to be available in Canada in 2014
- To be aware of promising IFN-free regimens for HCV
- To be aware of the pros and cons of treating patients for HCV now versus deferring treatment, and how to discuss this with patients

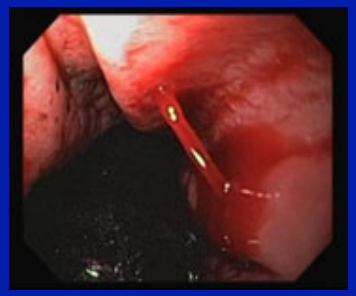
Hepatitis C Epidemiology

- ~170 million cases worldwide (c/w ~34M with HIV)
- HCV is the leading cause of chronic liver disease, cirrhosis, liver failure and liver cancer in western countries
- HCV is the leading indication for liver transplantation worldwide (~40-50% of cases)
- Unlike HAV & HBV, no vaccine is available (or imminent)
- HCV is ***curable*** with a finite course of antiviral therapy
- 6 major genotypes of HCV exist worldwide (1 to 6), and genotypes can be subtyped, e.g. 1a, 1b, etc.

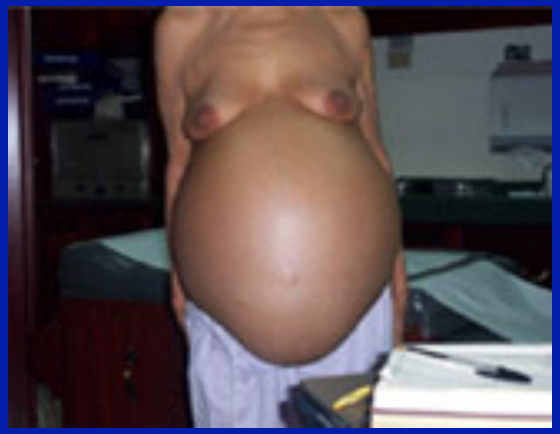
What We're Trying to Prevent with Successful Treatment of HCV



Jaundice

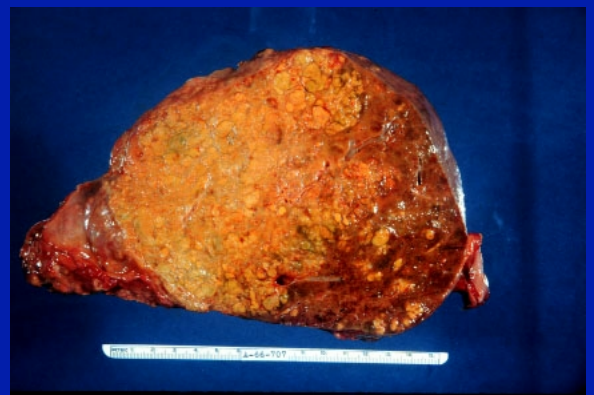


Esophageal Varices/ GI bleed



Ascites

Hepatic Encephalopathy



Liver Cancer

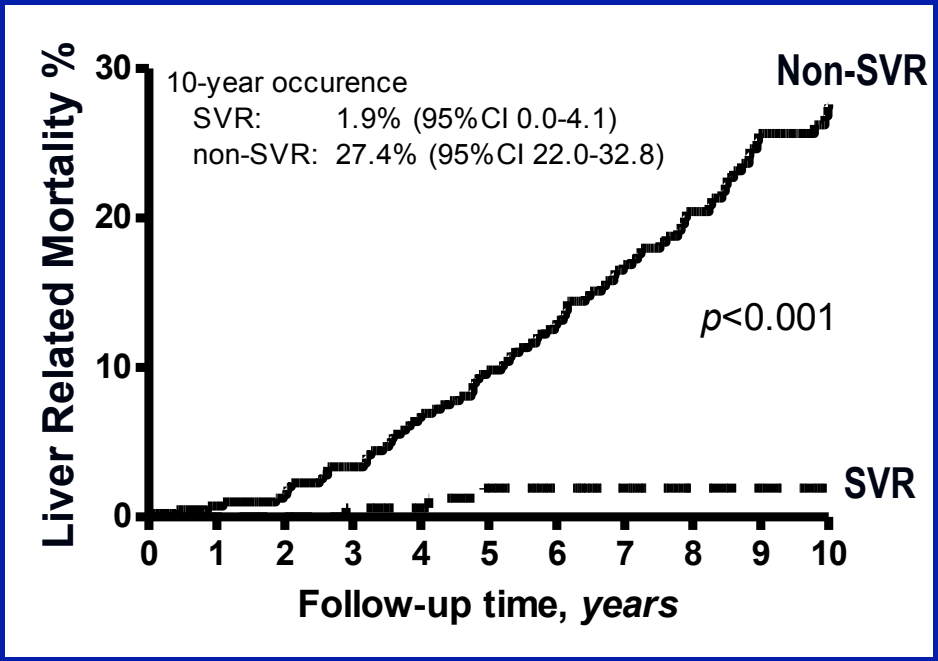
What Else Successful HCV Treatment Can Cure/Prevent

- Resolution of porphyria cutanea tarda (PCT)
- Resolution of membranoproliferative glomerulonephritis (MPGN)
- Resolution of symptomatic cryoglobulinemia (rash, arthritis)
- Vertical transmission (if women are cured before becoming pregnant)
- ? Sexual transmission in HIV+ MSM

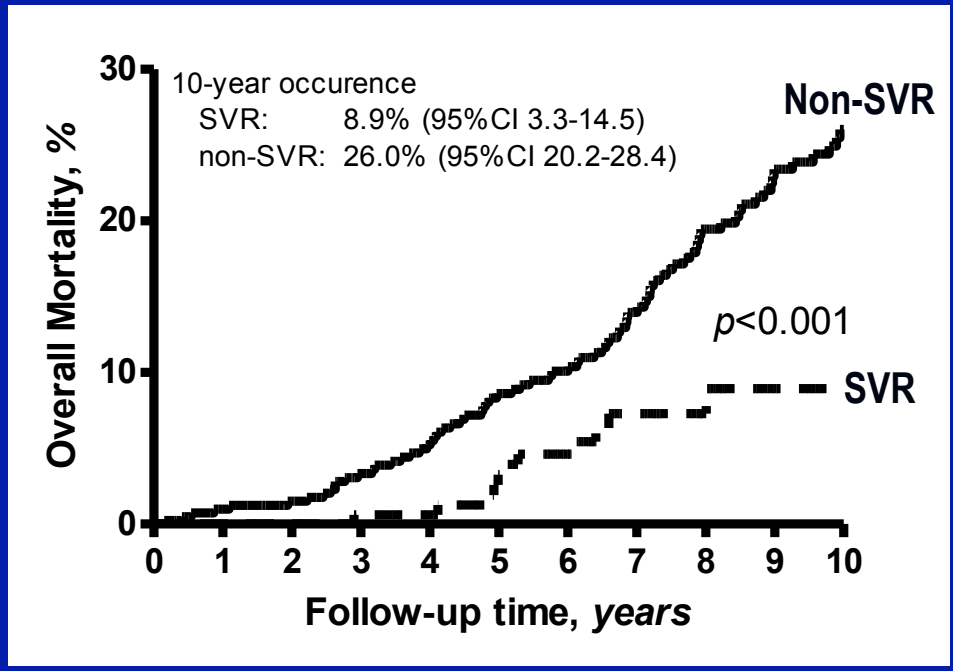
Curing HCV Saves Lives in the HCV Mono-infected

Long-term follow-up of patients treated for HCV with F3/F4 at baseline

Liver Related Mortality

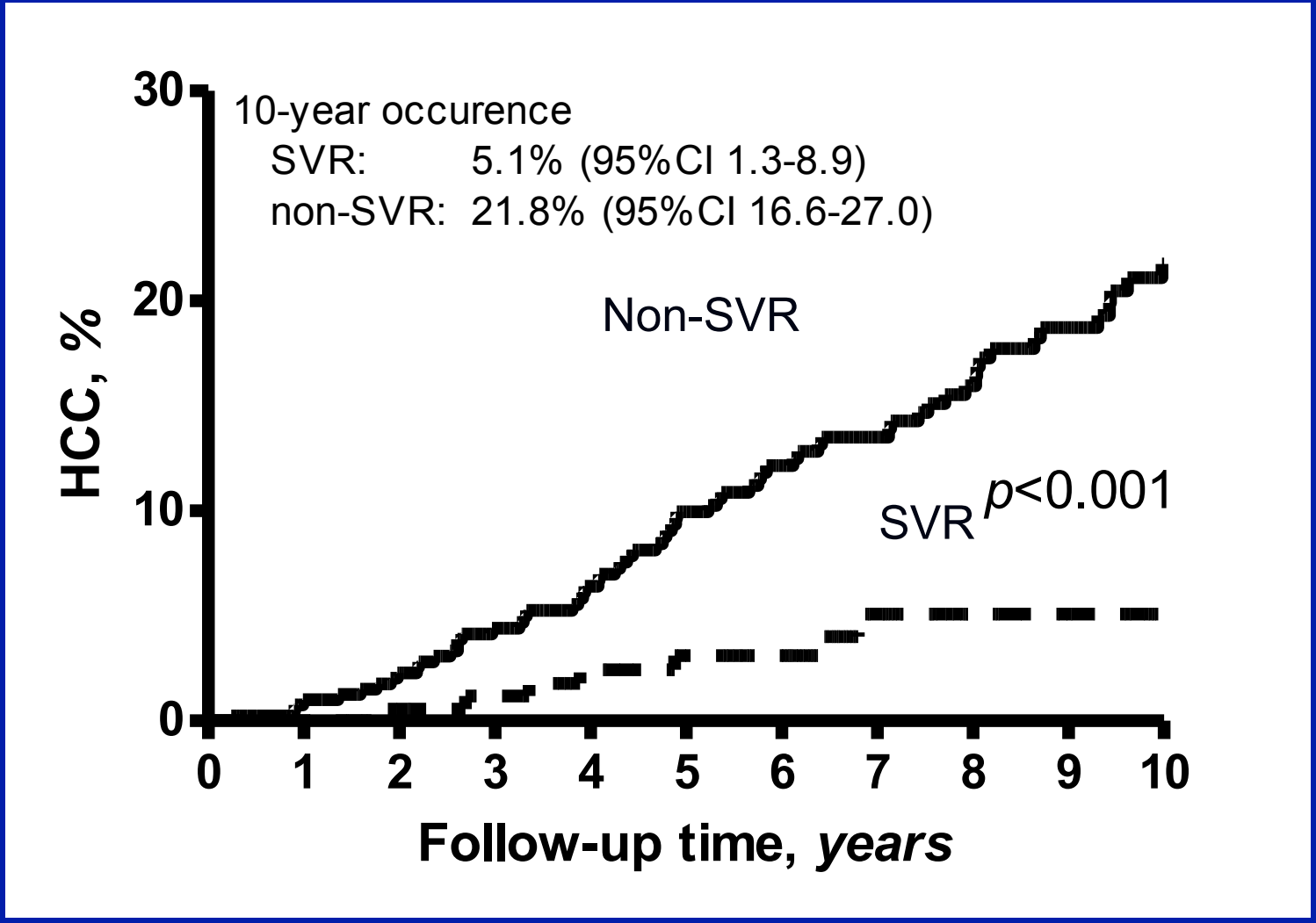


All Cause Mortality



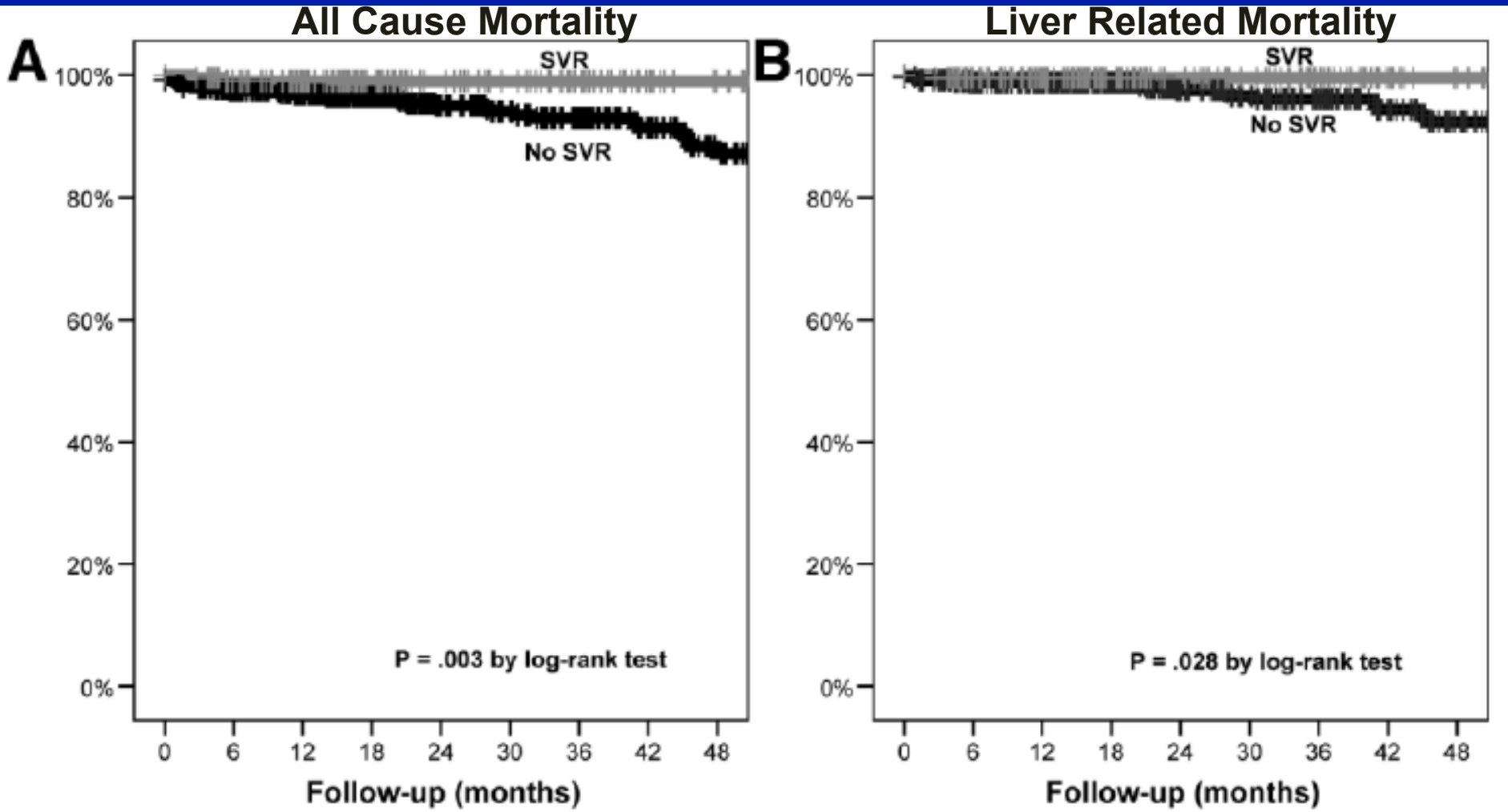
Van der Meer AJ, et al. *JAMA* 2012;308:2584-93.

