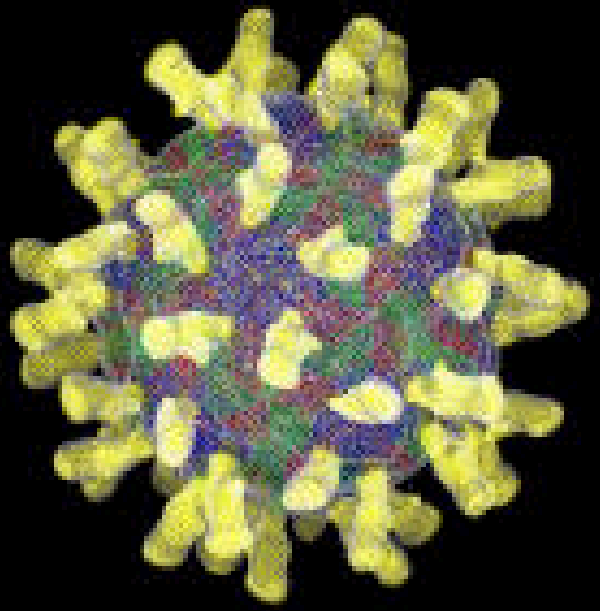
Hep C U Later



Ed Gane
NZ Liver Transplant Unit

Hepatitis C – Facts

- 200 million HCV+ worldwide
  - »>50,000 HCV+ New Zealanders
- >90% from recreational injecting drug use
  - »Peak incidence between 1970 and 1990
  - »Peak age of infection 15-25 years of age
- No vaccine available
  - »Education/harm reduction strategies

➡Incidence has been falling since 2000

- Most HCV+ New Zealanders now 40-60yrs

Life-Style Advice
Sexual Transmission

	No.	Follow-up	%Partner ⇨ HCV+
Mothers (contaminated anti-D)			
Meisel,1995	(94)	15 years	0%
Power,1995	(393)	20 years	0.3%
Haemophiliac			
Hallam,199			
Bresters,19			
Intravenous d			
Zylerberg,19			%
Vandelli,20			

HCV is NOT sexually transmitted

Life-Style Advice
Mother-to-infant Transmission

Author	(n)	follow-up	% children ⇨HCV RNA+
La			
Co			
Gibb,2000	(441)	18 months	6.7%

HCV IS vertically transmitted to baby

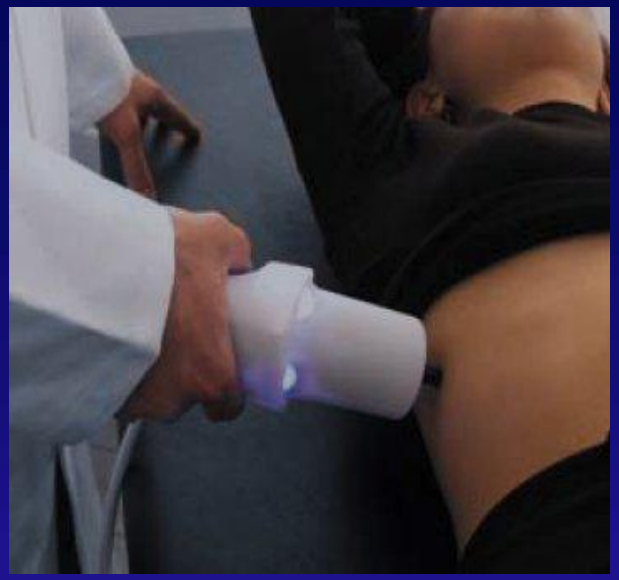
- Test baby at 18 months (after mum's anti-HCV has gone)
- Breast feeding is safe

Hep C diagnosis and staging

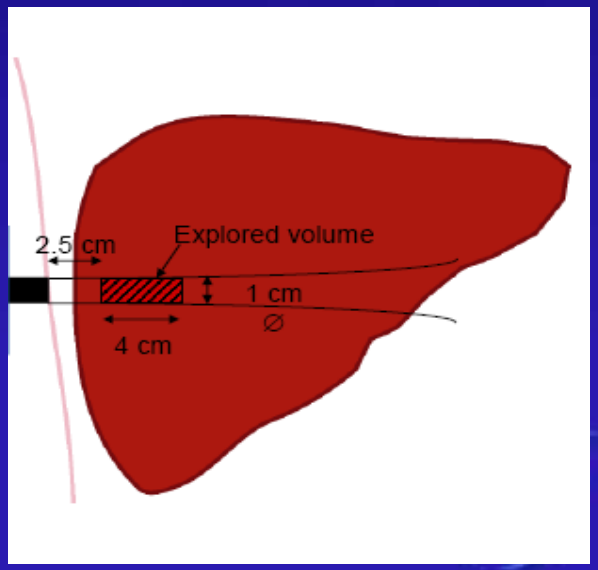
- **Symptoms and Signs**
  - »Unhelpful as nonspecific until advanced cirrhosis
- **Anti-HCV ELISA screening assay**
  - »Inexpensive ($15), performed daily at all labs
  - »Reflects HCV exposure, **not active infection**
    - may persist after viral clearance
- **Serum HCV RNA PCR assay**
  - »**Confirms active infection**
  - »Expensive ($200), only at reference laboratories
- **Liver Function Test**
  - »POOR marker of liver injury in HCV
  - »Need liver biopsy or Fibroscan

Fibroscan

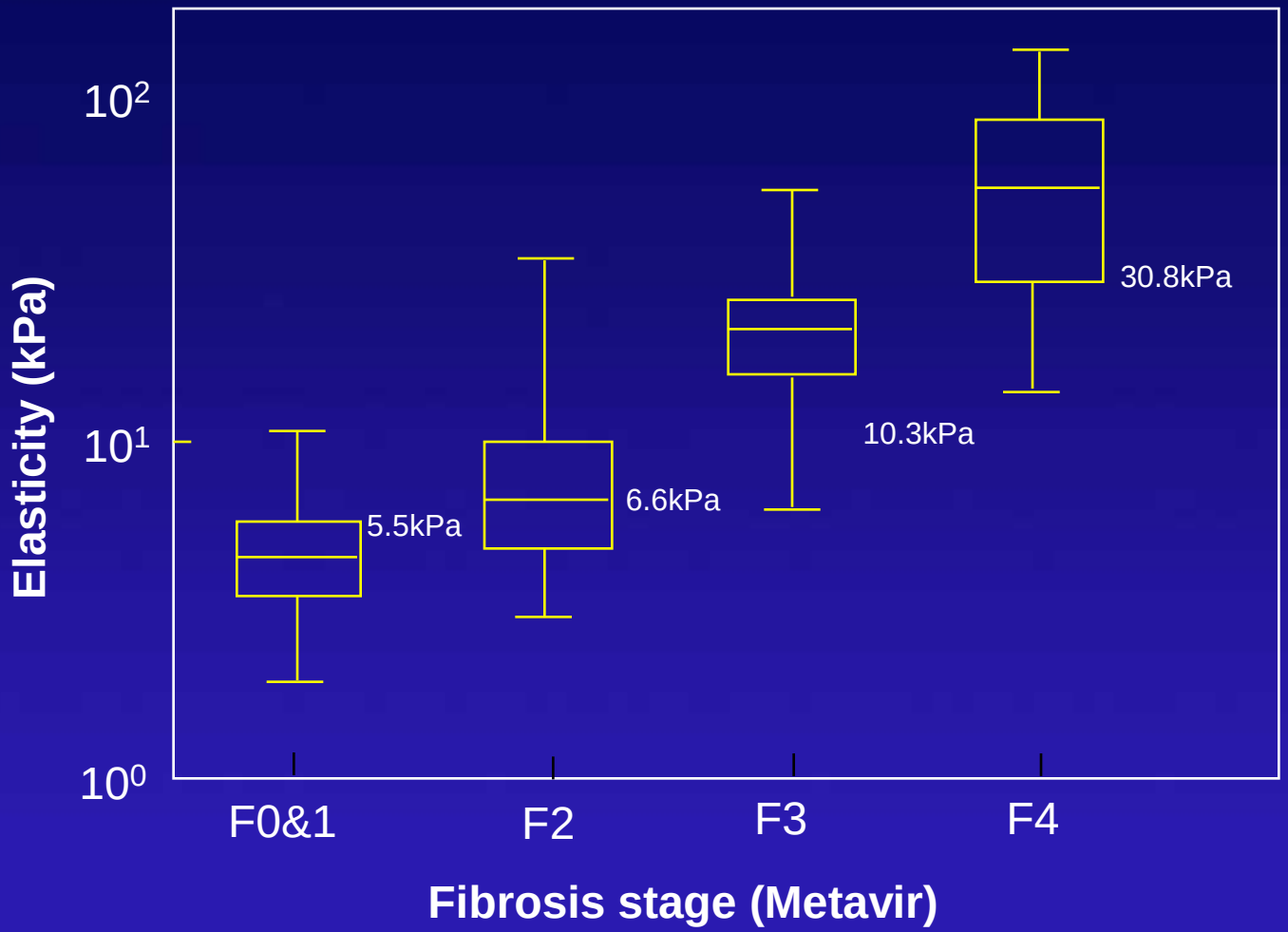
- Painless, noninvasive
- Takes 2-3 minutes
- Performed in clinic
- No sedation
- No complications