Hepatocellular Carcinoma (HCC) Incidence is Markedly Reduced Post-SVR



Van der Meer AJ, et al. *JAMA* 2012;308:2584-93.

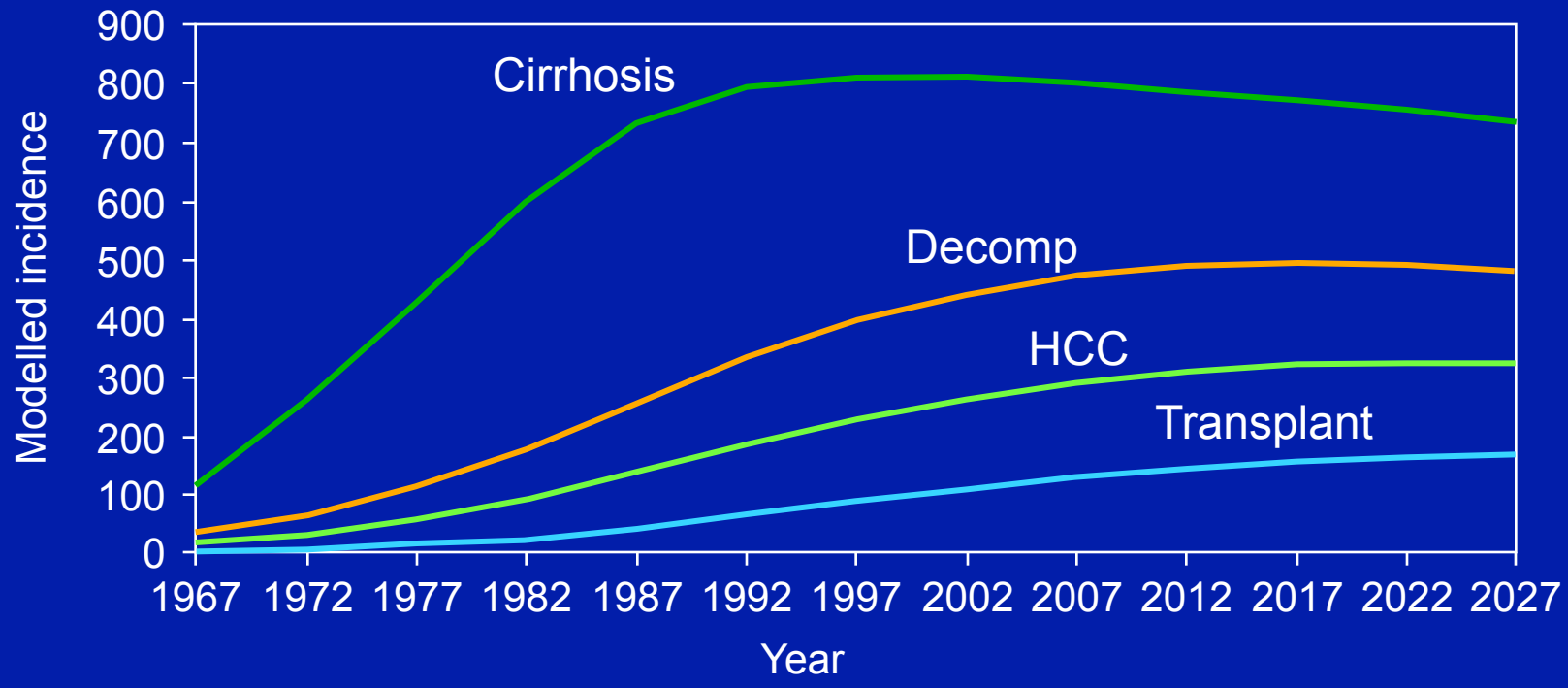
Curing HCV Also Saves Lives in the HIV-HCV Co-infected



Berenguer J, et al. *Hepatology* 2009;50:407-13.

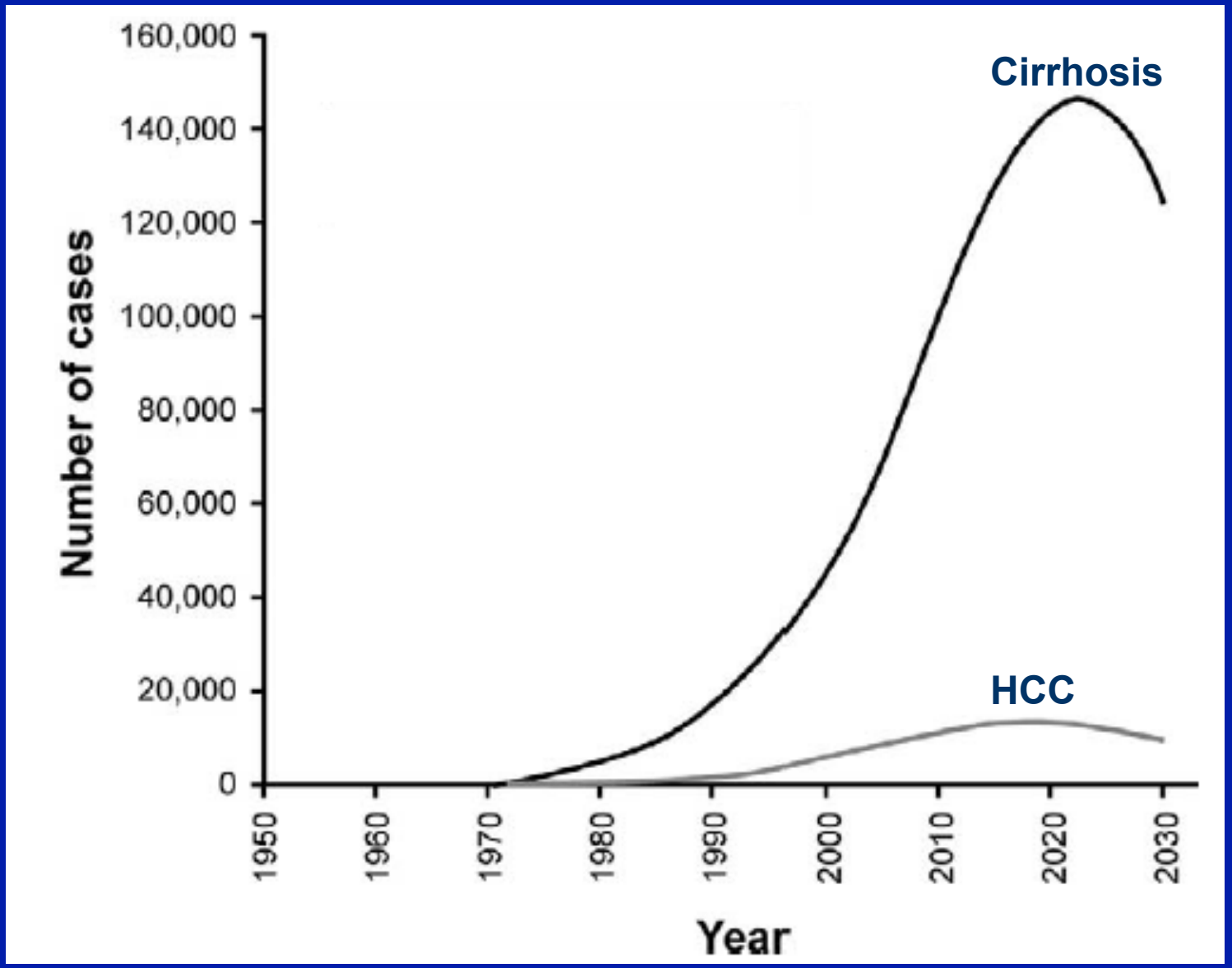
Burden of HCV in Canada

- ~8,000 incident cases annually (>80% IDUs)
- Proportion diagnosed uncertain
- HCV-related complications rising
- Insufficient manpower to treat all cases



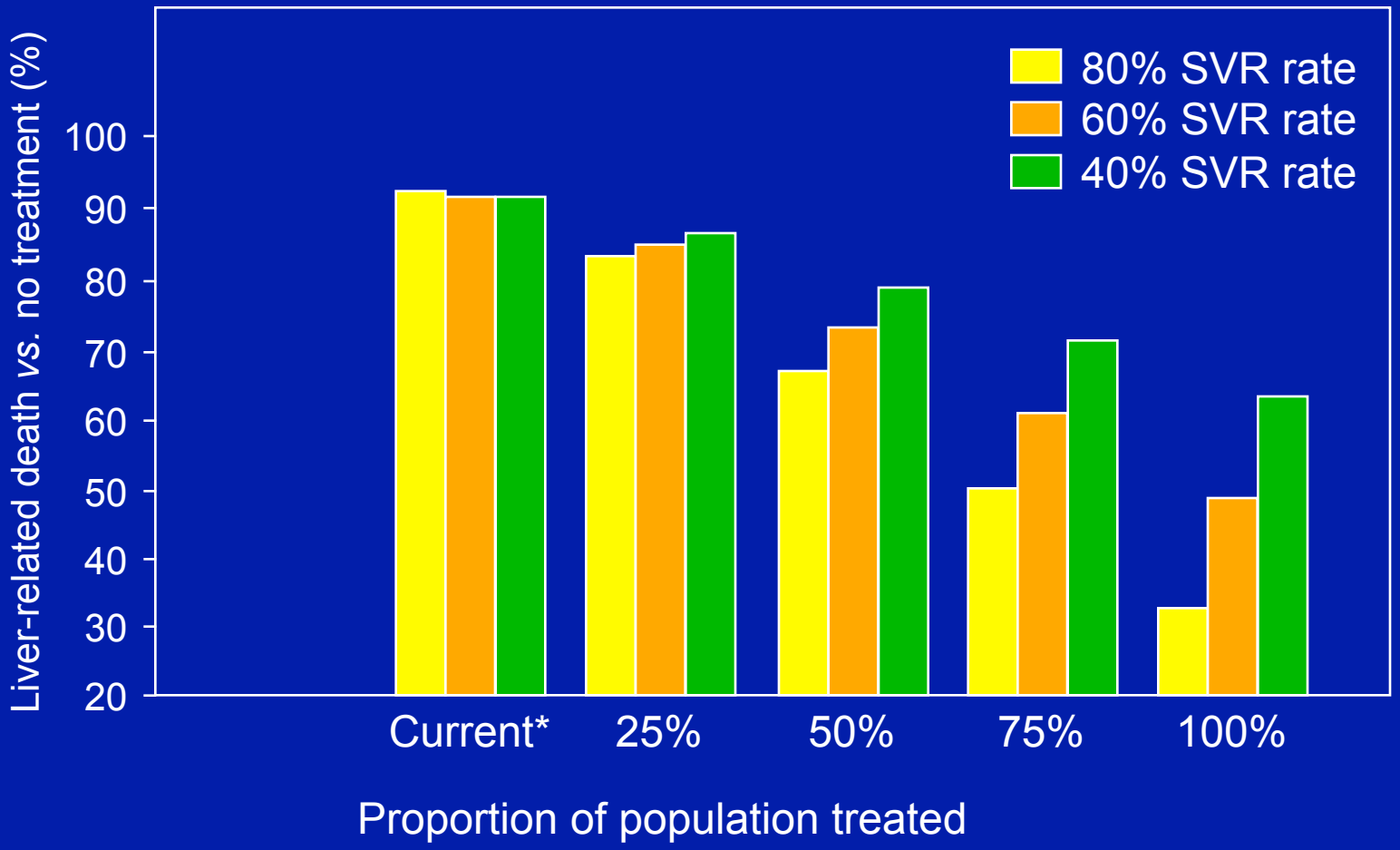
Remis R, et al. PHAC 2007

Projected HCV Related Cirrhosis and HCC in the USA



Davis GL, et al. *Gastroenterology* 2010; 138: 513-21.