- Measures 1/500 of liver (c.f. biopsy=1/50,000)
- Less sampling error



Fibroscan in Chronic Hepatitis C



**** Biopsies performed within 6 months of fibroscan***

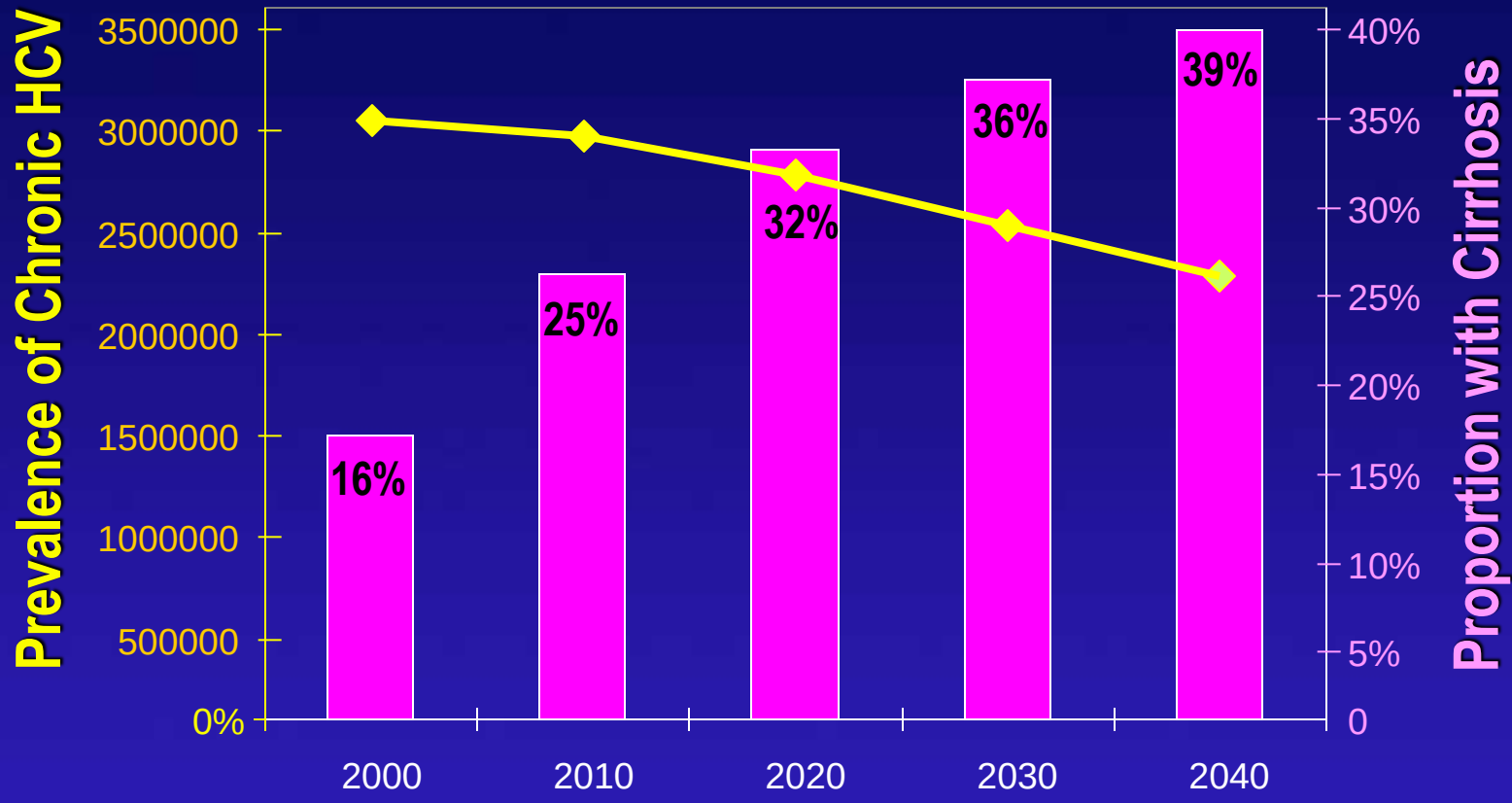
Ziol M. 2005 Hepatology;41:48-54

Hep C – what Factors are associated with progression to cirrhosis

- **Alcohol > 5 drinks/day**
  - »Paralyses immune response to HCV
    - Increases HCV replication + injury
  - »Keep below ALAC guidelines
  - »Nil if cirrhosis or on IFN
- **Cannabis >2 joints per day**
  - »Cannabinoid receptors in liver cause fibrosis
- **Liver steatosis**
  - » Metabolic syndrome

Chronic Hepatitis C - the Problem

1. Aging cohort , with progressive disease



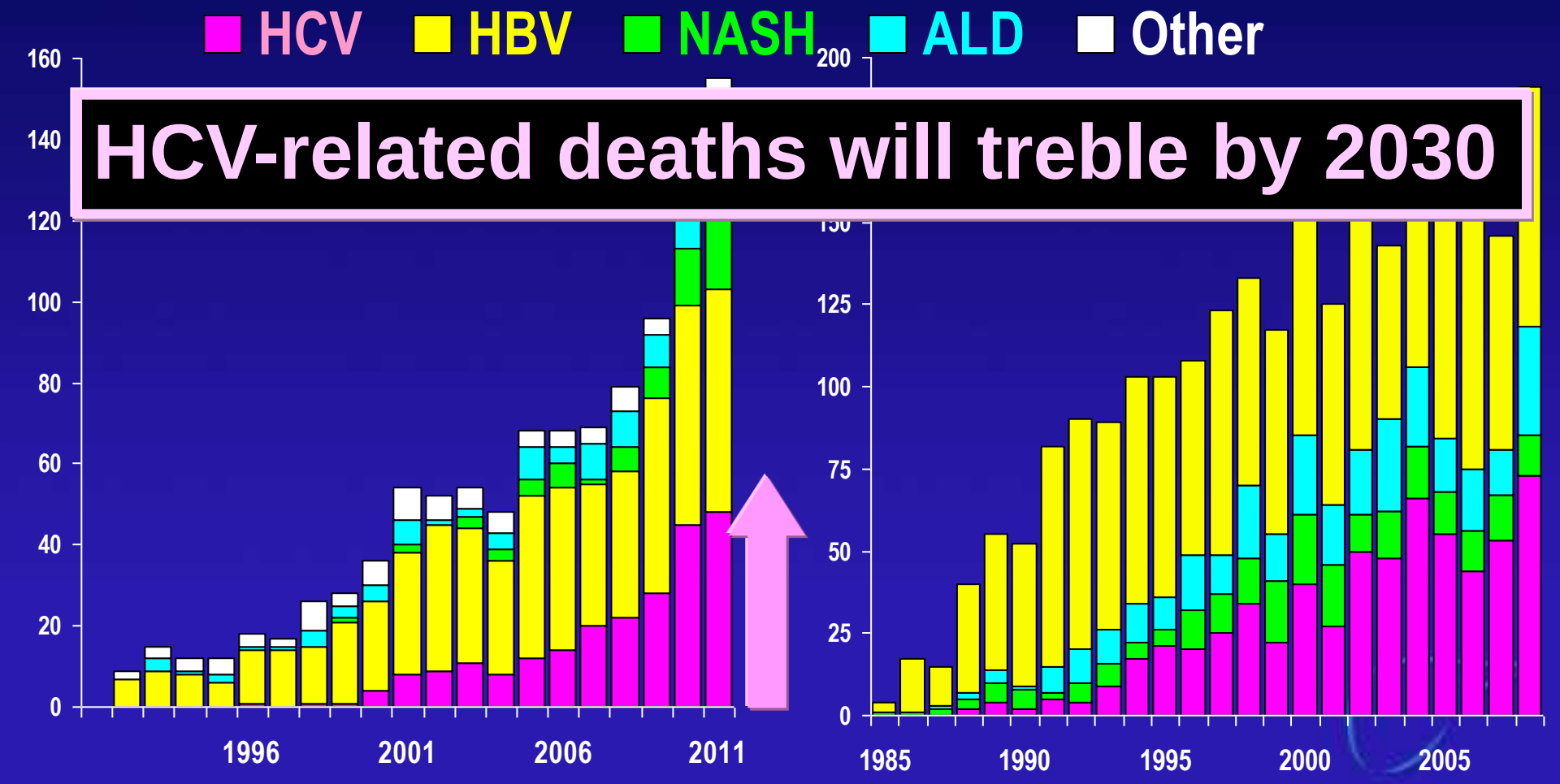
Davis G, et al Gastroenterol 2010; 138: 513-21

Chronic Hepatitis C - the Problem

2. Increasing liver-related complications

(2) Liver Cancer at ACH

(2) Liver Transplants in ANZ



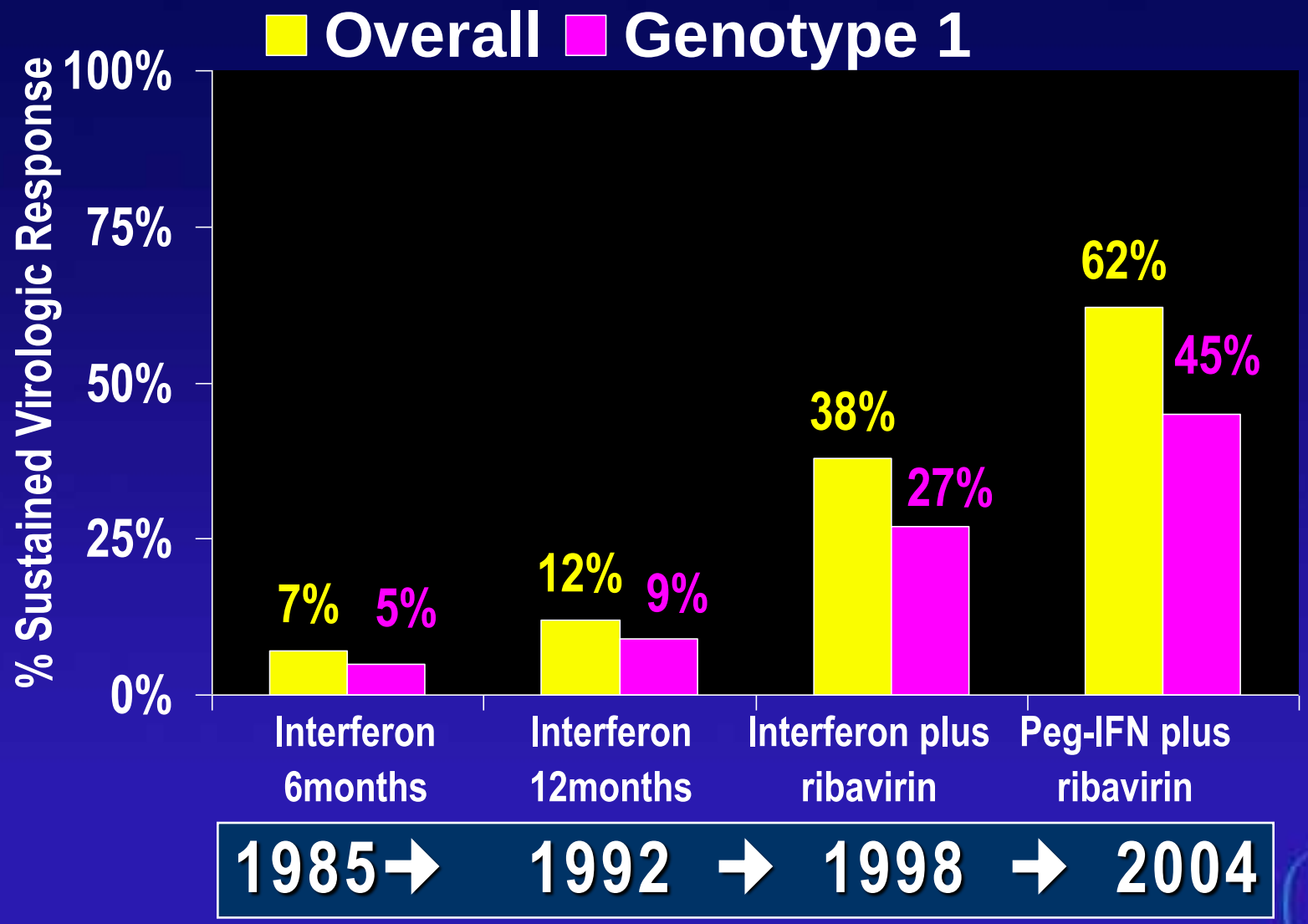
HCV-related deaths will treble by 2030

Chronic Hepatitis C - the Solution

Aims of Therapy

1. Prevent death
2. Prevent transplant
3. Prevent cirrhosis
4. Improve quality of life

Improving results of antiviral therapy



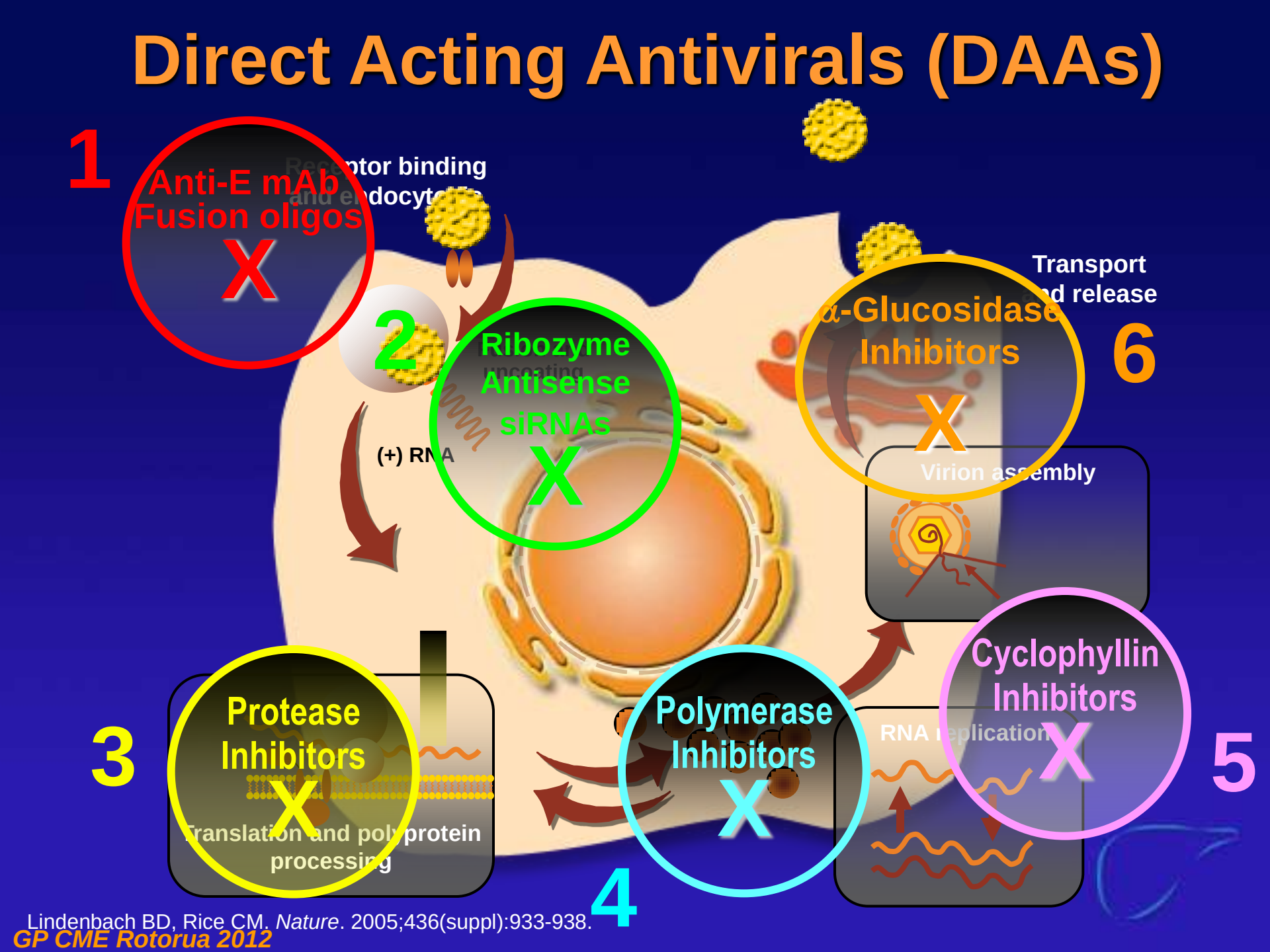
Treatment is POORLY tolerated

1. **Side effects of Interferon**
   1. Flue-like syndrome in 100%
   2. Anorexia, weight loss in 100%
   3. Insomnia in >90%
   4. Bone marrow suppression in >50%
   5. Depression in 40%

2. **Contraindications to Peg or RBV**
   1.
   2
   5.

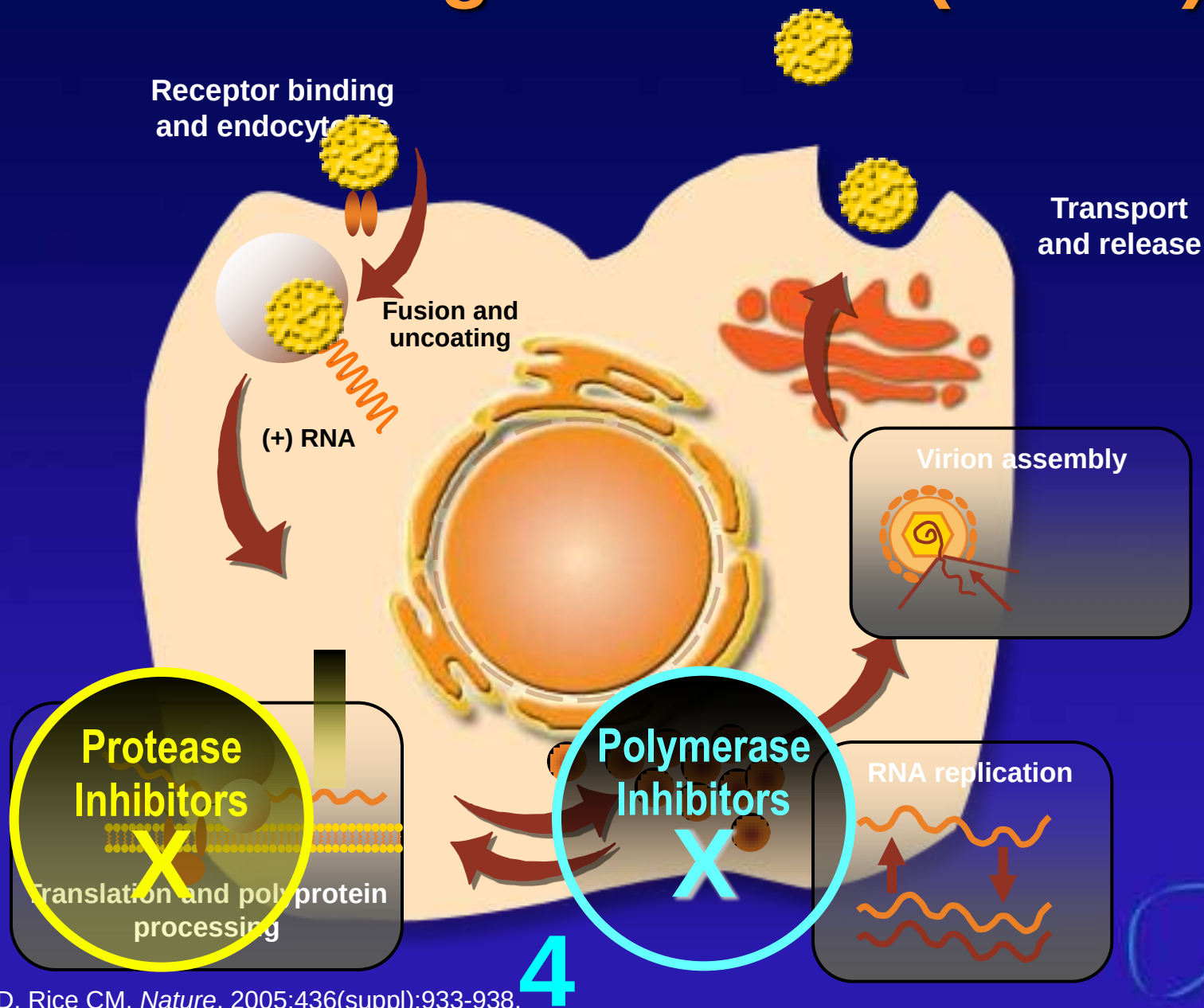
NEW THERAPUTIC APPROACHES

Direct Acting Antivirals (DAAs)



Lindenbach BD, Rice CM. *Nature*. 2005;436(suppl):933-938.

Direct Acting Antivirals (DAAs)



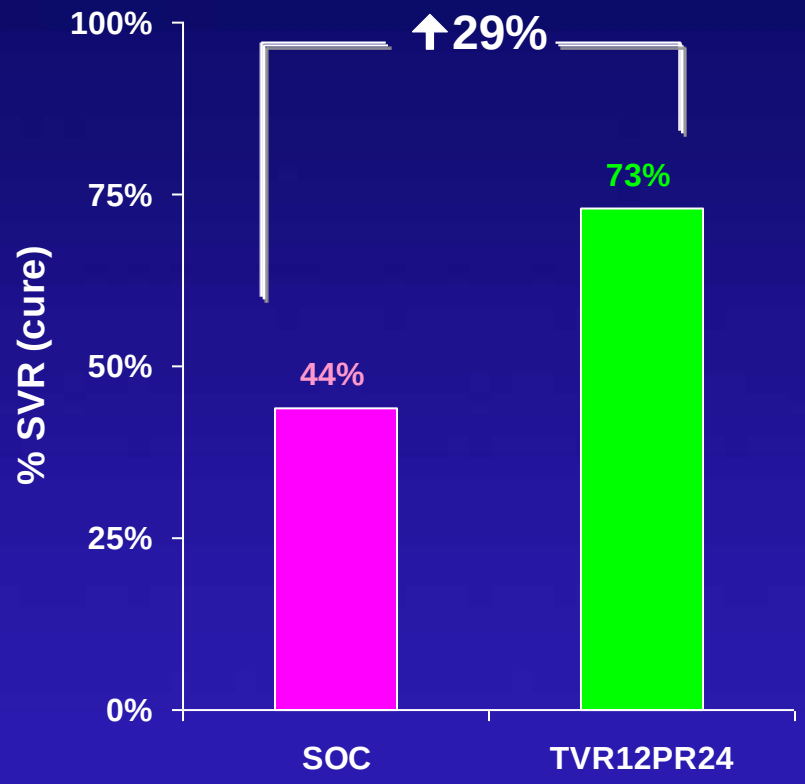
Lindenbach BD, Rice CM. *Nature*. 2005;436(suppl):933-938.