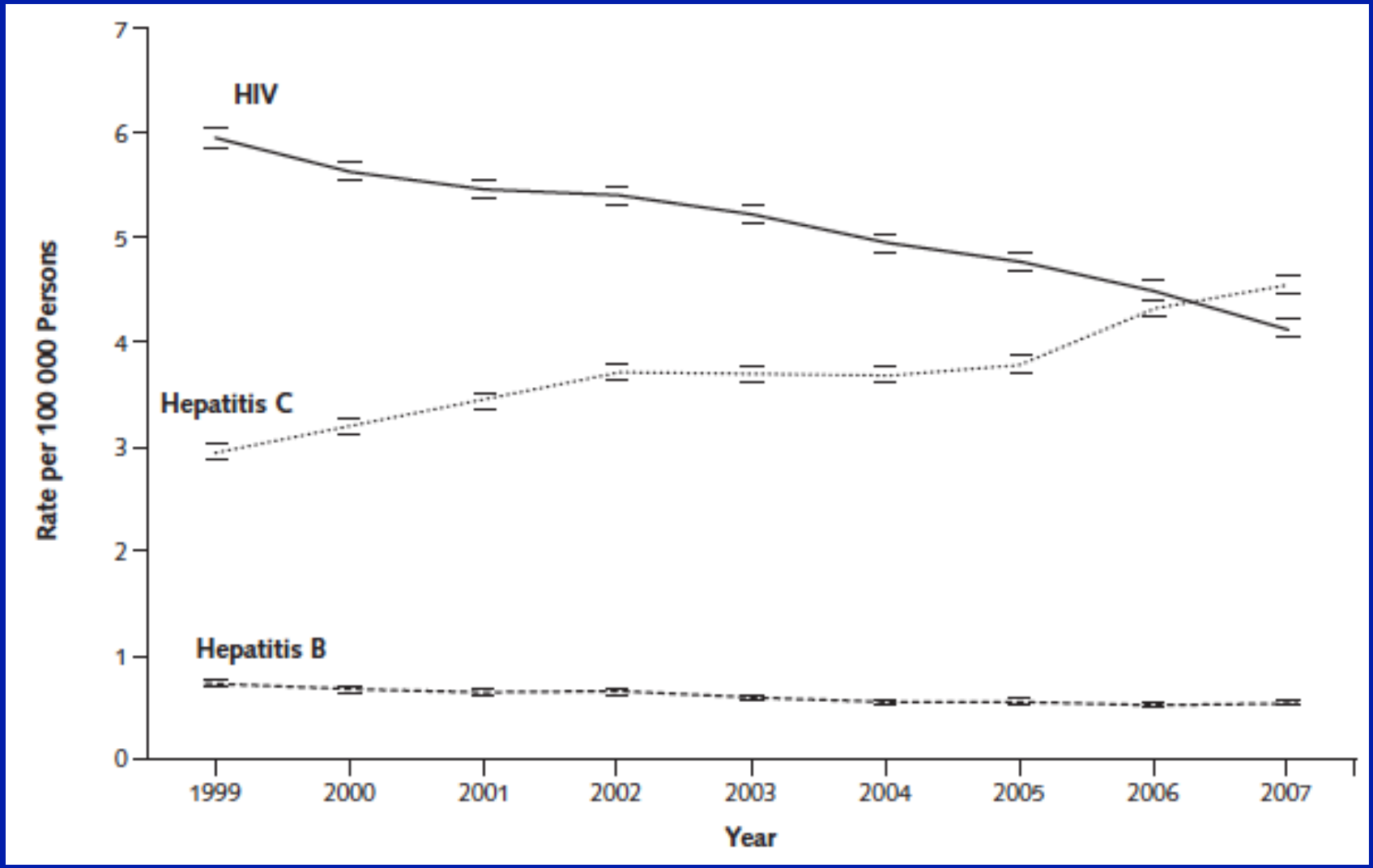
Anti-HCV Therapy Uptake Must be Greatly Increased to Make a Societal Impact



** Assumes 30% Dx & up to 25% Rx'd in 2010. Outcomes at 2020.*

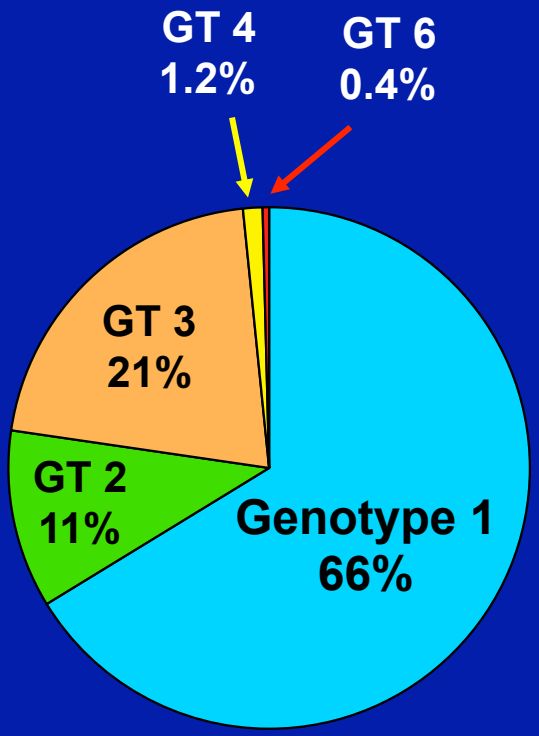
Davis GL, et al. *Gastroenterology* 2010; 138: 513-21.

Annual Age-Adjusted Mortality of HIV, HCV and HBV in the USA, 1999-2007



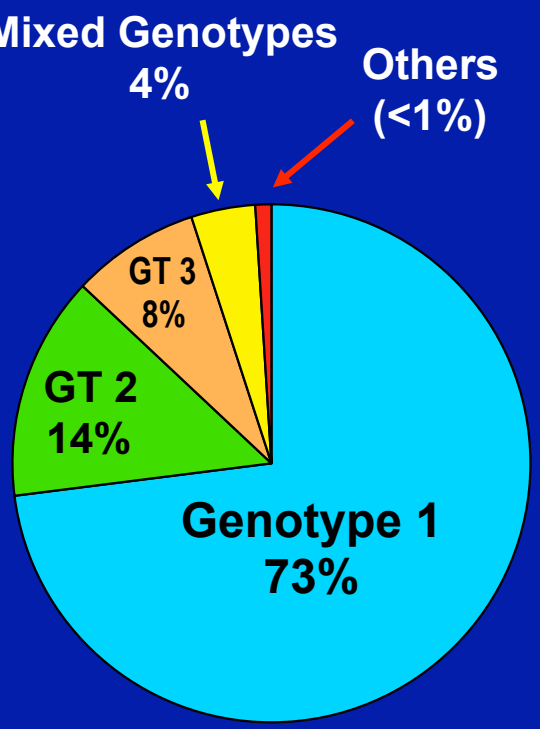
Ly K, et al. *Ann Intern Med* 2012;156:271-8.

Distribution of HCV Genotypes in Alberta and the United States



n=14,192
(2000-2012)

Tang J. Alberta Provincial Laboratory of Public Health



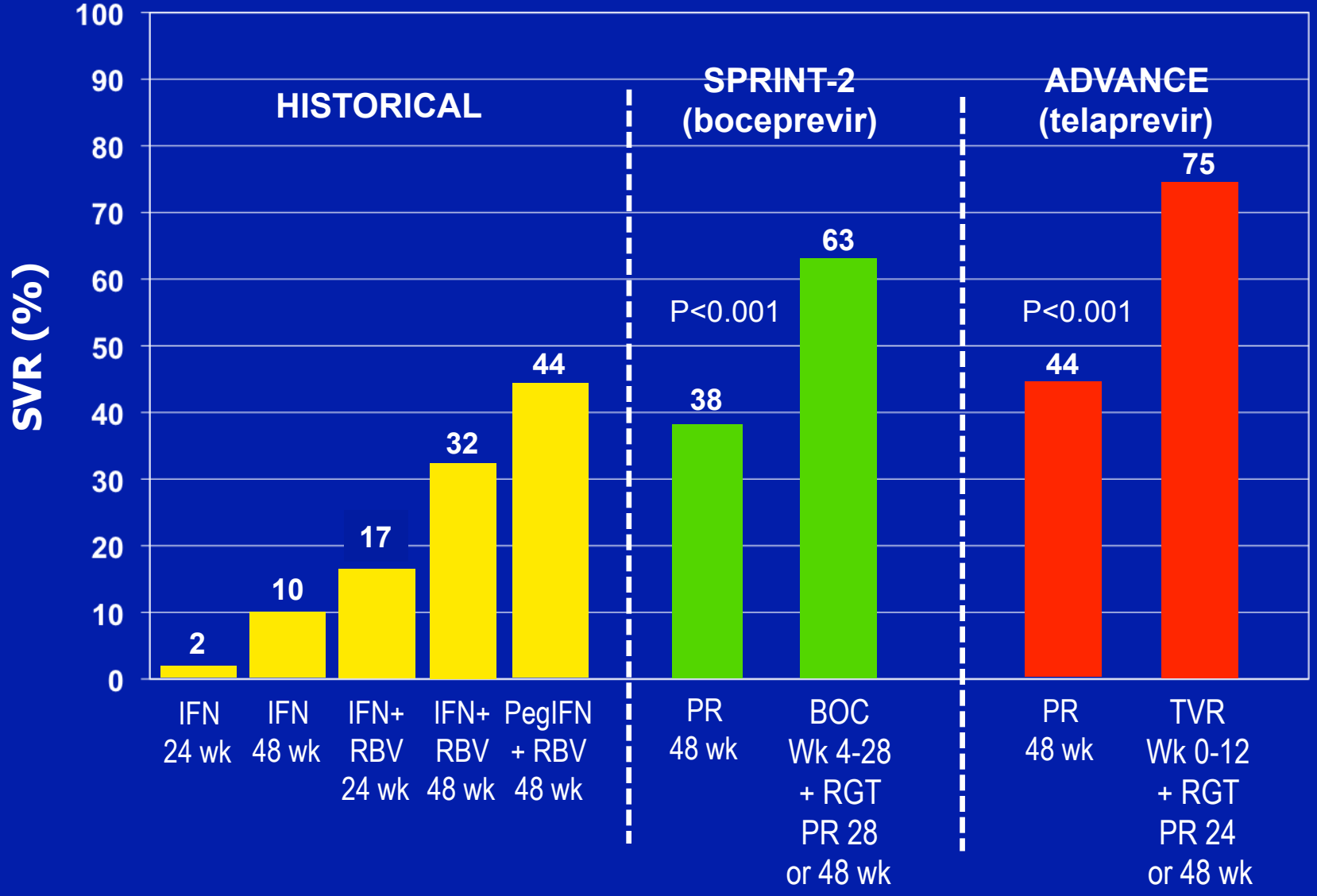
n=6807

Blatt M, et al. *J Viral Hepatitis* 2000;7:196-202.

Importance of HCV Genotype 1

- The most common HCV genotype worldwide
- Responds less well to interferon (IFN) ± ribavirin (RBV) therapy than do other genotypes
- Requires 48 weeks of therapy with PegIFNα + RBV vs 24 weeks for genotypes 2 and 3
- Expected cure rates with PegIFNα + RBV dual Rx:
  - Genotype 1 ~45% (~25% in the HIV co-infected)
  - Genotype 2 ~85%
  - Genotype 3 ~75% (~62% in the HIV co-infected)
  - Genotype 4 ~65%

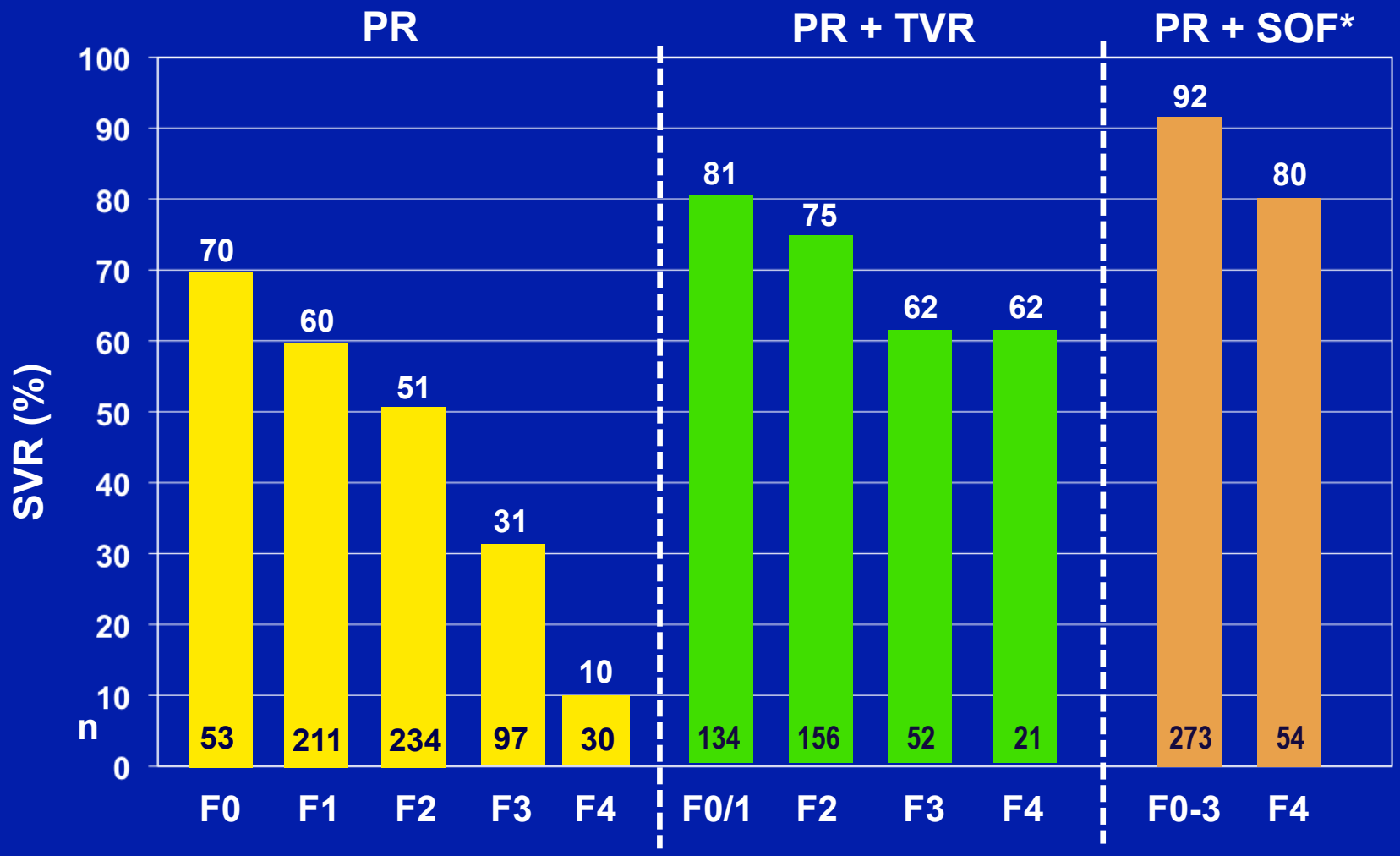
SVR in GT 1 Treatment Naïve Patients Over Time (up to 2011)