Protease Inhibitors in Clinical Development

Target	Agent	Company	Phase
NS3/4a Serine Protease	Boceprevir	Merck	Phase III
	Telaprevir	Vertex	Phase III
	Danoprevir	Roche	Phase III
	TMC435	Tibotec	Phase III
	MK-7009	Merk	Phase III
	BI201335	Boehringer	Phase III
	MK-5172	Merck	Phase II
	SCH900518	Merck	Phase II
	ABT450	Abbott	Phase II
	BMS-650032	BMS	Phase II
	GS 9256	Gilead	Phase II
	GS 9451	Gilead	Phase II
	VX-985	Vertex	Phase I
	ACH1625	Achillon	Phase I
	IDX-320	Idenix	Phase I
	ACH1284	Achillon	Phase I
	BMS-791325	BMS	Phase I
	VX-500	Vertex	Phase I
	PHX1766	Pfizer	Phase I

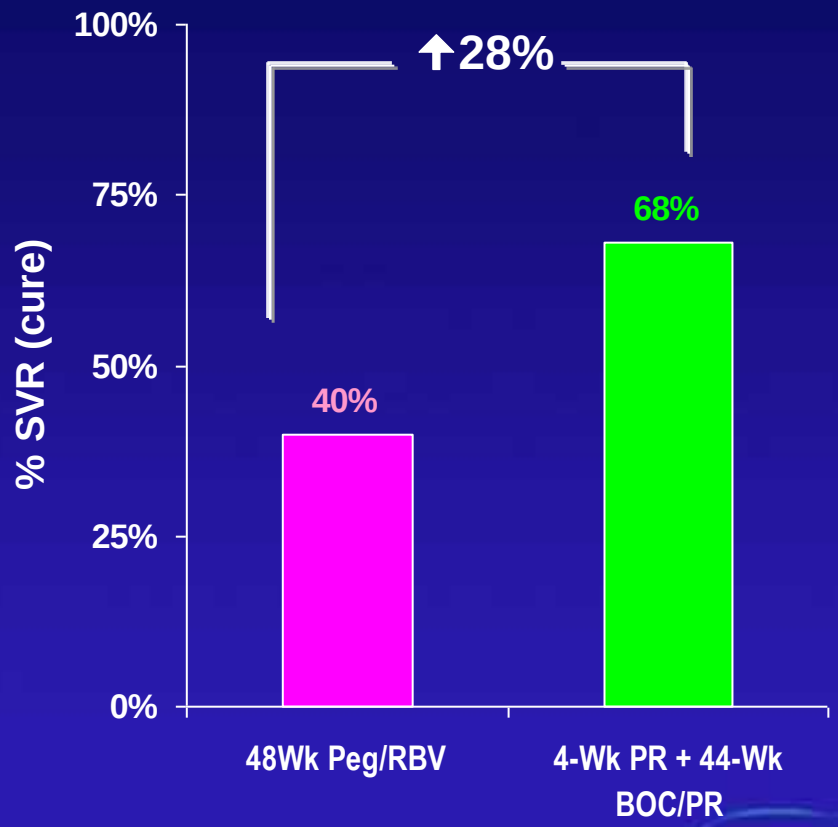
Triple Therapy in Patients who have never been treated before (treatment-naïve)

Telaprevir Phase III



Jacobson I, et al. *N Engl J Med* 2011; 364: 2405-16

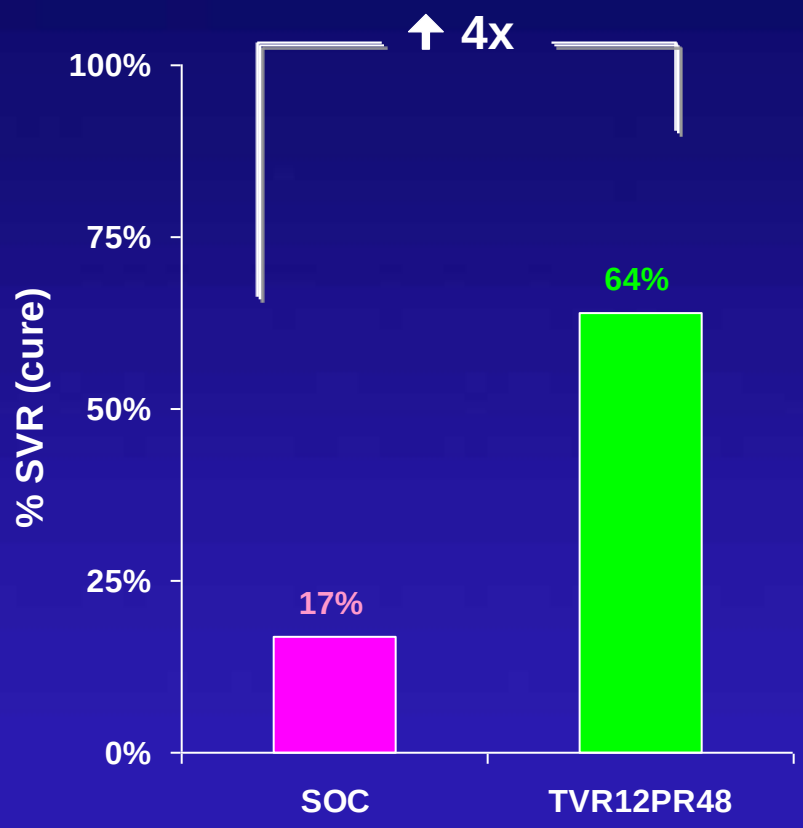
Boceprevir Phase III



Poordad F, et al. *N Engl J* 2011; 364: 1195-206

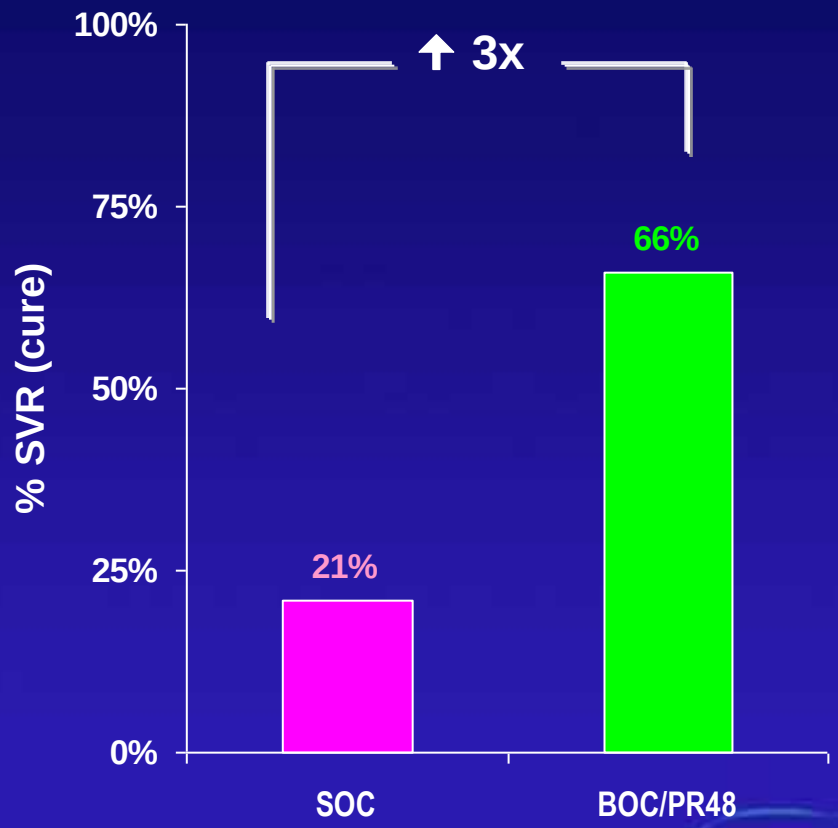
Triple therapy in patients who have previously failed to respond to Peg-Interferon/Ribavirin

Telaprevir Phase III



Zeuzem S, et al. *N Engl J Med* 2011; 364: 2417-28

Boceprevir Phase III



Bacon B, et al. *N Engl J* 2011; 364: 1207-17

Will Triple therapy meet the current unmet medical need post-transplant?

1. **Poor efficacy**

- HCV Gt 3 (⇨ 30% of HCV in ANZ)
- HCV Gt 1a (⇨ 40% of HCV in ANZ)
- Patients already failed PEG/RBV

2. **Limited tolerability**

- inconvenient, q8hrly dosing
- still need interferon ⇨ side effects
- PIs ⇨ specific S/E rash, anaemia
- multiple direct drug interactions

	BOC	TVR
Analgesics		
Buprenorphine	■	◆
Codeine	■	■
Diflunisal	◆	◇
Fentanyl	■	■
Ibuprofen	◆	◇
Methadone	■	■
Morphine	◆	◆
Paracetamol	◇	◇
Tramadol	■	■
Antiarrhythmics		
Amiodarone	■	●
Bepridil	●	●
Digoxin	■	■
Flecainide	■	■
Lidocaine (lignocaine)	□	■
Propafenone	■	■
Quinidine	■	●
Antibacterials		
Aminoglycosides (IV)	◇	◇
Azithromycin	◆	◆
Ciprofloxacin	◆	◆
Clarithromycin	■	■
Clindamycin	■	■
Dapsone	◇	◇
Ertapenem	◆	◆
Erythromycin	□	■
Ethambutol	◆	◆
Isoniazid	■	■
Linezolid	◆	◆
Meropenem	◆	◆
Moxifloxacin	◇	◇
Ofloxacin	■	■
Pyrazinamide	◆	◆
Rifabutin	■	■
Rifampicin	●	●
Rifapentine	■	■
Rifaximin	◆	◆
Streptomycin	◆	◆
Sulphadiazine	◆	◆
Telithromycin	□	■
Tetracyclines	■	■
Trimethoprim/Sulfamethoxazole	◇	◇
Vancomycin	◇	◇
Anticoagulants		
Dabigatran	■	■
Warfarin	■	■
Anticonvulsants		
Carbamazepine	●	●
Clonazepam	■	■
Gabapentin	◆	◆
Lamotrigine	◆	◆
Levetiracetam	◆	◆
Phenobarbital	●	●
Phenytoin	●	●
Valproate (Divalproex)	◆	◆
Antidepressants		
Bupropion	■	■
Citalopram	■	■
Desipramine	■	■
Duloxetine	■	■
Escitalopram	◆	■
Fluoxetine	■	■
Milnacipran	■	■
Mirtazapine	■	■
Paroxetine	■	■
Sertraline	■	■
Tianeptine	◆	◆
Trazodone	■	■

	BOC	TVR
Antidiabetics		
Metformin	■	■
Tolbutamide	◇	◇
Antifungals		
Amphotericin B	◇	◇
Caspofungin	■	■
Fluconazole	■	■
Flucytosine	◆	◆
Itraconazole	■	■
Ketoconazole	■	■
Posaconazole	■	■
Terbinafine	■	■
Voriconazole	■	■
Antihistamines		
Chlorpheniramine	◆	◆
Diphenhydramine	■	■
Antimigraine Agents		
Dihydoergotamine	●	●
Ergonovine	●	●
Ergotamine	●	●
Methylergonovine	●	●
Rizatriptan	◆	◆
Antiprotozoals		
Atovaquone	◆	◆
Pentamidine	■	◇
Pyrimethamine	◆	◆
Sulphadoxine	◆	◆
Antipsychotics/Neuroleptics		
Clozapine	□	□
Olanzapine	◆	◆
Pimozide	●	●
Prochlorperazine	■	■
Quetiapine	■	■
Risperidone	■	■
Antivirals		
Amantadine	◇	◇
Cidofovir	◇	◇
Foscarnet	◇	◇
Anxiolytics/Hypnotics/Sedatives		
Alprazolam	■	■
Diazepam	■	■
Lorazepam	◆	◆
Midazolam (oral)	●	●
Midazolam (parenteral)	■	■
Oxazepam	◆	◆
Triazolam	●	●
Zolpidem	□	■
Zopiclone	■	■
Beta Blockers		
Metoprolol	■	■
Nebivolol	■	■
Propanolol	◆	◆
Bronchodilators		
Salmeterol	■	■
Theophylline	◇	◇
Calcium Channel Blockers		
Amlodipine	□	■
Diltiazem	□	■
Felodipine	■	■
Nicardipine	■	■
Nifedipine	■	■
Nisoldipine	□	■
Verapamil	□	■
Contraceptives and Hormonal Replacements		
Drospirenone	●	□
Ethinylestradiol	■	■
Norethisterone (norethindrone)	□	■
Erectile Dysfunction Agents		
Sildenafil	■	■
Tadalafil	■	■

		BOC	TVR
Gastrointestinal Agents			
Antacids		◇	◇
Cimetidine		□	□
Cisapride		●	●
Domperidone		□	■
Esomeprazole		◇	◆
Lansoprazole		■	■
Metoclopramide		■	■
Omeprazole		◆	◆
Pantoprazole		◆	◆
Ranitidine		□	□
Hepatitis Drugs			
Adefovir		◇	◇
Entecavir		◇	◇
Lamivudine		◇	◇
Peg Interferon alfa		◆	◆
Ribavirin		◆	◆
Telbivudine		◇	◇
Tenofovir		◆	■
Herbals/Supplements/Vitamins			
Grapefruit juice		■	■
St John's wort		●	●
HIV Drugs			
Entry/Integrase Inhibitors			
	Maraviroc	□	□
	Raltegravir	◆	◆
NNRTIs	Delavirdine	□	□
	Efavirenz	■	■
	Etravirine	□	□
	Nevirapine	□	□
	Rilpivirine	□	□
NRTIs	Abacavir	◇	■
	Didanosine	◇	◇
	Emtricitabine	◇	◇
	Stavudine	◇	◇
	Zidovudine	■	■
PIs	Atazanavir	■	■
	Darunavir	■	■
	Fosamprenavir	■	■
	Indinavir	■	□
	Lopinavir	■	■
	Nelfinavir	□	□
	Ritonavir	■	■
	Saquinavir	■	□
	Tipranavir	■	□
Hypertension/Heart Failure Agents			
Bosentan		■	■
Furosemide		◆	◆
Sildenafil		●	●
Tadalafil		●	●
Immunosuppressants			
Azathioprine		◇	◇
Ciclosporin		■	■
Sirolimus		■	■
Tacrolimus		■	■
Lipid Lowering Agents			
Atorvastatin		■	●
Fibrates		◇	◇
Lovastatin		●	●
Pravastatin		■	□
Rosuvastatin		■	■
Simvastatin		●	●
Other Drugs			
Alfuzosin		●	●
Colchicine		■	■
Dietary purines		◇	◇
Filgrastim		◆	◆
Platinum compounds		◇	◇
Spironolactone		◆	◆
Thalidomide		◇	◇
Steroids			
Budesonide		■	■
Dexamethasone		■	■
Fluticasone		■	■
Methylprednisolone		□	■

What about combining two Direct Antivirals and getting rid of Interferon?

Target different steps of life cycle

- ➡ Additive/synergistic antiviral effect
- ➡ Non-overlapping resistance profiles

3

4

Lindenbach BD, Rice CM. *Nature*. 2005;436(suppl):933-938.

Inhibitors of the HCV Polymerase Complex

Target	Agent	Phase
NS5b Non-nucleoside analogue (NNA)	Filibuvir	Phase II
	Tegobuvir	Phase II
	JTK-003	Phase II
	BI207127	Phase II
	BMS-824393	Phase II
	VX-222	Phase II
	ABT-072	Phase II
	ABT-333	Phase II
	MK3281	Phase II
	ANA598	Phase II
	HCV-796	Phase I
	IDX375	Phase I
	VX759	Phase II
	PF4878691	Phase I
	RO5471354	Phase I
	GS-9669	Phase I

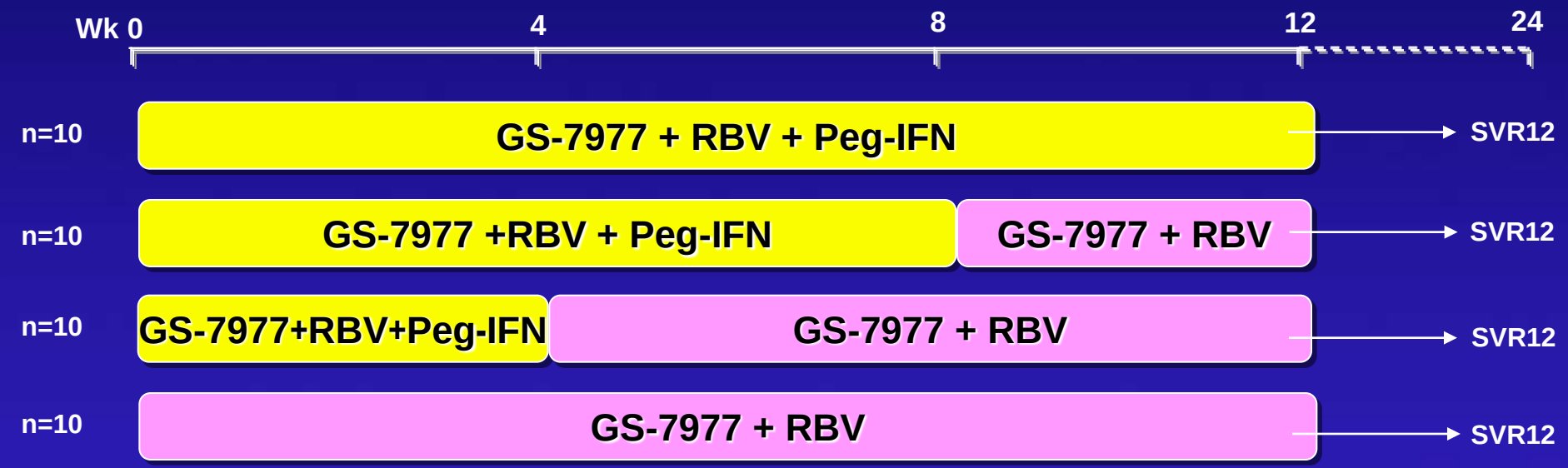
Target	Agent	Phase
Cyclophyllin B inhibitors	Alisporivir	Phase III
	NIM811	Phase I
	SYC-635	Phase I

Target	Agent	Phase
NS5a Non-nucleoside analogue	BMS790052	Phase III
	ABT-267	Phase II
	AZD7295	Phase II
	GS-5885	Phase II
	PPI-461	Phase II
	PPI-668	Phase I
	PPI-1833	Phase I
	ACH-2928	Preclin
	ACH-3102	Preclin
	BMS-824393	Preclin
	PPI-437	Preclin

Target	Agent	Phase
NS5b Nucleoside Analogue (NA)	RG7128	Phase III
	GS-7977	Phase III
	NM283	Phase II
	INX-189	Phase II
	PSI-938	Phase I
	ALS-002158	Phase I
	ALS-002200	Phase I
	GS-6620	Phase I
	IDX184	Phase I
	RG7348	Phase I
	MK-0608	Phase I

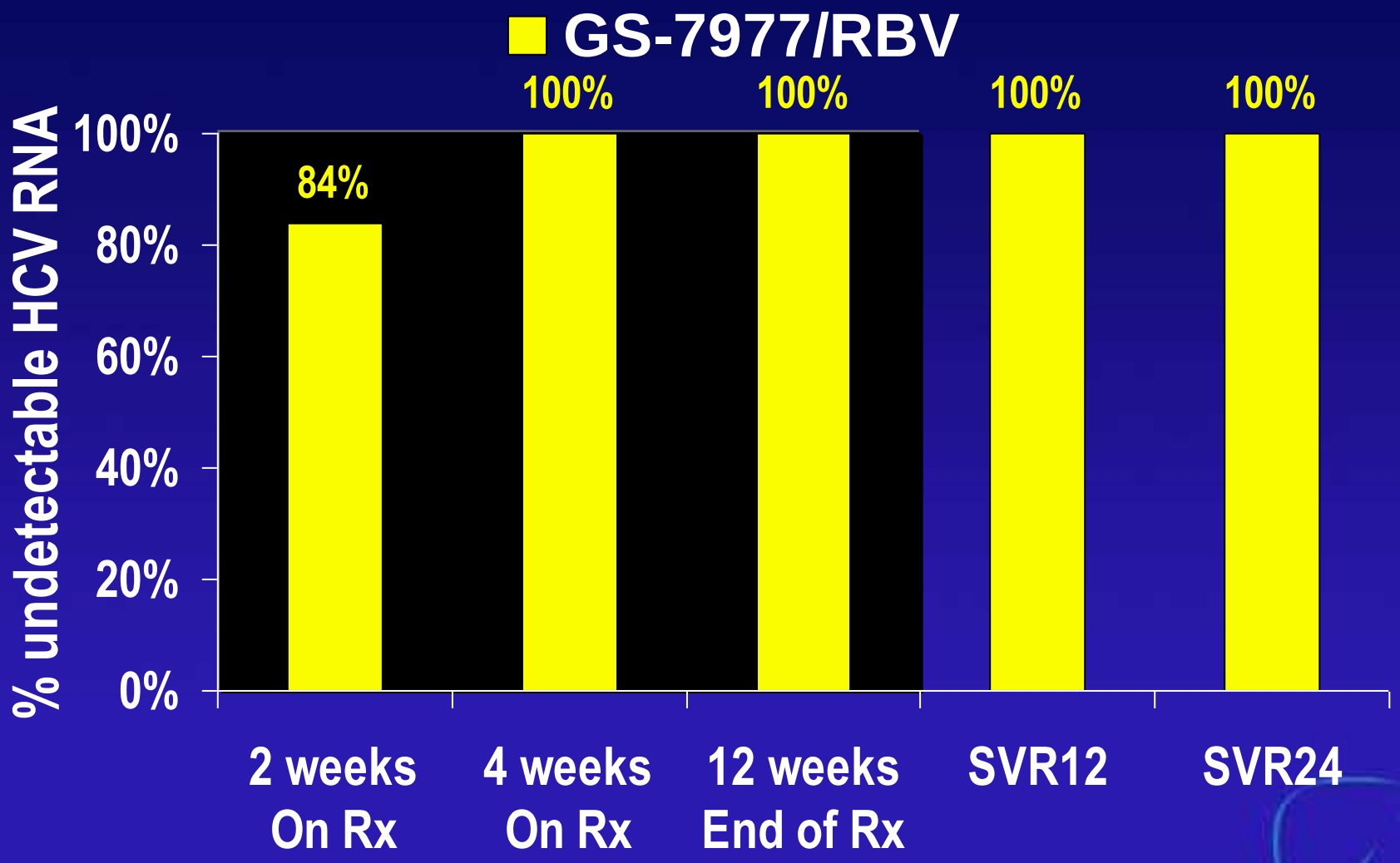
GS-7977 ELECTRON
Study Design for HCV GT2/3

- GS-7977 is a once daily oral nucleostide analog
  - »No drug interactions (give with methadone)
- 40 NZers randomised to IFN-sparing or IFN-free for only 12 weeks