Hepatic Fibrosis Adversely Affects Response Rates to HCV Rx

- SVR rates decline with advancing degrees of hepatic fibrosis
- The adverse effect of increasing hepatic fibrosis on SVR is strongest with dual Rx with PR, but is still true of DAA-based therapy
- So, the clinical reality: those HCV patients who most need to be cured have lower cure rates than those in whom treatment is not urgent

Effect of Hepatic Fibrosis (METAVIR) on SVR in G1

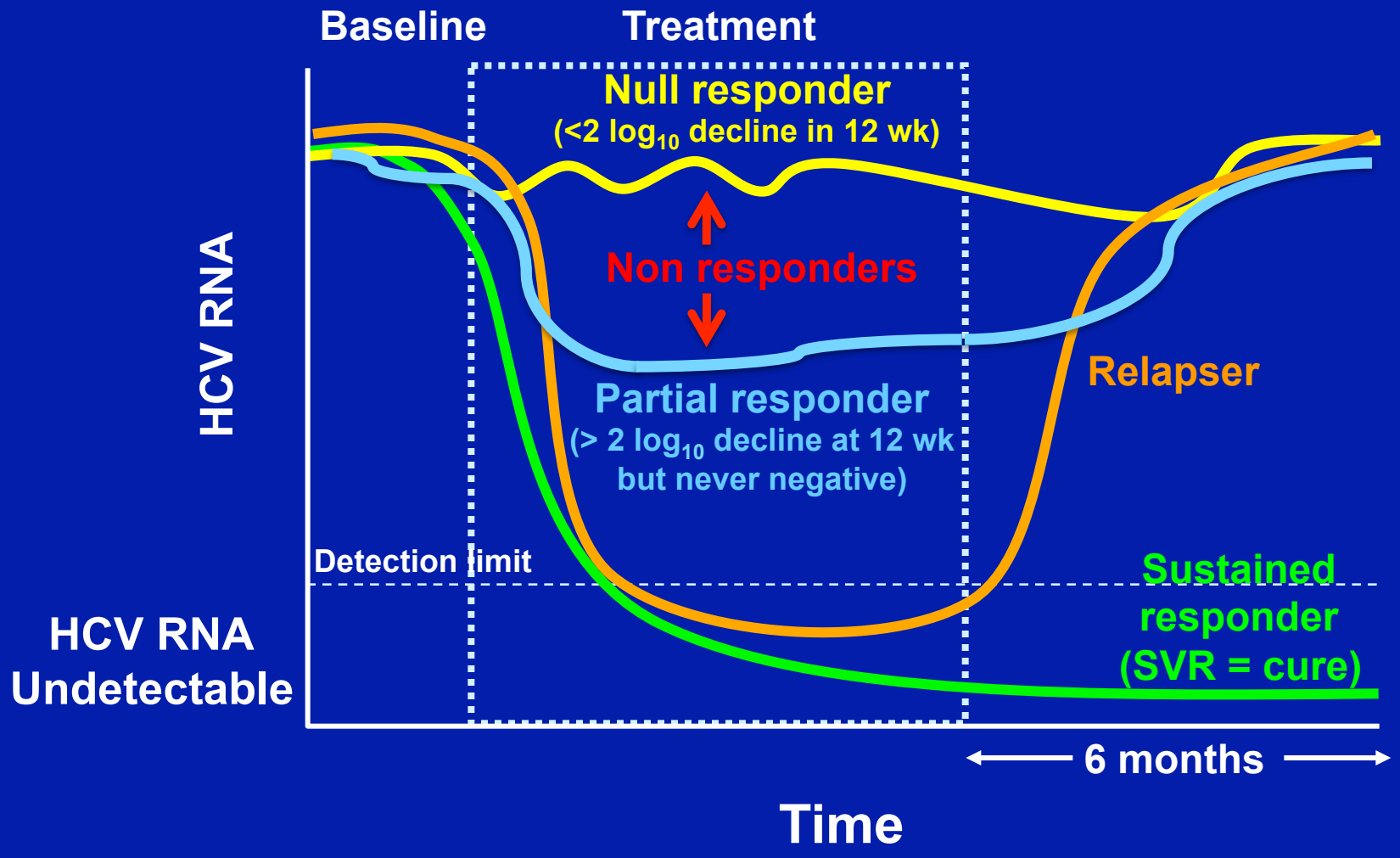


* 89% were G1; 11% G4-6

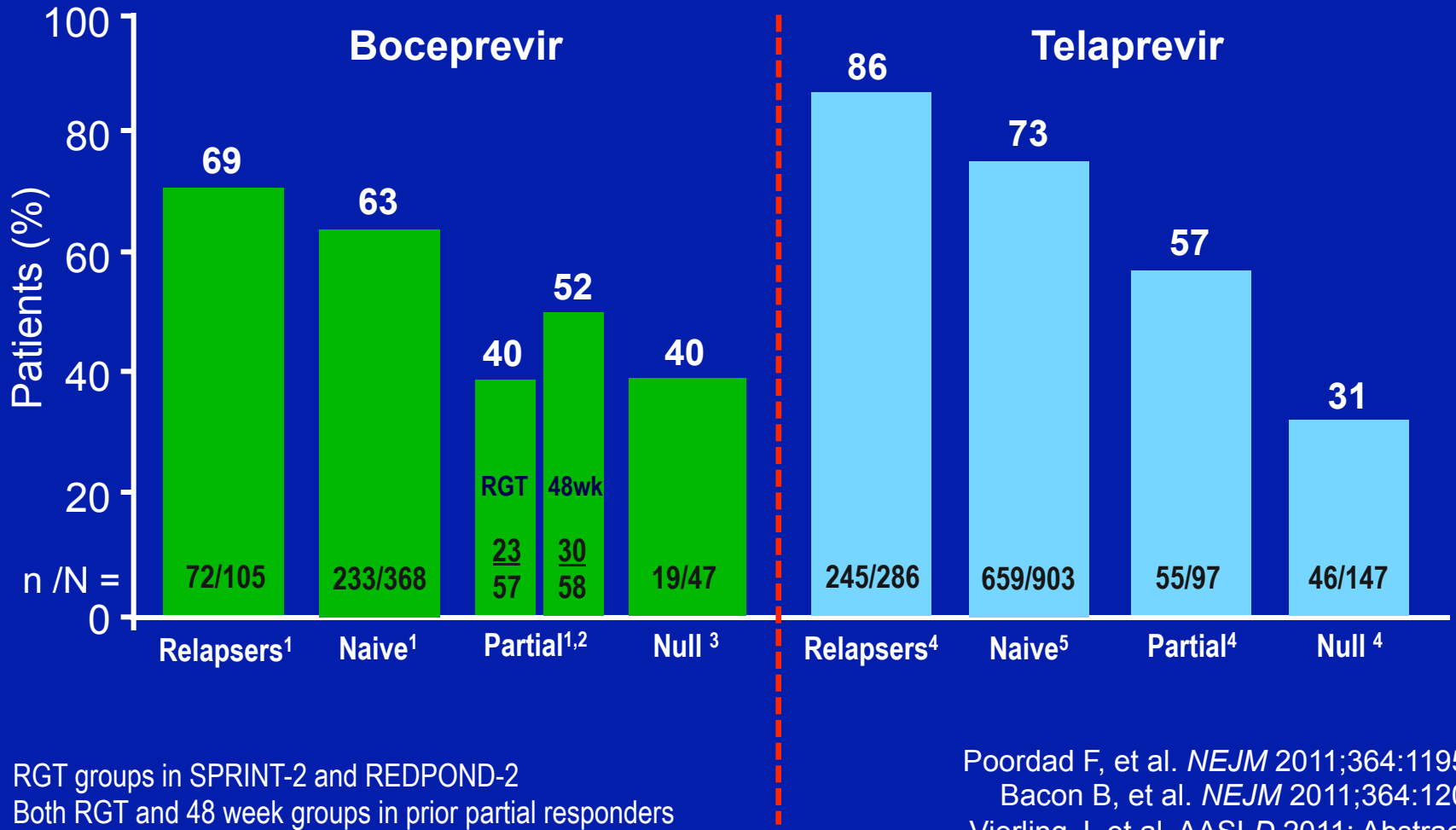
1. Cheng WSC, et al. *J Hepatol* 2010;53:616-23.
2. Jacobson I, et al. *NEJM* 2011;364:2405-16.
3. Lawitz E, et al. *N Engl J Med* 2013;368:1878-87.

Prior Treatment Status Strongly Affects SVR Rates with PR + BOC/TVR

Patterns of Virologic Response to PR Therapy



Triple Therapy with PR + Boceprevir or Telaprevir: SVR by Prior PR Treatment

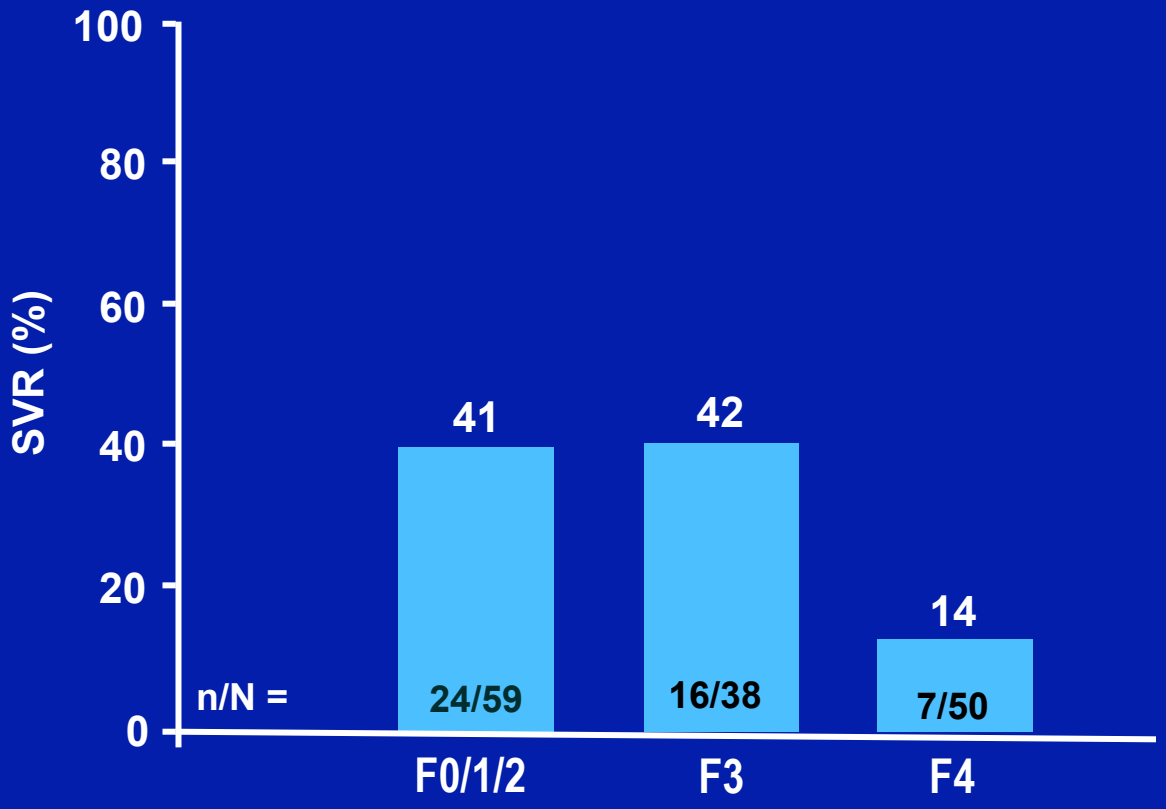


1. RGT groups in SPRINT-2 and REDPOND-2
2. Both RGT and 48 week groups in prior partial responders
3. PR4 PRB44 in PROVIDE
4. Both T12PR48 groups combined from REALIZE
5. ADVANCE and ILLUMINATE combined

Poordad F, et al. *NEJM* 2011;364:1195-206.
Bacon B, et al. *NEJM* 2011;364:1207-17.
Vierling J, et al. AASL*D* 2011; Abstract 931.
Jacobson I, et al. *NEJM* 2011;364:2405-16.
Zeuzem S, et al. *NEJM* 2011;364:2417-28.
Sherman K, et al. *NEJM* 2011;365:1014-24.

Null Response to Prior PR Therapy Plus Cirrhosis: A Bad Combination for Current Triple Rx

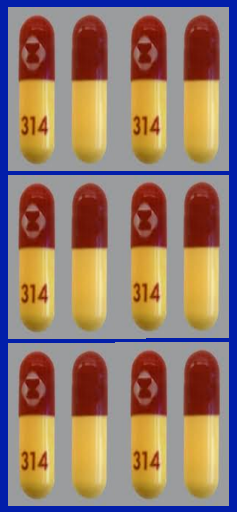
(all treated with PR + TVR in REALIZE)



Pol S, et al. AASLD 2011.