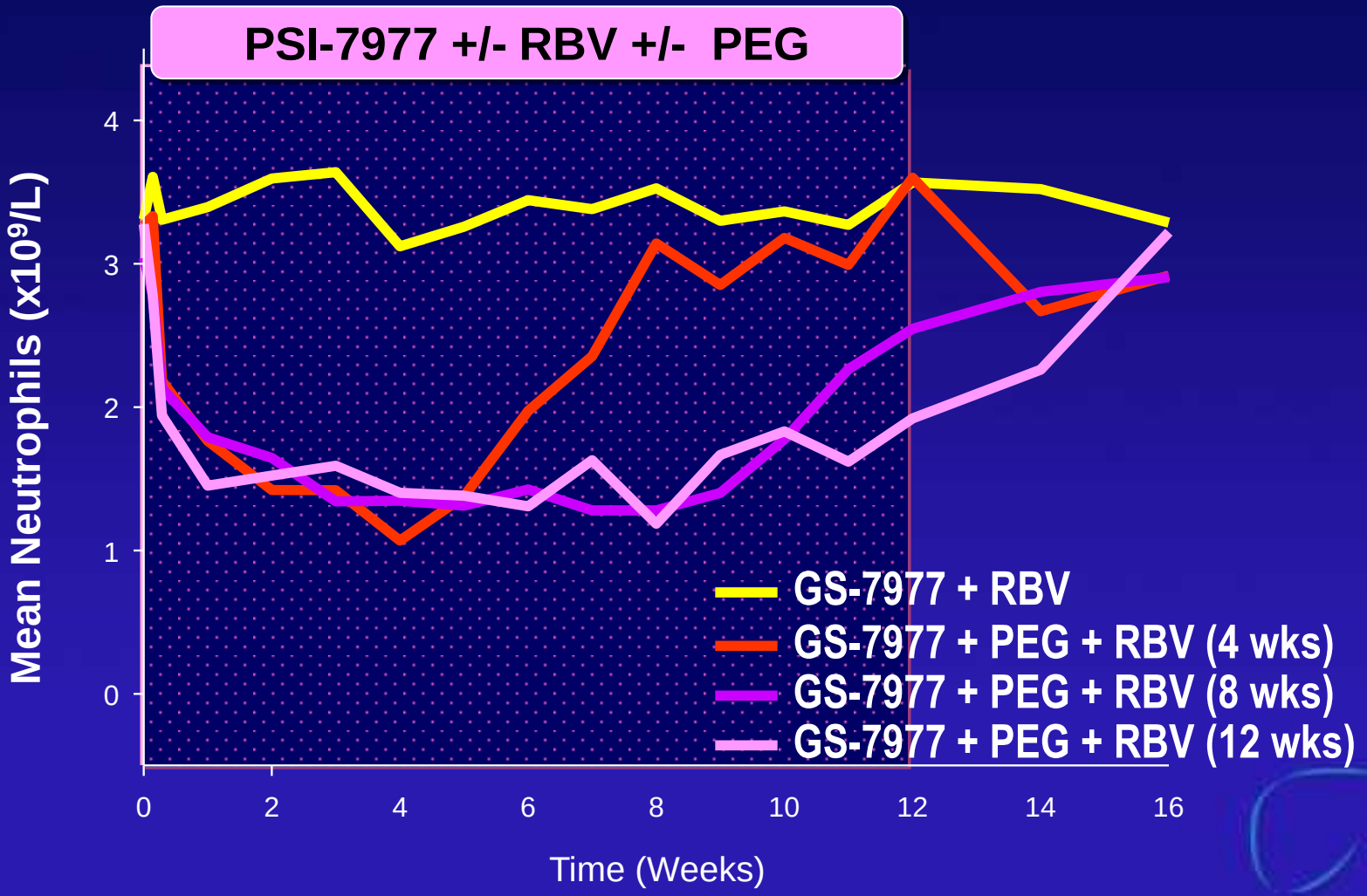
Gane E, et al. *Hepatology* 2011; 54: 377A

ELECTRON: GS-7977/Ribavirin±PEG for 12 wks in Treatment-Naïve GT2/3 (n=40)



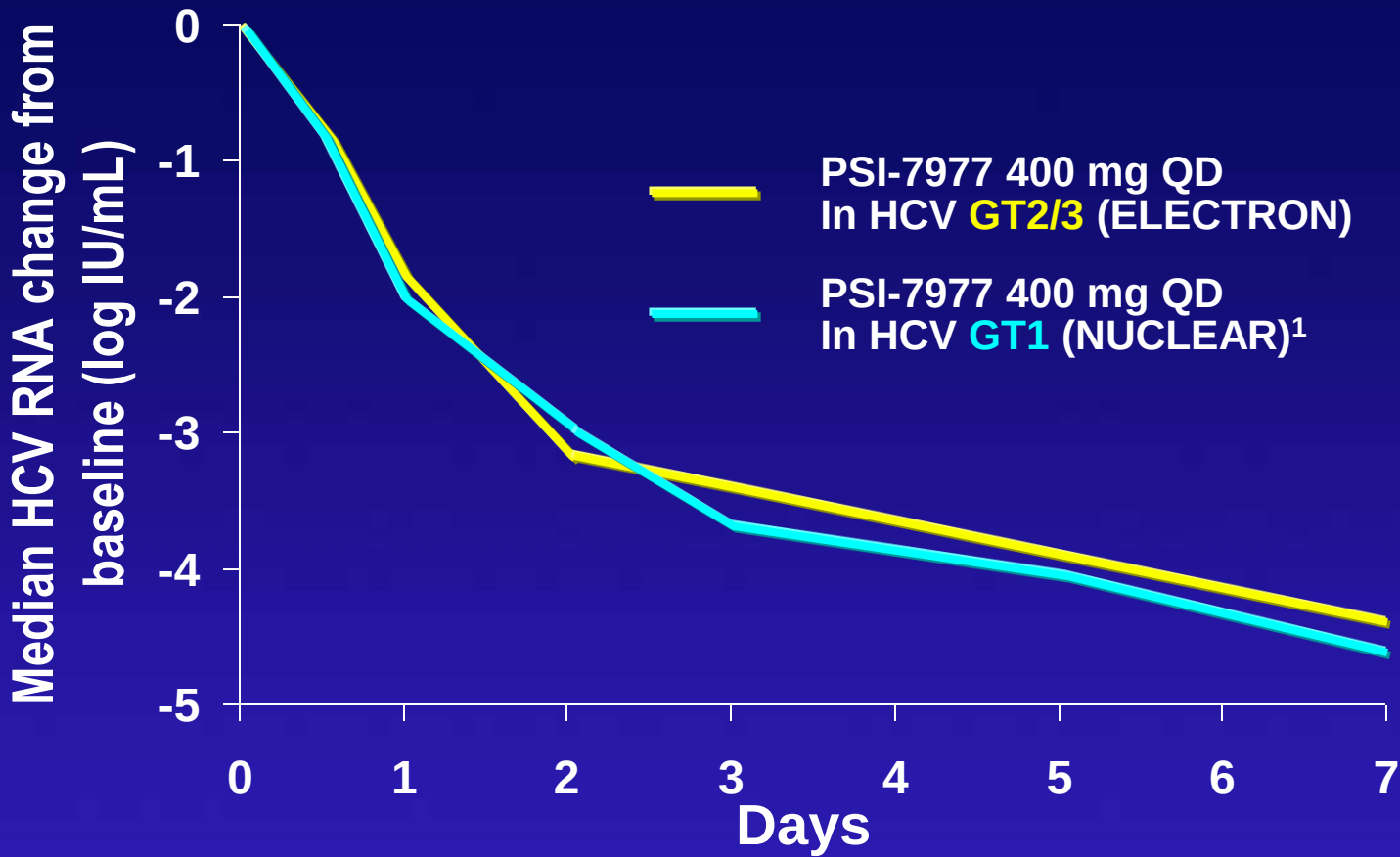
Gane E, et al. *J Hepatol* 2012; 56: S438

ELECTRON: GS-7977/Ribavirin±PEG
No Neutropaenia



Gane E, et al. *Hepatology* 2011; 54: 377A

What about in HCV Genotype 1?