Challenges with BOC/TVR-based Therapy

Pill Burden



BOC = 12/d

TVR = 6/d

RBV = 4-7/d

Food Requirement

Resistance

Drug-Drug Interactions

PI

Metabolites

Compatibility of BOC or TVR with ARVs

Specific ARVs	Boceprevir	Telaprevir
NRTIs		
ZDV, d4T, ddI	Not recommended (NR) with PegIFN + RBV	
3TC, FTC, TDF	Compatible	
Abacavir	11 patients; probably OK	No data; probably OK
NNRTIs		
Efavirenz	NR (44%↓ BOC C_{min})	OK with 50% ↑ TVR dose (47%↓ TVR C_{min})
Nevirapine	No data	No data
Rilpivirine	Compatible	
Etravirine	NR (29% ↓ ETR C_{min})	Compatible
PIs		
Atazanavir/r	NR (49%↓ ATZ C_{min})	Compatible
Darunavir/r	NR (59%↓ DRV C_{min}, 35%↓BOC C_{min})	NR (42%↓ DRV C_{min}, 32%↓ TVR C_{min})
Lopinavir/r	NR (43%↓ LPV C_{min}, 57%↓BOC C_{min})	NR (53% ↓ TVR C_{min})
Fosamprenavir/r	No data	NR (56%↓ FPV C_{min}, 30%↓ TVR C_{min})
Others		
Raltegravir	Compatible	
Dolutegravir	Compatible	
Maraviroc	3.0-fold ↑MVC AUC	9.5-fold ↑MVC AUC

Treating Cirrhotic Patients with PR + BOC or TVR: Not for the Faint of Heart

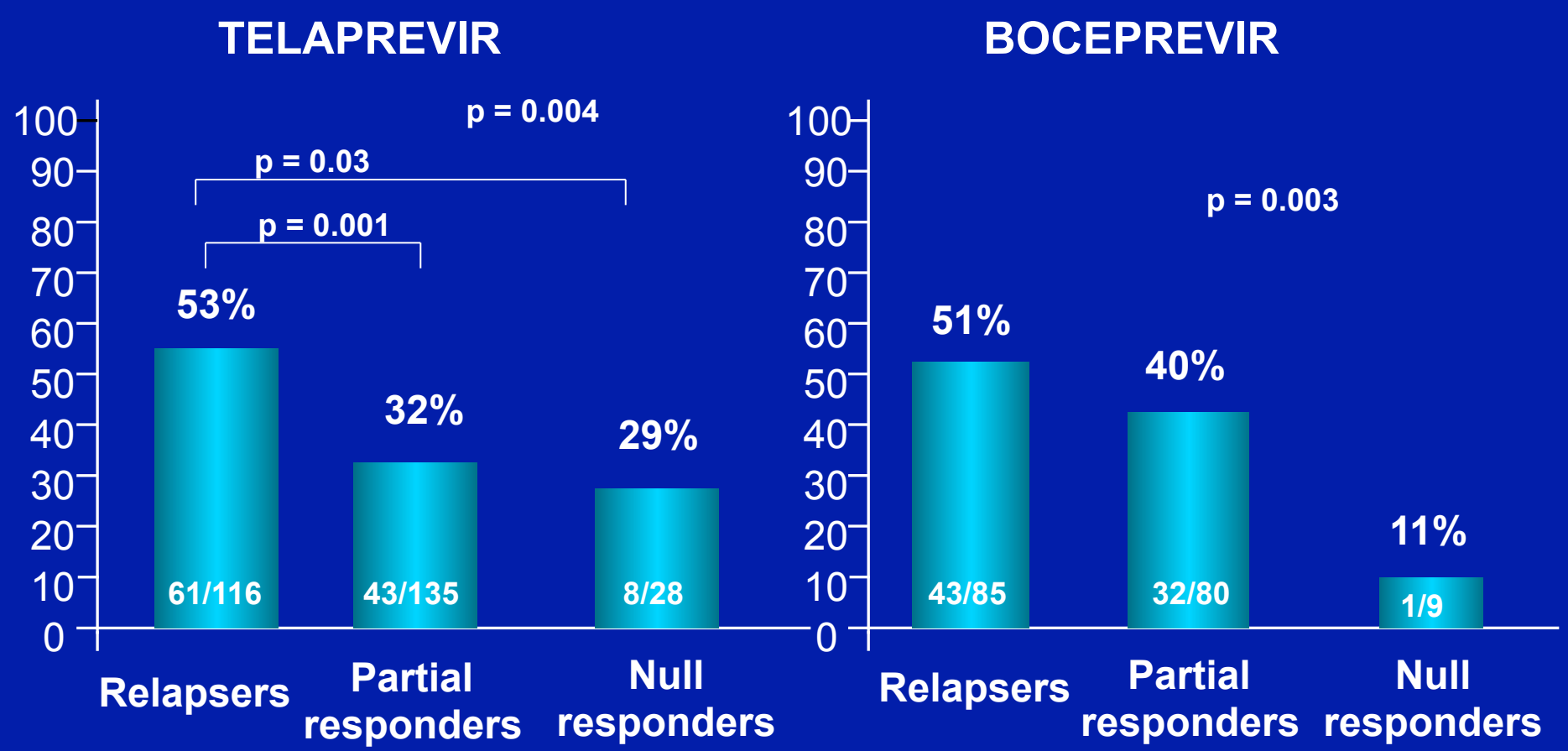
- SVR rates, while much improved compared with dual PR Rx, are still lower than in non cirrhotics
- RGT not recommended in cirrhotics. 48 weeks of PR is recommended for all cirrhotics, even if rapid HCV RNA clearance occurs
- Higher rate of anemia than in non cirrhotics
- Higher rate of thrombocytopenia than in non cirrhotics
- Risk of sepsis
- Risk of hepatic decompensation
- Risk of death

CUPIC: Patient Baseline Demographics and Disease Characteristics (patients were NOT randomized)

Characteristic	Telaprevir N=295	Boceprevir N=190
Male, %	201 (68)	133 (70)
Mean age, years (range) Mean BMI, SD (kg/m^2)	57 (27-83) 26.5 (18.2-40.4)	57 (34–79) 26.2 (18.1-39.4)
HCV genotype 1 subtype, n (%) 1a 1b Other	 98 (33) 162 (55) 33 (11)	 77 (41) 96 (51) 16 (8)
HCV RNA ≥ 800,000 IU/mL, n (%)	182 (62)	122 (64)
Treatment history, n (%) Prior relapse Prior partial response Prior null response Others	 116 (39) 135 (46) 28 (10) 15 (5)	 85 (45) 80 (42) 9 (5) 16 (8)
Exclusion criteria, n (%) REALIZE (TVR) RESPOND-2 (BOC)	 99 (34) 137 (46)	 52 (27) 73 (38)

Fontaine H, et al. EASL 2013. Abstract 60.

CUPIC: SVR12 According to Prior Treatment Response



Fontaine H, et al. EASL 2013. Abstract 60.

CUPIC: Which Cirrhotics Get in Trouble?

Combined Incidence of Sepsis, Liver Decompensation and Death in Cirrhotics Treated with PR + BOC or TVR, n=429

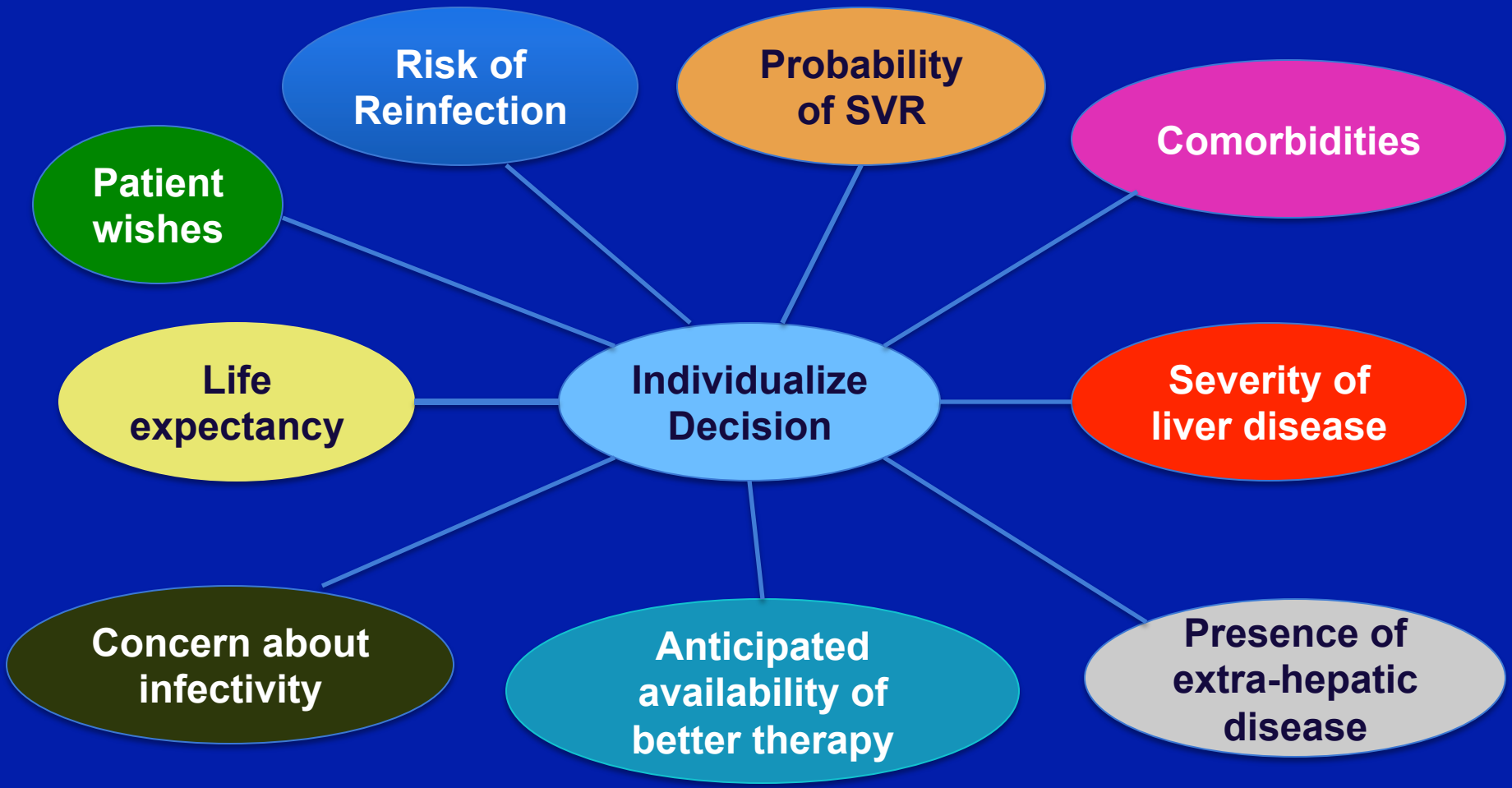
	Platelets > 100,000	Platelets ≤ 100,000
Albumin ≥ 35	3.4% (10/298)	4.3% (3/69)
Albumin < 35	7.1% (2/28)	44.1% (15/34)

Only 8% of patients in CUPIC

Fontaine H, et al. EASL 2013. Abstract 60.

HCV: Treat Now or Wait for Better Treatment Options?

Factors to Consider in Deciding Whom to Treat for HCV



Important Comorbidities to Consider in Deciding Whether to Treat for HCV

- Injection drug use
  - Risk of reinfection
  - Commitment to Rx
- Non injection drug abuse, including EtOH
- Mental illness
- Concomitant medications
- Competing risks for mortality
- Patient motivation

The Case for Treating HCV Now

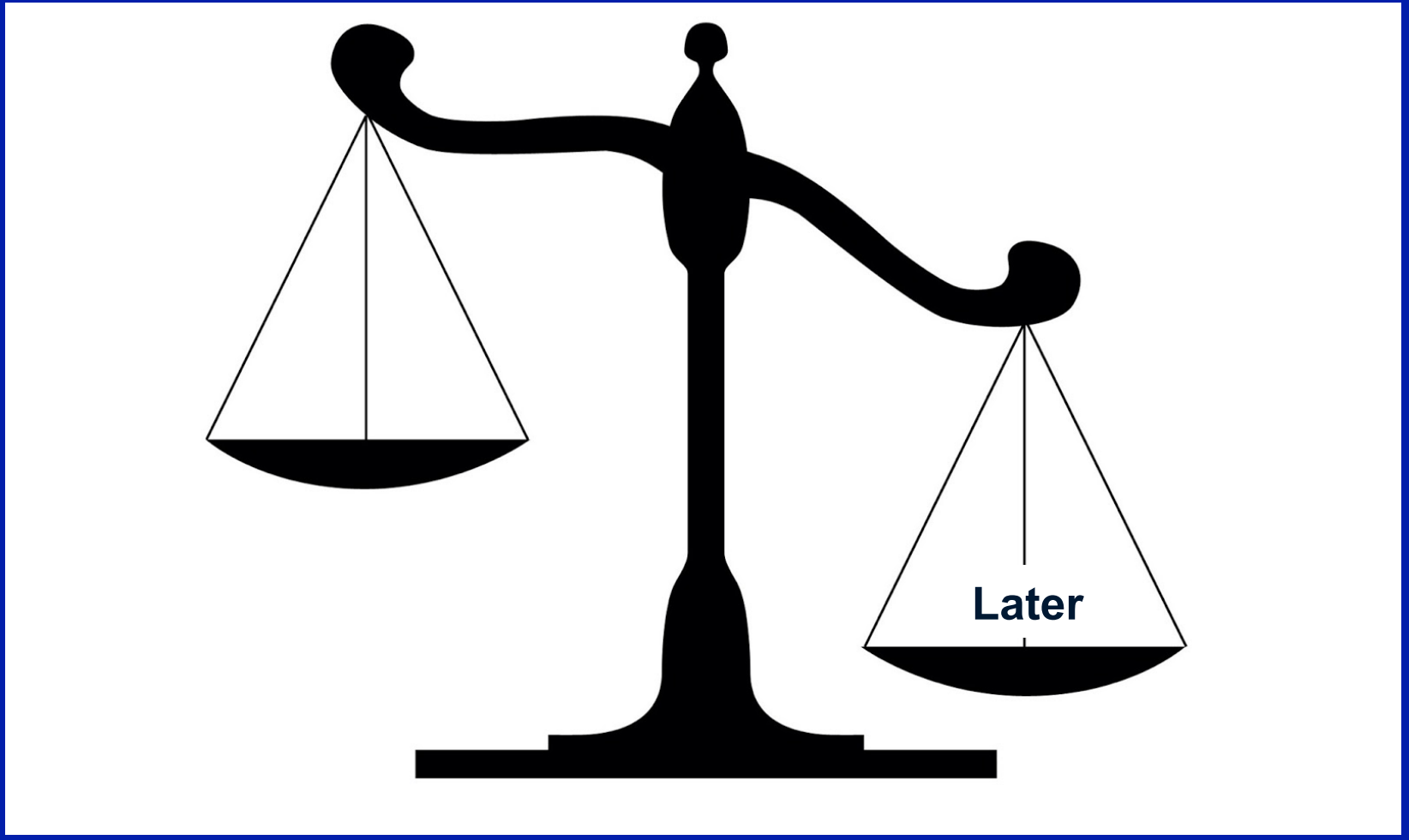
The Case for Treating HCV Now

- The glass is more than half full. Current treatment can cure > 60% of Rx naïve patients with GTs 1-4.
- Some patients *want* treatment now.
- Some patients *need* treatment now.
- Some patients who are deferred will be lost to follow-up.
- Some patients who are deferred will develop comorbidities which make future treatment more difficult, or occasionally contraindicated.
- Some patients who are deferred will experience disease progression to the point that IFN-based treatment is not possible.

The Case for Treating HCV Now

- Public reimbursement of first generation DAAs in Canada was so slow that it bodes poorly for subsequent DAAs.
- The next advance in treatment for G1 is still PR-based triple therapy, so that PR-related AEs won't be avoided.
- PR + BOC/TVR failures can be "rescued" with SOF + DCV, so no need to fear triple Rx treatment failure.
- We simply don't know:
  - When the new DAAs will be readily available (i.e. publicly funded)
  - Under what conditions they will be available

The Case for Treating HCV Later



The Case for Treating HCV Later

- Some patients will never develop advanced liver disease. They will die of other natural causes and HCV Rx would have been an unnecessary use of resources with decreased QoL while on treatment.
- Hepatic fibrosis occurs very slowly. With FibroScan, fibrosis can easily be monitored frequently, and treatment started in the F2-F3 range, before cirrhosis occurs. This strategy will reduce the numbers of patients who receive IFN (all GTs) and first generation DAAs (G1).

The Case for Treating HCV Later

- Current therapy is not well tolerated, resulting in reduced QoL, time off work, occasional severe adverse effects, and rare cases of death.
- A significant proportion of patients will not accept IFN-based therapy.
- Some patients have contraindications to current therapy, including patients with advanced cirrhosis.
- Some patients have a very low probability of SVR with current Rx (esp. cirrhotic null responders to PR Rx).

The Case for Treating HCV Later

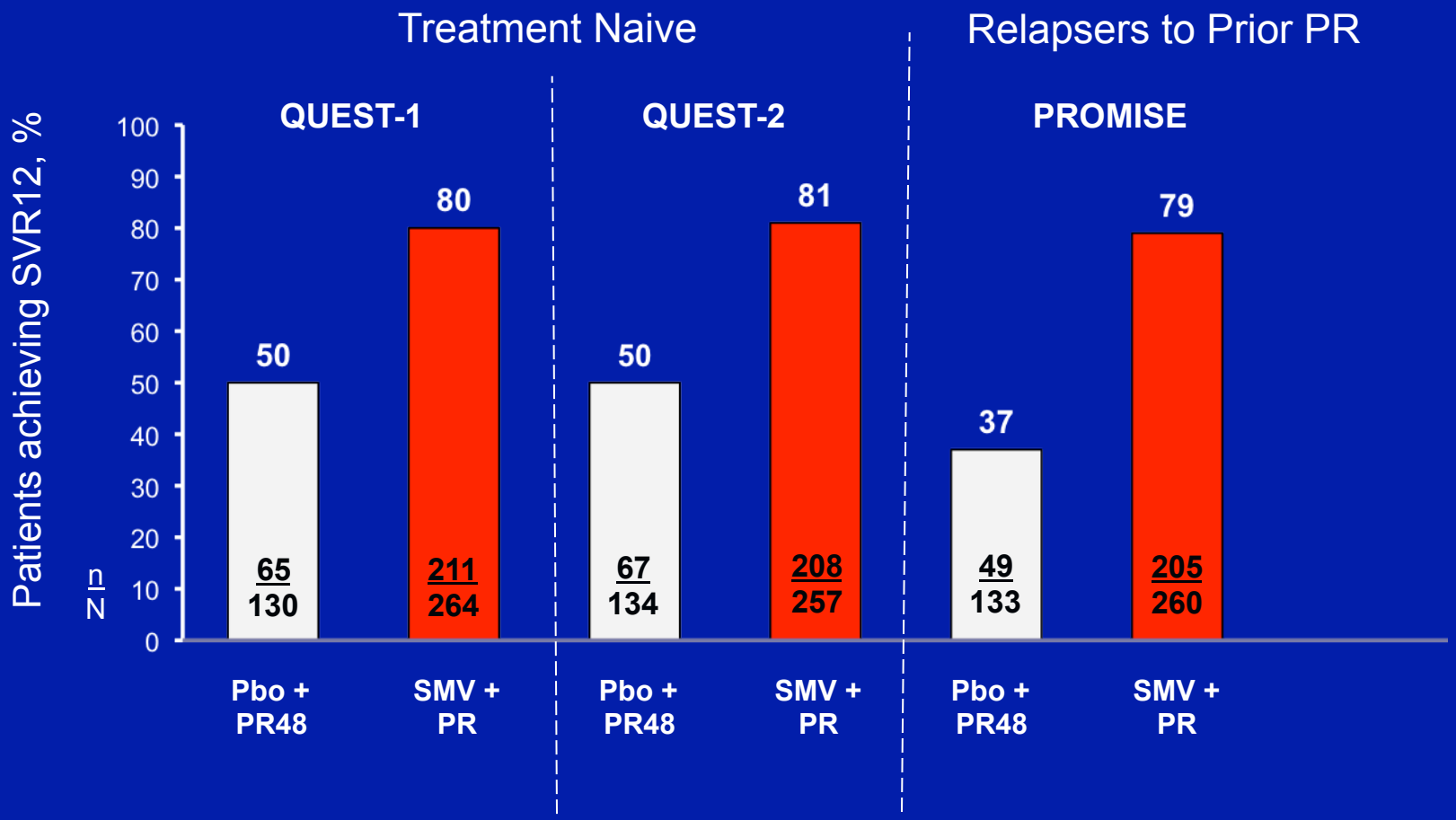
- Better tolerated PR-based triple therapy are likely to be available in 12-18 months. The increased risk of anemia with BOC/TVR and rash with TVR can be avoided.

- IFN-free therapy may be available in ~2 years. This will reduce adverse effects significantly and eliminate nearly all work absenteeism.

DAAs Under Development

Phase of Development	NS3 PIs ("previrs")	NS5A Inhibitors ("asvirs")	Nucleoside NS5B Polymerase Inhibitors ("buvirs")	Non nucleoside NS5B Polymerase Inhibitors ("buvirs")
Filed/Phase 3	Simeprevir		Sofosbuvir	
Phase 3	Faldaprevir	Daclatasvir		ABT-333
	ABT-450/r	ABT-267		BI-207127
		Ledipasvir		
Phase 2	Asunaprevir	IDX-719	Mericitabine	Tegobuvir
	Sovaprevir	PPI-668	VX-135	Setrobuvir
	Danoprevir/r	GS-5816		VX-222
	GS-9451	ACH-3102		TMC-647055
	MK-5172	MK-8742		GS-9669
		GSK-2336805		PPI-383
				BMS-791325

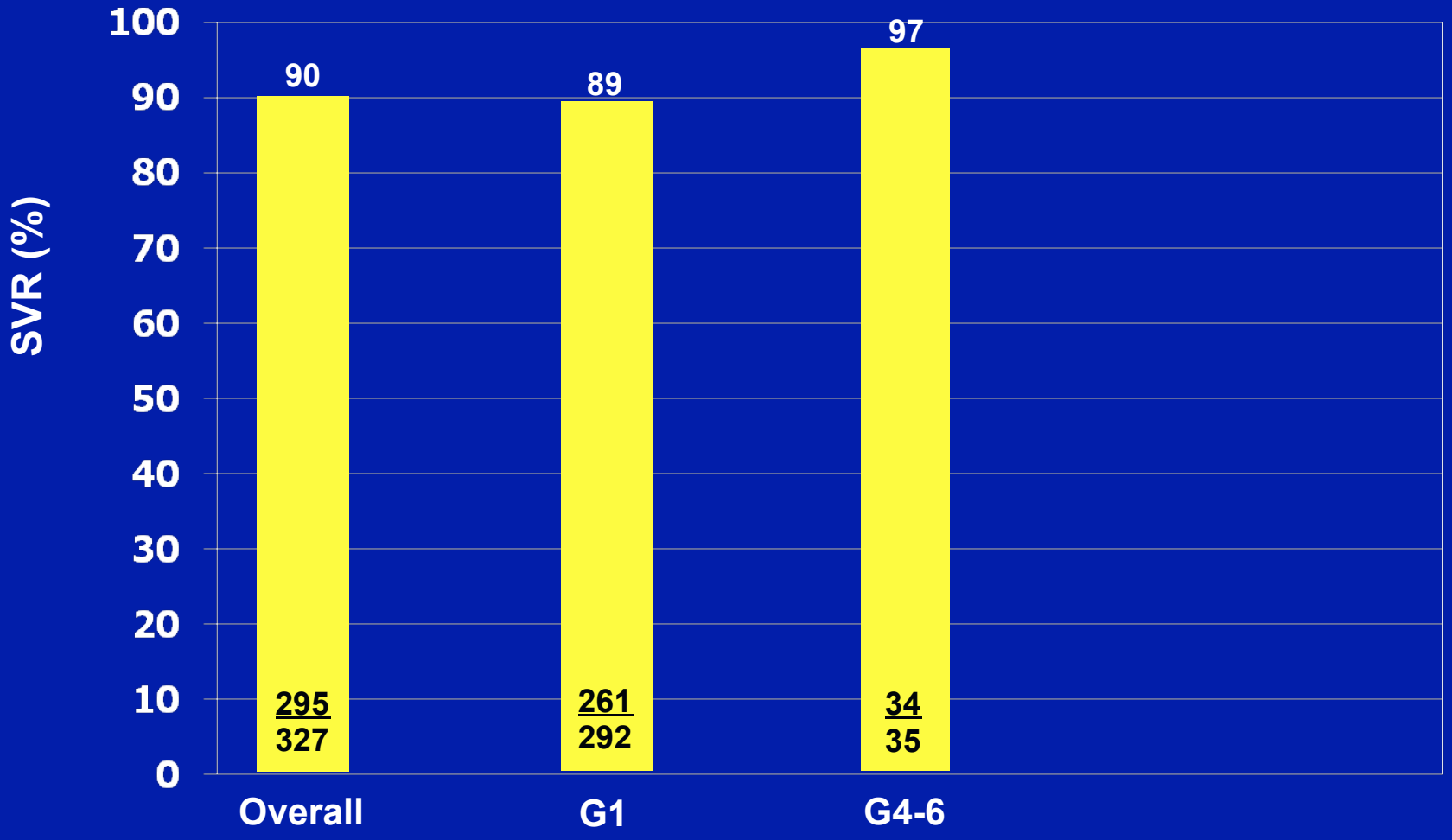
Simeprevir Phase 3 SVR12 Results



- 85-93% of SMV treated patients met criteria for 24 week PR Rx
- Presence of Q80K polymorphism in G1a reduces PR + SMV SVR to 60% (present in 34% of G1a patients in QUEST-1 and 2.)

Jacobson I, et al., Manns M, et al. EASL 2013.

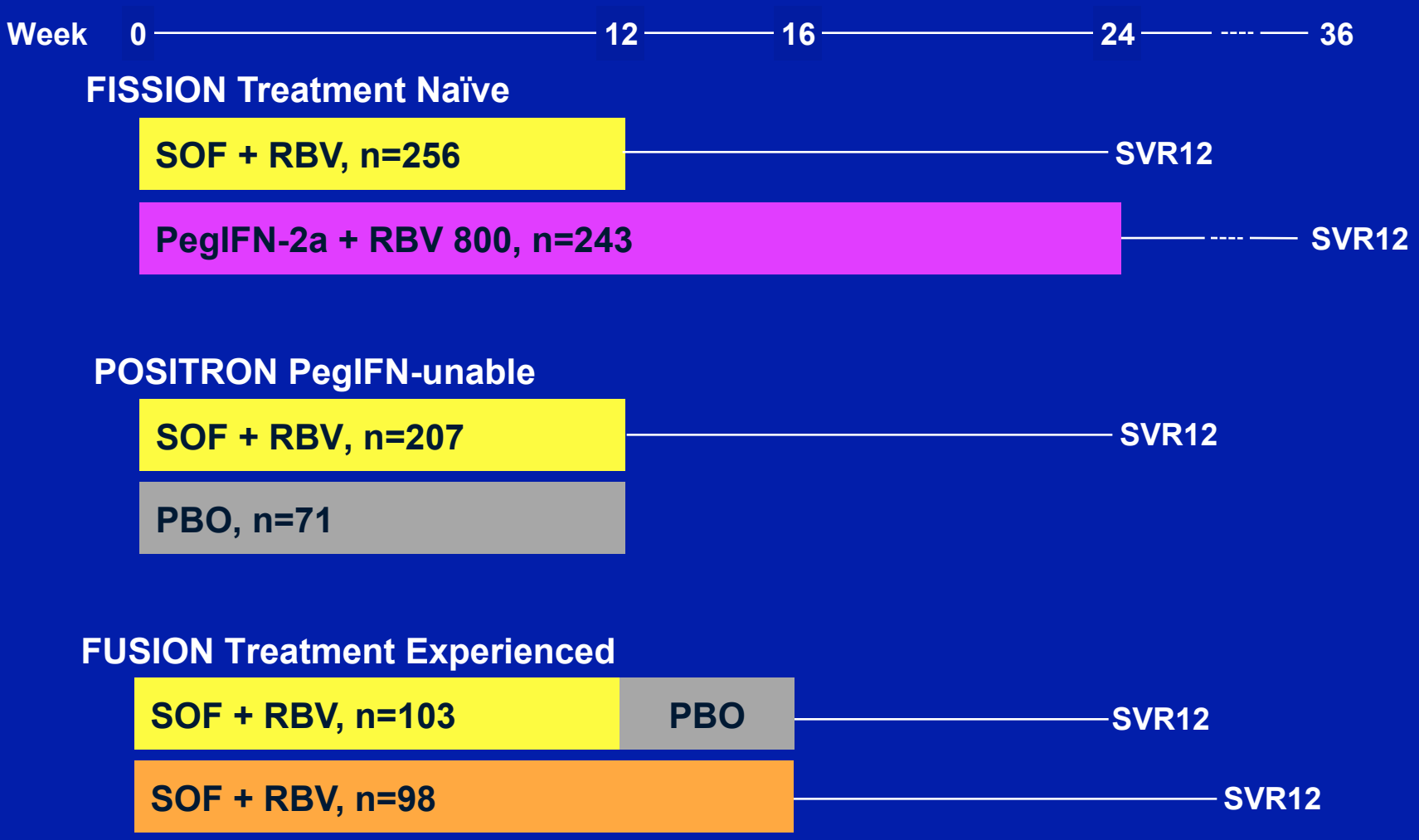
NEUTRINO Phase 3 Clinical Trial of PegIFN + RBV + SOF x 12 wk in G1, 4, 5, 6 Treatment Naive: SVR12



All failures were due to relapse; no SOF resistance detected.