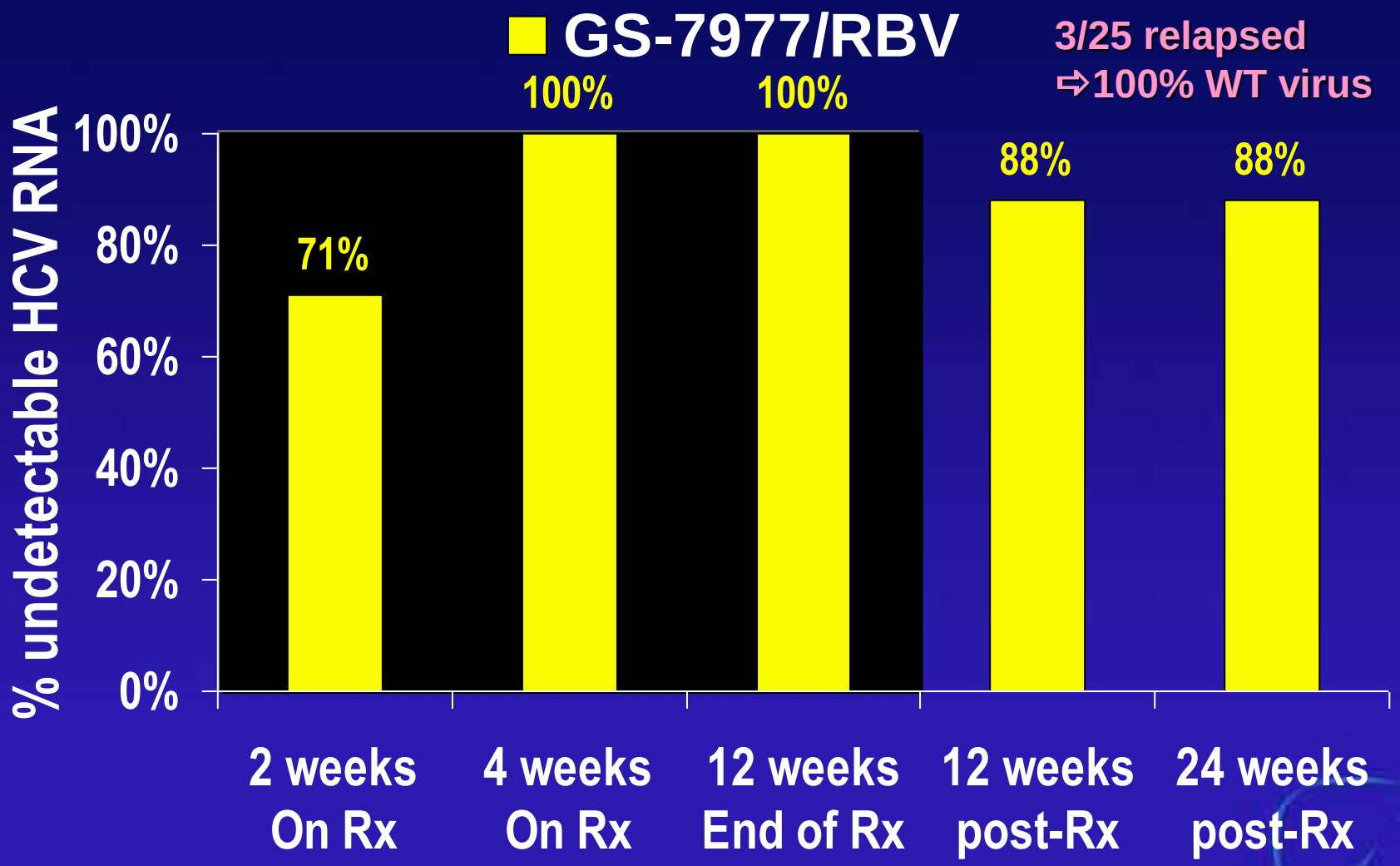


Confirms *in vitro* potency of GS-7977 across HCV genotypes

[1]Lawitz E, et al. *J Hepatol* 2011; 54: S543

Gane E, et al. *Hepatology* 2011; 54: 377A

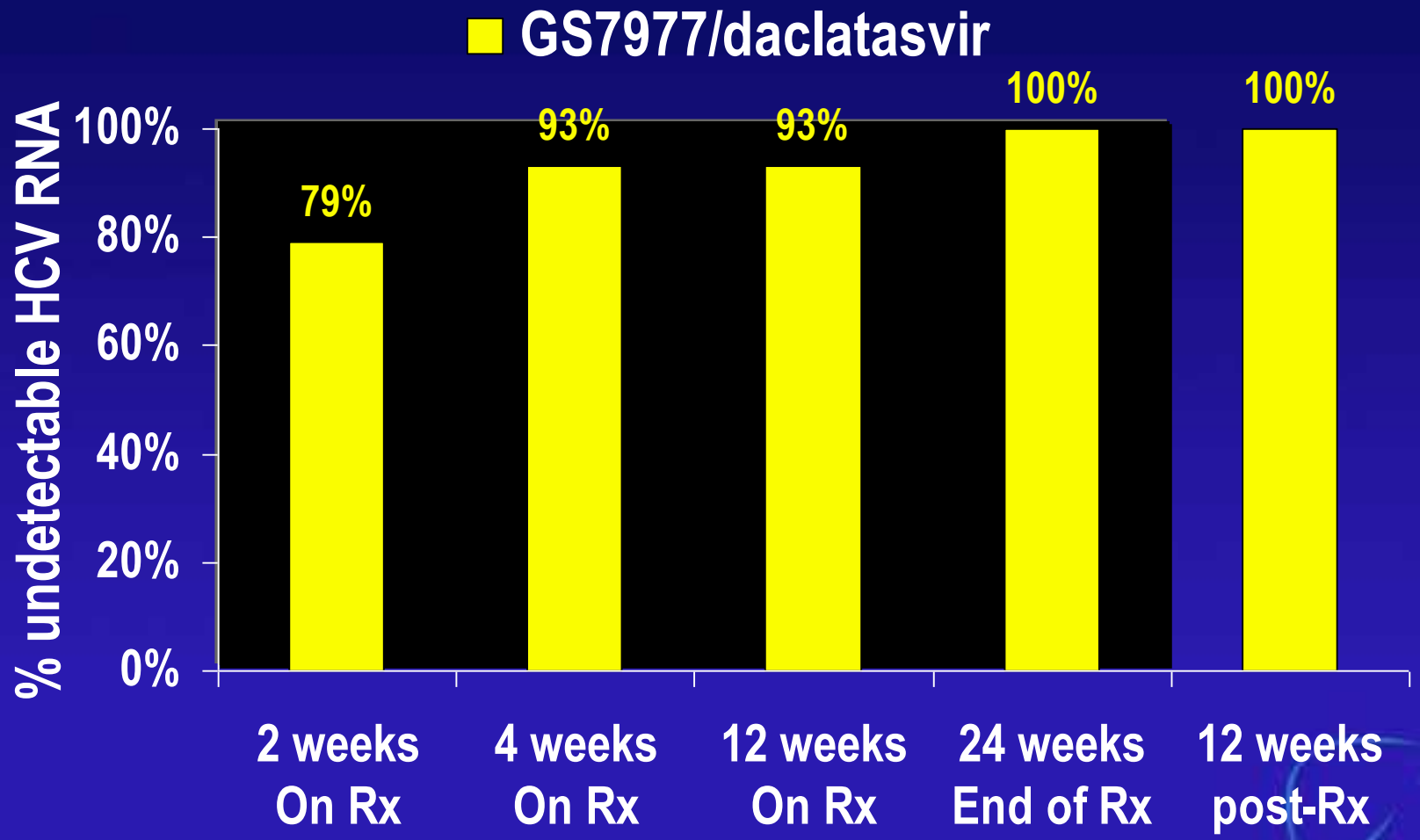
ELECTRON: GS-7977/Ribavirin for 12 wks in Treatment-naïve GT1 (n=25)



Gane E, et al. *J Hepatol* 2012; 56: S438

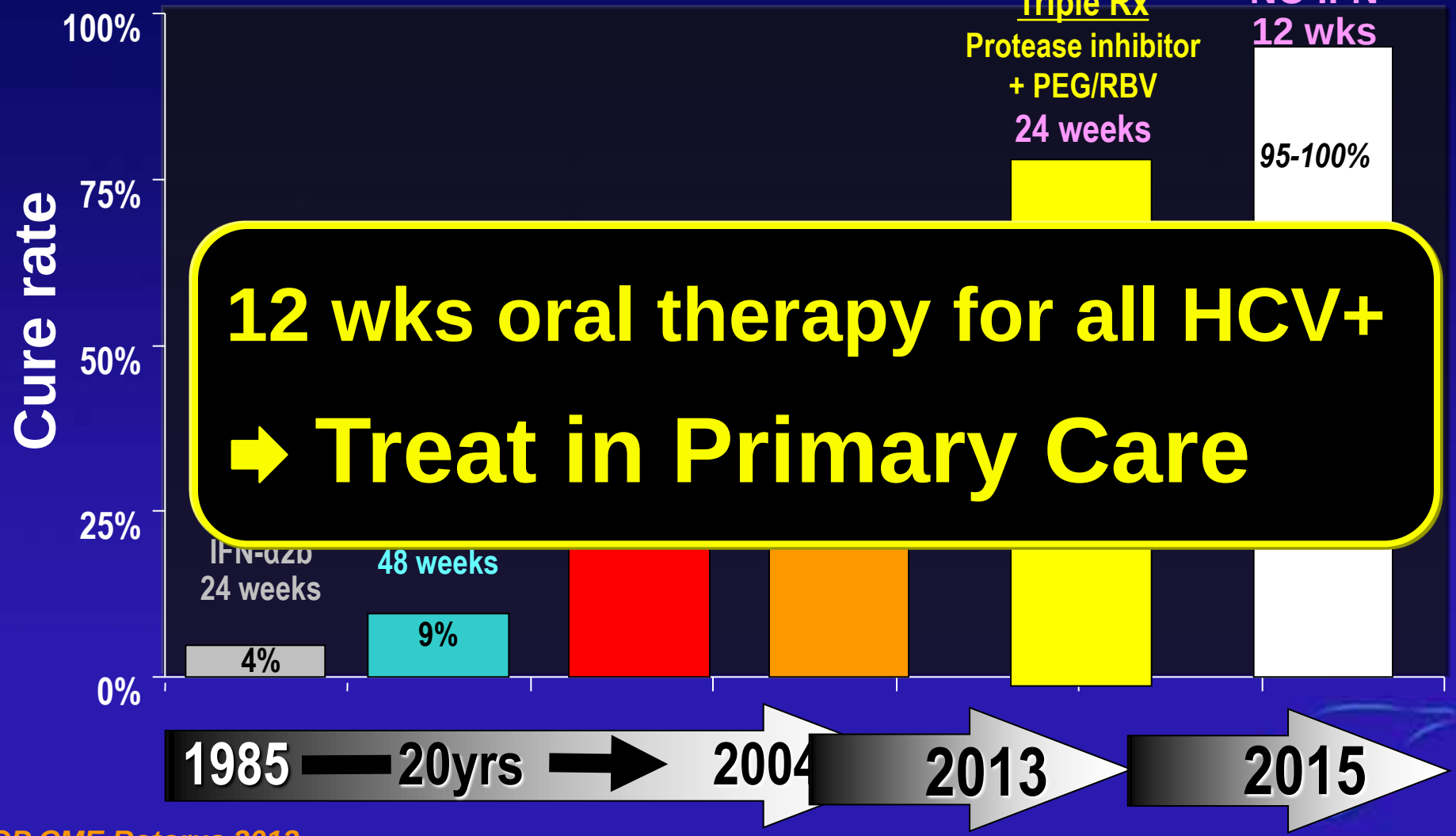
NUC NS5B inhibitor GS-7977 plus NS5A inhibitor Daclatasvir ± RBV

(a) In HCV Genotype 1 (n=45)



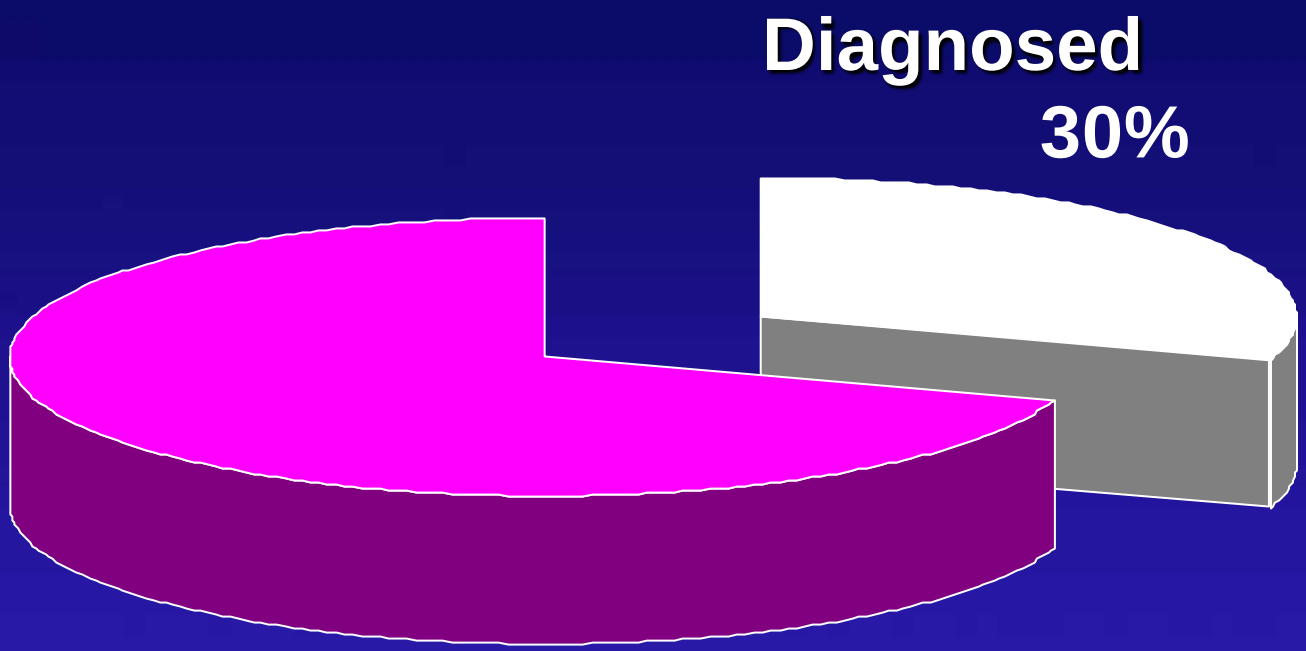
Sulkowski M, et al. *J Hepatol* 2012; 56: S1422