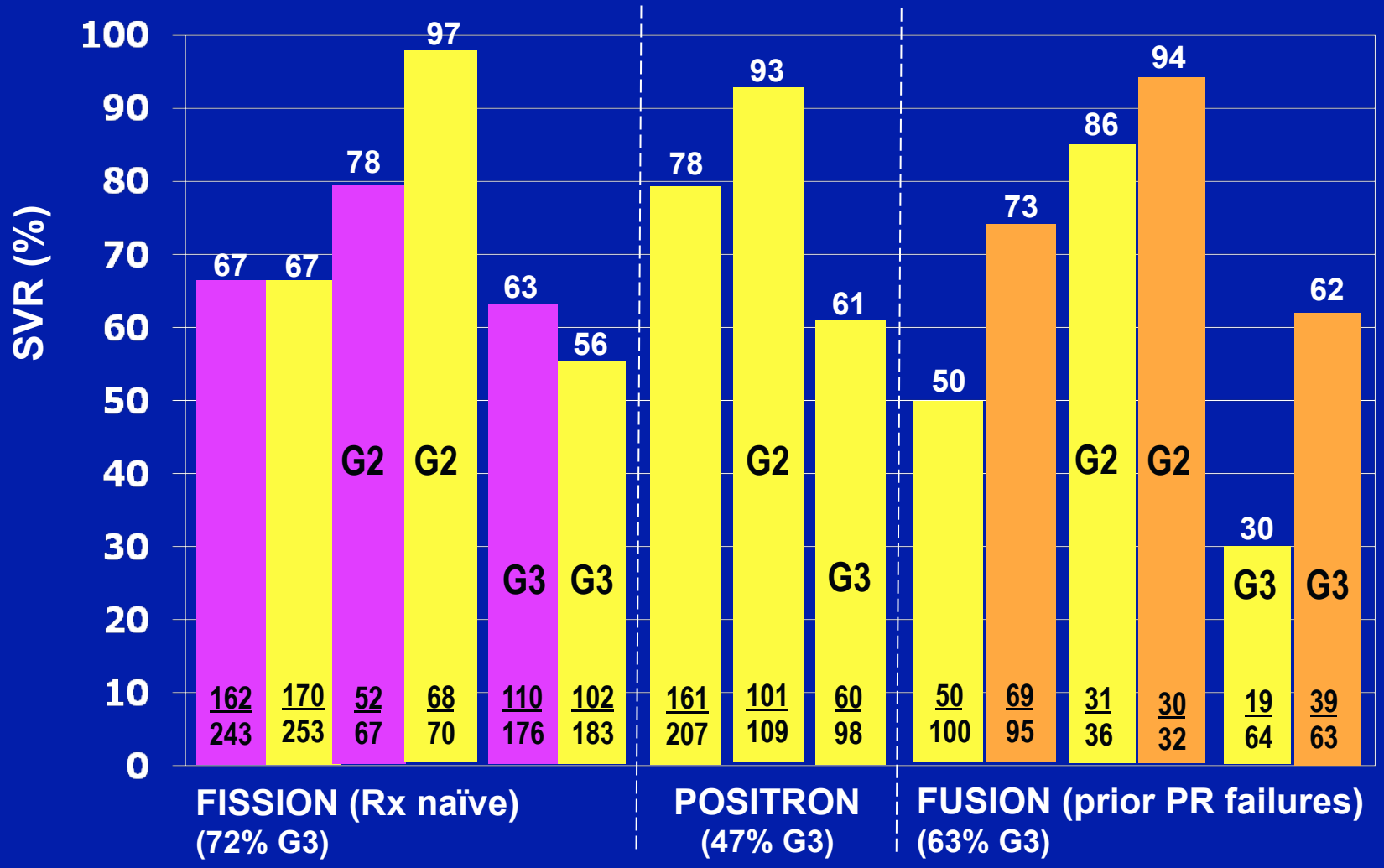
Lawitz E, et al. *N Engl J Med* 2013;368:1878-87.

Sofosbuvir Phase 3 Studies for GT2 and 3



Jacobson et al, Nelson et al, Gane et al. EASL 2013. Amsterdam.

SOF + RBV Phase 3 Clinical Trials in GT2 and 3: SVR12



PegIFNα-2a 180 + RBV 800 x 24 wk

SOF 400 + RBV 1000/1200 x 12 wk

SOF 400 + RBV 1000/1200 x 16 wk

All SOF + RBV failures were due to relapse; no SOF resistance detected.

Jacobson et al, Nelson et al, Gane et al. EASL 2013. Amsterdam.

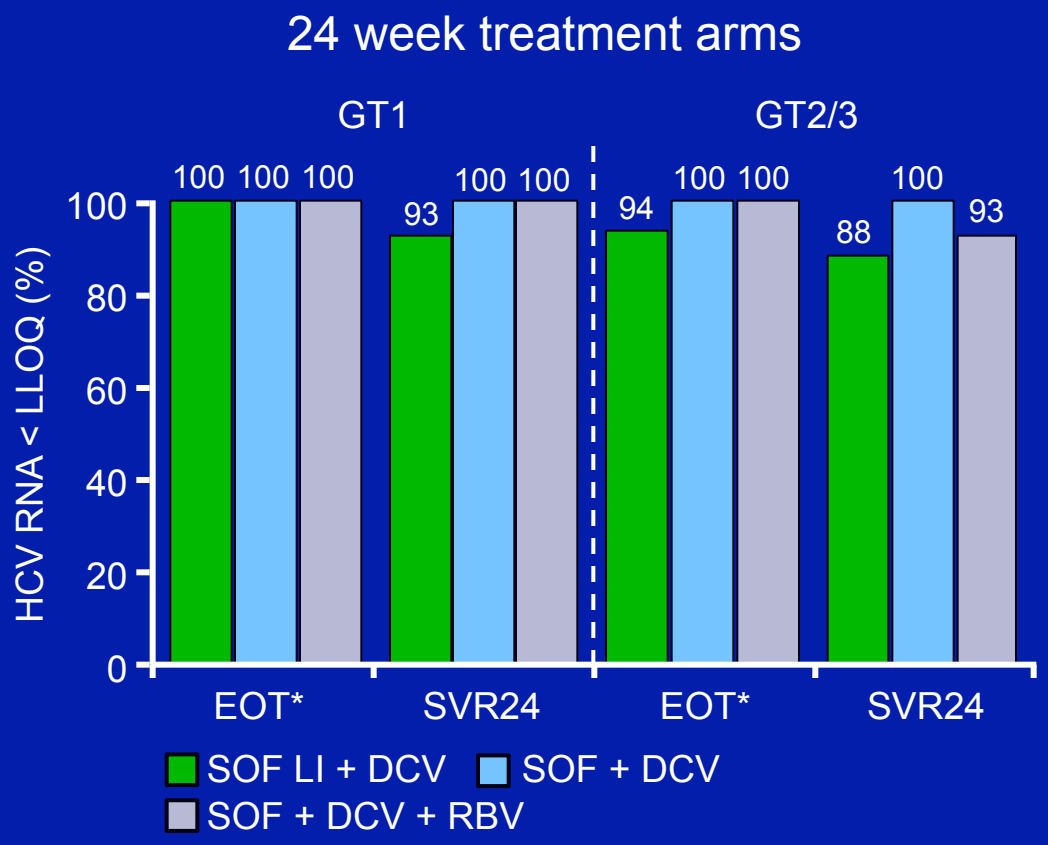
IFN-free Treatment for GT 1

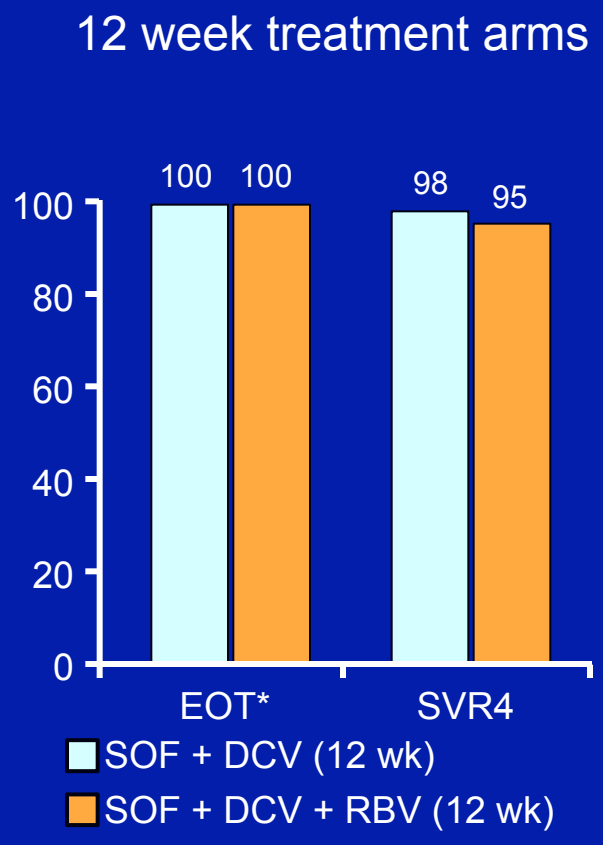
IFN-Free Rx for HCV GT1

- Between EASL 2011 and CROI 2013, 7 pharmaceutical companies have demonstrated IFN-free cures in GT1:

Company	IFN-free regimen	Comments
AbbVie	ABT-450/rABT-267 + ABT-333 + RBV	12 wk regimen; SVR12 77/79 (98%) in phase 2; now in phase 3; ABT-450/ABT-267/r one pill
Boehringer Ingelheim	FDV + BI 207127 + RBV	In phase 3 for genotype 1b
BMS	DCV + Asunaprevir	Genotype 1b only; ASV has hepatotoxicity
Gilead	SOF + RBV	Relapse is a problem in G1 (and G3)
Gilead	GS-9451 + LDV +TGV + RBV	Borderline potency; no further development
Gilead	SOF + LDV ± RBV	12 wk regimen; SOF/LDV now co-formulated
Roche	Danoprevir/r + Mericitabine + RBV	Genotype 1b only; development uncertain
Vertex	TVR + VX-222 + RBV	Potency marginal (BT and relapse), esp in 1a
BMS + Gilead	DCV + SOF	Impressive in G1,2,3; Gilead will "fly solo" by combining SOF with their own NS5A LDV
Janssen + Gilead	Simeprevir + SOF ± RBV	12 & 24 wk regimens being studied, with and without RBV;

SVR Rates With SOF + DCV ± RBV x 24 or 12 Wk (all non cirrhotic, treatment naive)





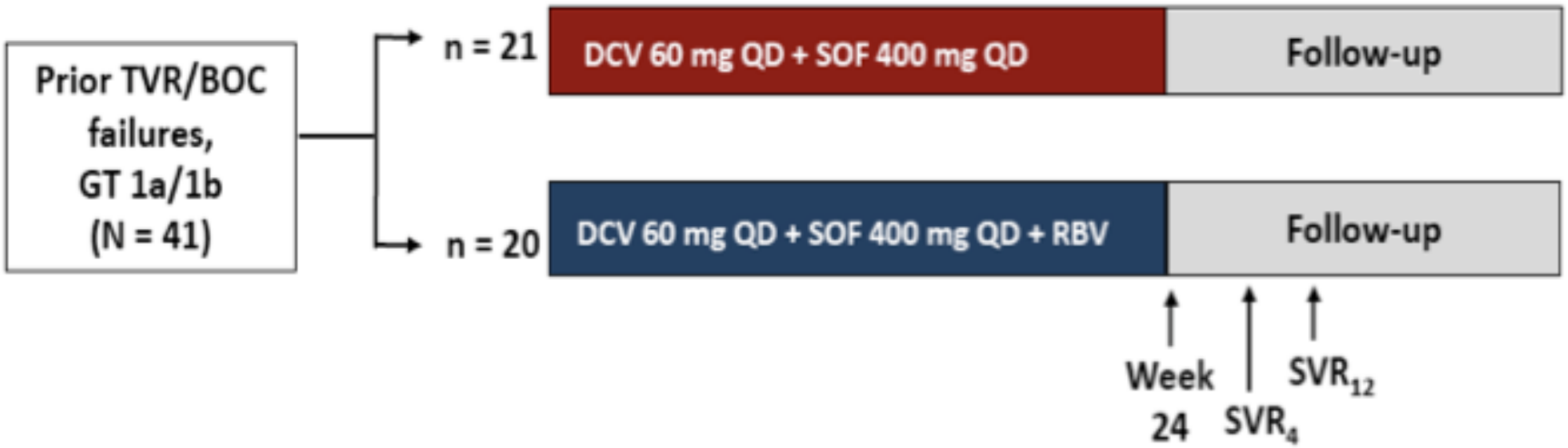
- SVR12 in all 68 patients who have reached time point

*EOT includes patients who discontinued early, with last visit considered EOT.