Future Trends in HCV Therapy



Chronic Hepatitis C - the Solution

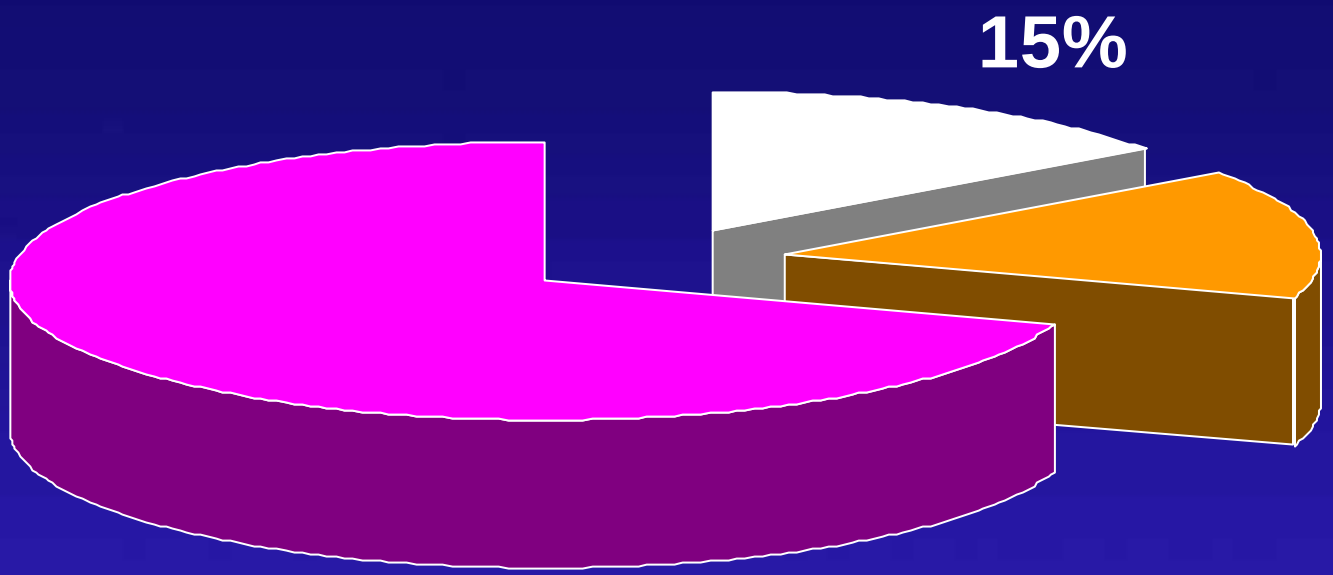
Antiviral Efficacy in the "Real World"



Chronic Hepatitis C - the Solution

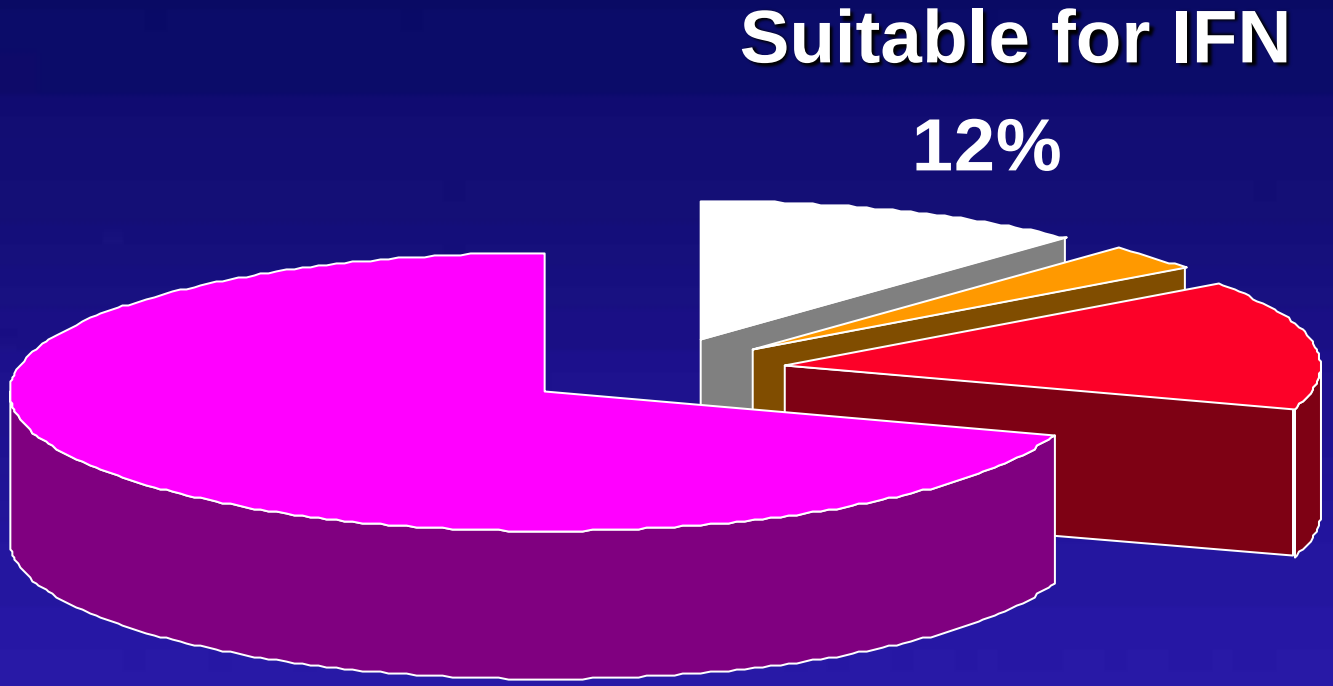
Antiviral Efficacy in the "Real World"

Assessed at clinic



Chronic Hepatitis C - the Solution

Antiviral Efficacy in the "Real World"



Chronic Hepatitis C - the Solution

Antiviral Efficacy in the "Real World"

Cured
6%

- In 2011, only 550 patients (~1%) received antiviral therapy
- Need to increase diagnosis and treatment uptake

A national approach to hepatitis C (1)

* *Hon Pete Hodgson, 5 December 2006*

"A $30 million package to provide one-off payments to an estimated 550 people is part of a way forward for people who were infected with hepatitis C through the New Zealand blood supply"

"In addition, MoH will provide $5 mill/year to improve access to and uptake of hepatitis C treatment services.

The HCV Treatment Advisory Group will assist the Ministry improve services to all people with HCV. It will include consumer, clinical and DHB representatives".

A national approach to hepatitis C (2)

2006-9: MoH Hep C Treatment Advisory Group

- May 2009 –final report "Strategic Directions for Hepatitis C: To improve access to and uptake of treatment services for hepatitis C"
- July 2009 – Plan approved by Tony Ryall
- Dec 2009 - Tenders called for "Improvements in Hepatitis C Services" project

Objectives of "Improvements in Hepatitis C Services" Programme

1. increase awareness & remove stigma of Hep C
2. improve access to and uptake of hepatitis C testing and assessment
3. improve uptake of treatment
4. improve health outcomes for people living with hepatitis C in New Zealand
5. improve disease surveillance

A national approach to hepatitis C (4)

2010 Dec : National Action Plan Feasibility contracted to the Hepatitis Foundation of NZ

1. Stock-take of current Hep C services
   * all 21 DHBs, CADS and Prisons
2. Education needs for Primary Care
3. Support needs for the HCV+ community
4. E-referrals for GPs (HealthLink)
5. Feasibility for Fibroscan (Liver Unit, ADHB)
6. IT data sharing (Health Alliance, ADHB)

A national approach to hepatitis C (5)

2012 June : National Action Plan implementation contracted to the Hepatitis Foundation of NZ

1. 2012 July: 3 pilots (urban/rural) commence
2. 2014 June: pilots cease
3. 2014 July-Dec: independent evaluation
4. 2015-20: national roll-out across all DHBs

Goals of the Pilots

1. Increasing public awareness
2. Targeted Testing Programme
3. Community assessment and support (*including access to genotyping and Fibroscan*)
4. Integrated service delivery
5. Improved disease surveillance & data collection
6. Education, resources, and training

1. Increasing Awareness

Increase awareness of risk factors for hepatitis C and of pathways to access testing and care

1. Media campaign
2. Provider education and training
3. Educational Resources
4. Helpline (0800-332010)
5. Client-centred quarterly magazine
6. Website

2. Targeted Testing

* **6 risk factors**

1. Ever injected drugs
2. Ever transfused pre1992 or any time overseas?
3. Ever lived in or received health care in SE Asia, the Middle East, or Eastern Europe?
4. Ever been jaundiced or had acute hepatitis
5. Ever imprisoned
6. Mother has HCV

➡ **Strategies to provide easy access to testing via GPs, CADS, Needle Exchange, Sexual Health**

3. Community-based Assessment and Support Programme

* **Assessment and Support Programme** People diagnosed with hep C referred to community based programme
* **Community Hepatitis Nurse** providing community-based specialist clinical care
* **Enable secondary care** to focus on treatment

Tracing Patterns of Health
THEHEPATITISFOUNDATION

MINISTRY OF HEALTH
MANATŪ HAUORA

MoH e-Learning Module for HCV

http://learnonline.health.nz/course

Designed to meet needs of busy GP/practice nurse

* **On-line**
* **Accessible from home**
* **Easy to navigate and return to on multiple occasions**
* **Brief 30-40 minutes only**
* **Quiz at end (20 questions)**
* **Printable certificate (if >70%)**
* **Qualify for 2 CME points**

Tracing Patterns of Health
THEHEPATITISFOUNDATION

AUCKLAND DISTRICT HEALTH BOARD
Te Toka Tumai

MINISTRY OF HEALTH
MANATŪ HAUORA

Hepatitis C E-Learning for GPs

LearnHealth ▶ Hep C - Doctors

Welcome

Learn about hepatitis C by working through the five learning modules below.
Gain 1 CME credit by passing the assessment, completing the evaluation and then printing your certificate.

Access a range of resources to support you in your day-to-day work.
Help on using this programme.

Learn About

- 15 min — What Is Hepatitis C — Start
- 15 minutes — Identifying Hepatitis C — Start
- 15 minutes — Diagnosing Hepatitis C — Start
- 25 minutes — Treating Hepatitis C — Start
- 10 minutes — The Future - Hepatitis C — Start

Gain Accreditation

- Assessment
- Your feedback
- Print your certificate

Post-Learning Support

Quick facts

- What Is Hepatitis C
- Identifying Hepatitis C
- Diagnosing Hepatitis C
- Treating Hepatitis C
- The Future - Hepatitis C

Resources

- Patient Information Sheet
- GP Communication Guide
- Testing & Treatment Pathway
- Referral Form
- Programme References & Additional Reading

Got a question? Ask the experts
Find out more

Join the conversations
Find out more

Special thanks to

- John Hornell CEO Hepatitis Foundation of NZ
- Kelly Barclay, HCV Project Manager, HFNZ
- Helen Payne, HFNZ
- Lucia Bercinskas, Ministry of Health

viral HEPATITIS

AUCKLAND 2012

8TH AUSTRALASIAN CONFERENCE

10–12 September 2012

SkyCity Convention Centre – Auckland, New Zealand

ashm

Supporting the HIV, Viral Hepatitis and Sexual Health Workforce

www.hepatitis.org.au