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

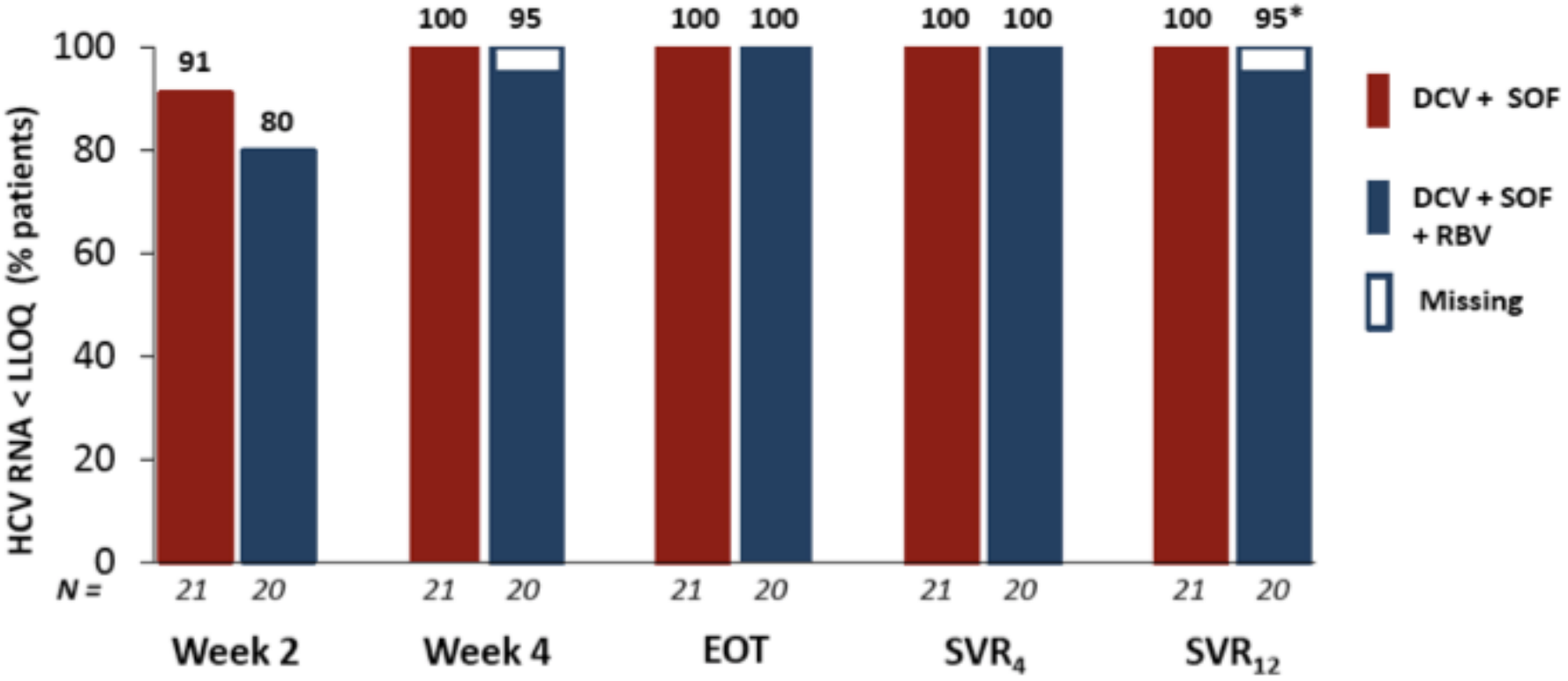
Randomized, Open-label, Parallel-Group Phase 2a Study: AI444-040

Aim: To evaluate the efficacy and safety of DCV plus SOF with or without RBV for 24 weeks in HCV GT 1-infected patients who failed prior treatment with TVR or BOC + pegIFN-alfa/RBV



Sulkowski M, et al. EASL 2013. Abstract 1417.

Virologic Response During and After Treatment (mITT)

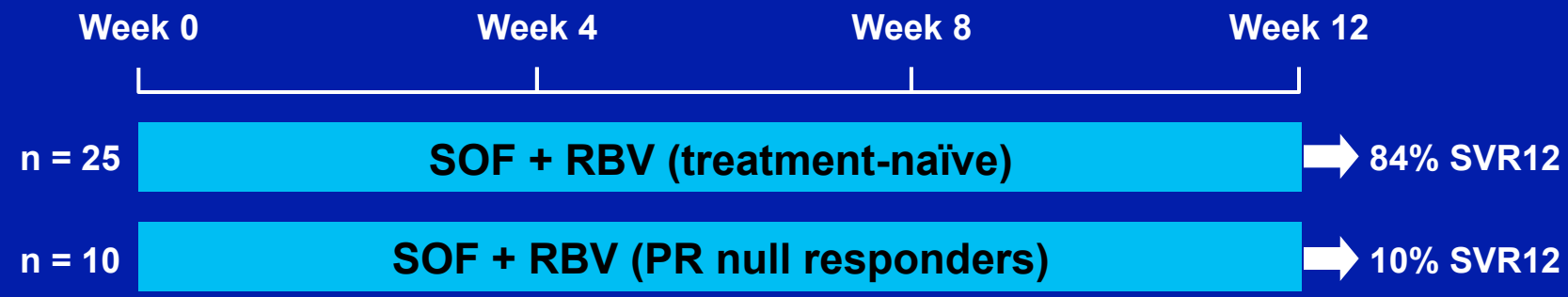


* 1 patient missing at post-treatment (PT) Week 12: HCV RNA was undetectable at PT Week 4 and at PT Week 24 (preliminary)

- 21/41 patients have reached PT Week 24; all have achieved SVR_{24}

Sulkowski M, et al. EASL 2013. Abstract 1417.

ELECTRON GT1 Update: CROI 2013



Addition of the HCV NS5A inhibitor ledipasvir was studied in the hope that it would reduce relapse, as suggested in AI444-040

4 clinical trials with SOF/LDV FDC ± RBV are ongoing:

- ION-1 (treatment naïve, n=800)
- ION-2 (treatment experienced, n= 400, fully enrolled)
- ION-3 (treatment naïve, non-cirrhotic, n= 600)
- LONESTAR (treatment naive and triple Rx failures, n=100, fully enrolled)

Gane E, et al. CROI 2013; Atlanta. 41LB.
Gilead Press Releases. Jan 7, Mar 26, May 2, 2013.

LONESTAR Preliminary Results

Treatment	Duration	Population	Results
SOF + LDV	8 wk	G1 naive	95% (19/20) SVR8
SOF + LDV + RBV	8 wk	G1 naive	100% (21/21) SVR 8
SOF + LDV	12 wk	G1 naive	100% (19/19) SVR4
SOF + LDV	12 wk	G1 TF	95% (18/19) SVR4
SOF + LDV + RBV	12 wk	G1 TF	95% (20/21) SVR4

ION-3 will randomize 600 non-cirrhotic G1 treatment naïve patients to:

SOF + LDV x 8 wk
SOF + LDV + RBV x 12 wk
SOF + LDV x 12 wk

Gilead Press Release. May 2, 2013.

Aviator Study: IFN-Free in HCV GT1, non Cirrhotics

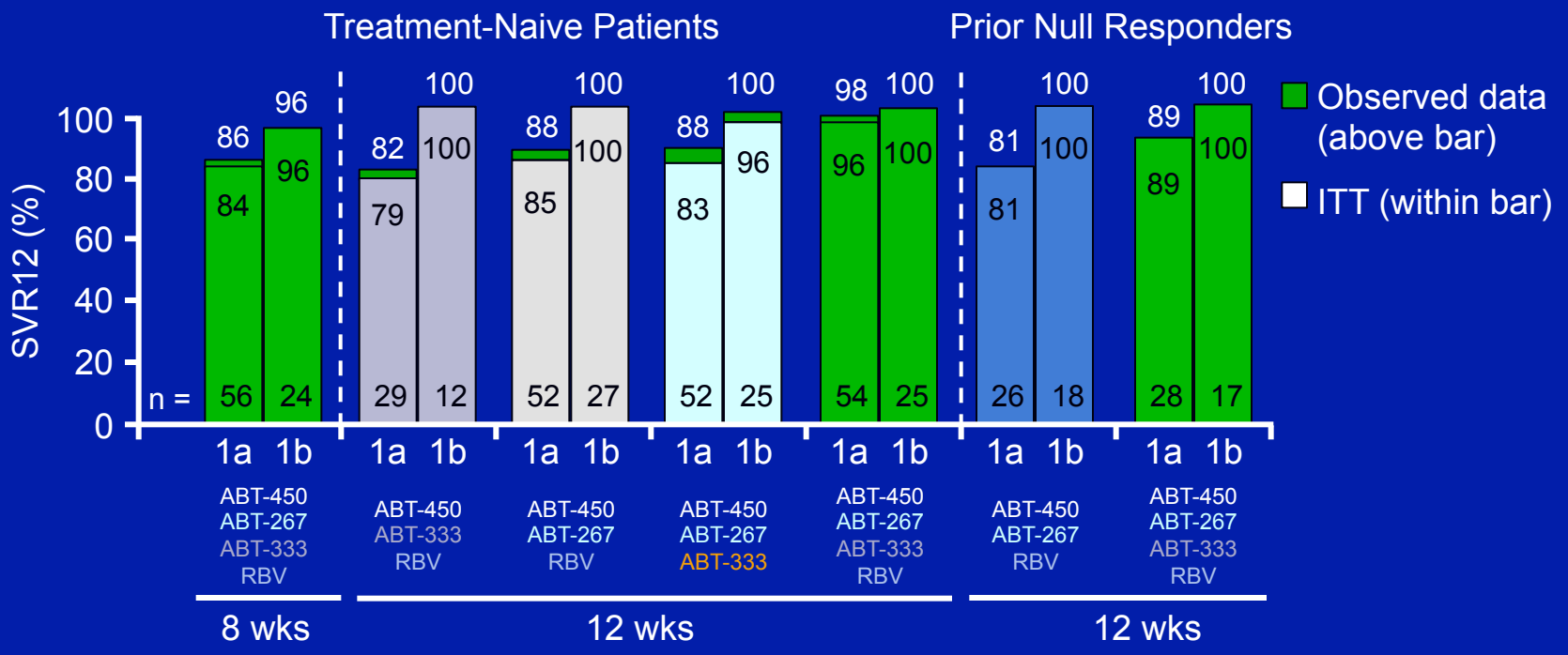
HCV GT1, non cirrhotics; RBV dose 1000/1200 mg/d;
ABT-267 dose 25 mg QD; ABT-333 dose 400 mg BID

ABT-450 is a NS3 PI; ABT-267 is a NS5AI; ABT-333 is a NNI

Kowley KV, et al. AASLD 2012.

AVIATOR: SVR12 Rates With ABT-450/RTV, ABT-267, ABT-333, and RBV

- SVR12 rates ~100% in pts with GT1b HCV but also high in pts with GT1a HCV
  - 12-wk regimen with all 3 DAAs + RBV produced highest SVR12 rates
- No drug-related SAEs reported; 2 pts discontinued tx due to drug-related AEs



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

Aviator Follow-Up

- Phase 3 trials of ABT-450/r + ABT-267 + ABT-333 + RBV started in Q1 2013, separately in GT1 naïve and GT1 treatment failure populations in non-cirrhotics (SAPPHIRE-1 and SAPPHIRE-2) and separately in cirrhotics (TURQUOISE-1)
- These studies use a single tablet of co-formulated ABT-450/ABT-267/ritonavir
- ABT-333 and RBV are dosed separately
- SVR data are expected Q4 2013 (noncirrhotics) and Q2 2014 (cirrhotics)

So, which patients should we treat for HCV now?

Patients to Treat Now for HCV: Treatment Naive

Non G1

- All, unless contra-indicated

G1, independent of fibrosis

- Extra-hepatic disease (PCT, MPGN, etc)
- Surgeons and dentists
- Young women who wish to have HCV cleared before becoming pregnant

G1, dependent on fibrosis

- F2 and F3 disease
- Cirrhotics with albumin $\geq$ 35 and PLT > 90
- F0-1 disease, if patients are keen to be treated AND they are informed that they have the alternative of waiting for IFN-free therapy

Patients to Treat Now for HCV: Treatment Failure

Non G1

- None, unless under-dosed and/or poorly adherent

G1 relapsers to PR

- These patents have a higher probability of achieving SVR with PR + BOC/TVR than treatment naïve patients. They should generally be treated now.

G1b partial responders to PR

- These patients have acceptable SVR rates to triple therapy (19/40 [48%] in BOC phase 3 trials and 27/40 (68%) in TVR phase 3 trial; They are worth considering for treatment now.

CUPIC Multivariate Analysis: Baseline Predictors of SVR

Predictors	OR	95%CI	p-value
Relapser vs Partial or null responders	2.03	1.38-3.00	0.0003
Genotype 1b vs Genotype non 1b	1.92	1.3-2.84	0.0011

G1b is more response than G1a to HIV NS3 PIs

Fontaine H, et al. EASL 2013. Abstract 60.

Patients to Treat Now for HCV: Treatment Failure

G1a partial responders to PR

- These patients have borderline SVR rates to triple therapy (21/53 [48%] in BOC phase 3 trials and 25/55 (47%) in TVR phase 3 trial.
- I favor deferral if F0-2, but will treat if patients insist

G1 null responders to PR

- These patients have low SVR rates with current triple Rx, especially if cirrhotic.
- I favor deferral