

“The Seven Myths of Hepatitis C”

**Associate Professor Joe Sasadeusz
Victorian Infectious Diseases Service
Royal Melbourne Hospital
Melbourne**



Myth # 1

- Hepatitis C is rare?



Hepatitis C - Epidemiology

- Over 170 million persons worldwide
- Prevalence ranges from 0.15% (Scandinavia) to >40% (Egypt and Cameroon)
- Western Europe, USA, Japan: 0.2-2.0%
- South America & Asia: 2-5%
- Australia
 - *150,000-200,000 infections*
 - *11,000 new infections/year*
 - *80% prevalence in IDUs*
- Most common indication for liver transplantation in USA and Australia



Myth # 2

- Hepatitis C is sexually transmitted



Hepatitis C Transmission

- Exposure to blood and body fluids
- Percutaneous
 - *Injecting drug use*
 - *Most efficient and common*
 - *70% if > 3 years of use*
 - *> 80% HCV infections in Australia*
 - *Transfusion/blood products*
 - *now 1 in 4 million units due to NAT testing of pooled samples*
 - *esp. haemophiliacs prior to 1991*



Transmission of HCV

- Percutaneous ctd.
 - *Tattoos, piercing*
 - *Therapeutic (contaminated equipment, unsafe injection practices)*
 - *Haemodialysis*
 - *Endemic e.g. Schistosomiasis program in Egypt*
 - *Occupational (needlestick) (5%)*
 - *Transplant from infected donor*
- Permucosal
 - *Perinatal (5%)*
 - *Sexual (inefficient), only HIV + MSM*
- 40% unknown



Heterosexual Transmission and HCV

- Long -term prospective study of 895 monogamous heterosexual partners of chronically HCV-infected individuals (RNA+)
- 8,060 person years of follow up
- 726 (86.7%) followed followed 10 years
- No anal IC or sex during menstruation but also no condoms
- 3 infections, 0.37/1,000 person-years
- One had different genotype
- Other 2 had concordant genotypes but sequencing and phylogenetic analysis demonstrated different viruses



Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy

Jeanne Serpaggi^{a,b}, Marie-Laure Chaix^c, Dominique Batisse^d,
Caroline Dupont^e, Anaïs Vallet-Pichard^{a,b}, Hélène Fontaine^{a,b},
Jean-Paul Viard^f, Christophe Piketty^d, Elisabeth Rouveix^e,
Christine Rouzioux^c, Laurence Weiss^d and Stanislas Pol^{a,b}

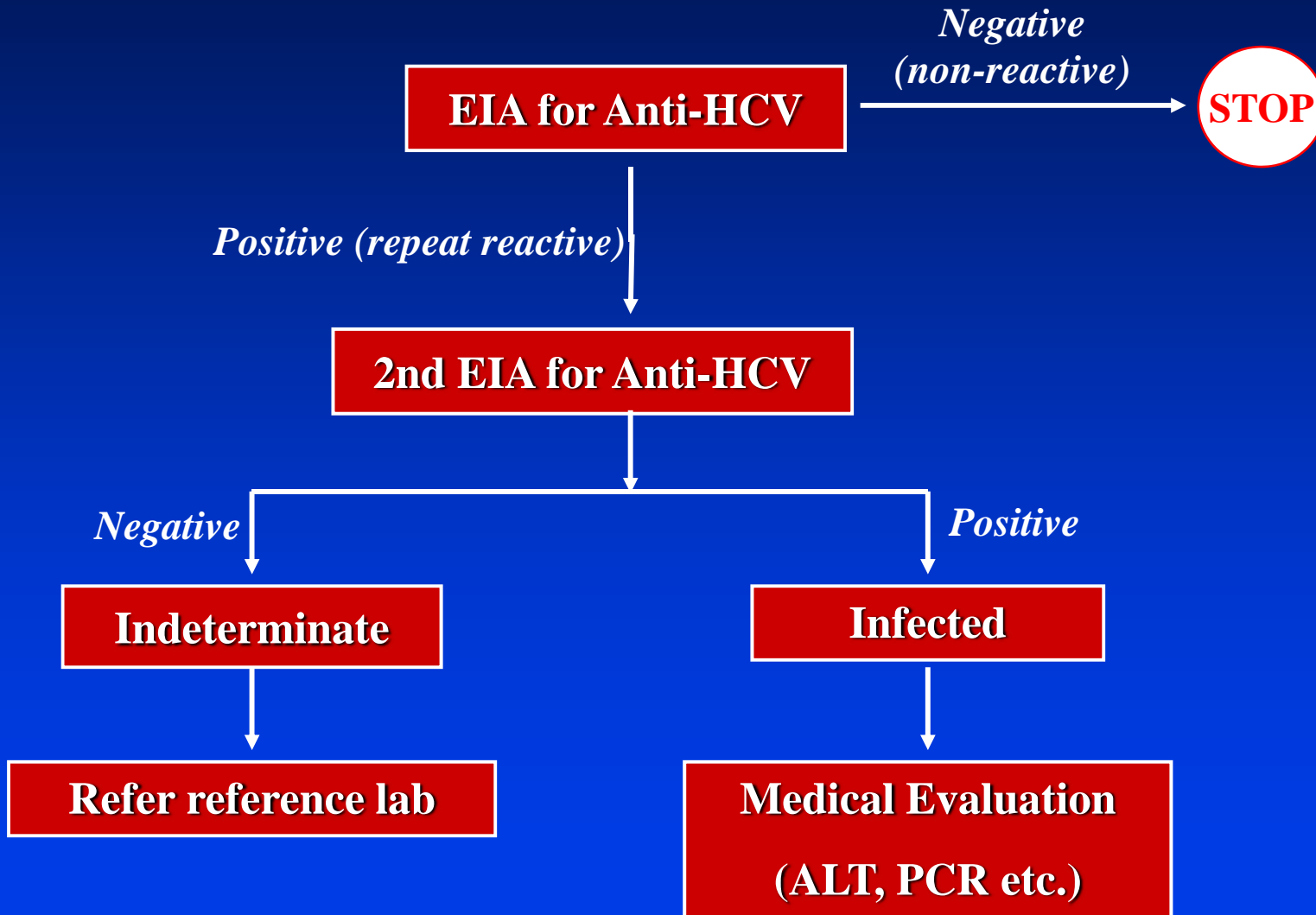
- All had UPAI as only risk factor
- 10/12 genotype 4, all common source

Myth # 3

- Hepatitis C antibody means current infection



HCV Infection Testing Algorithm NHMRC strategy



Hepatitis C – Diagnosis Serology

- Anti-HCV
 - detects that immune system has seen virus at some point
 - does not detect current infection
 - delay in appearance in acute disease: “window period”, 90% positive at 6 months
 - if suspect acute HCV, may be negative, do PCR



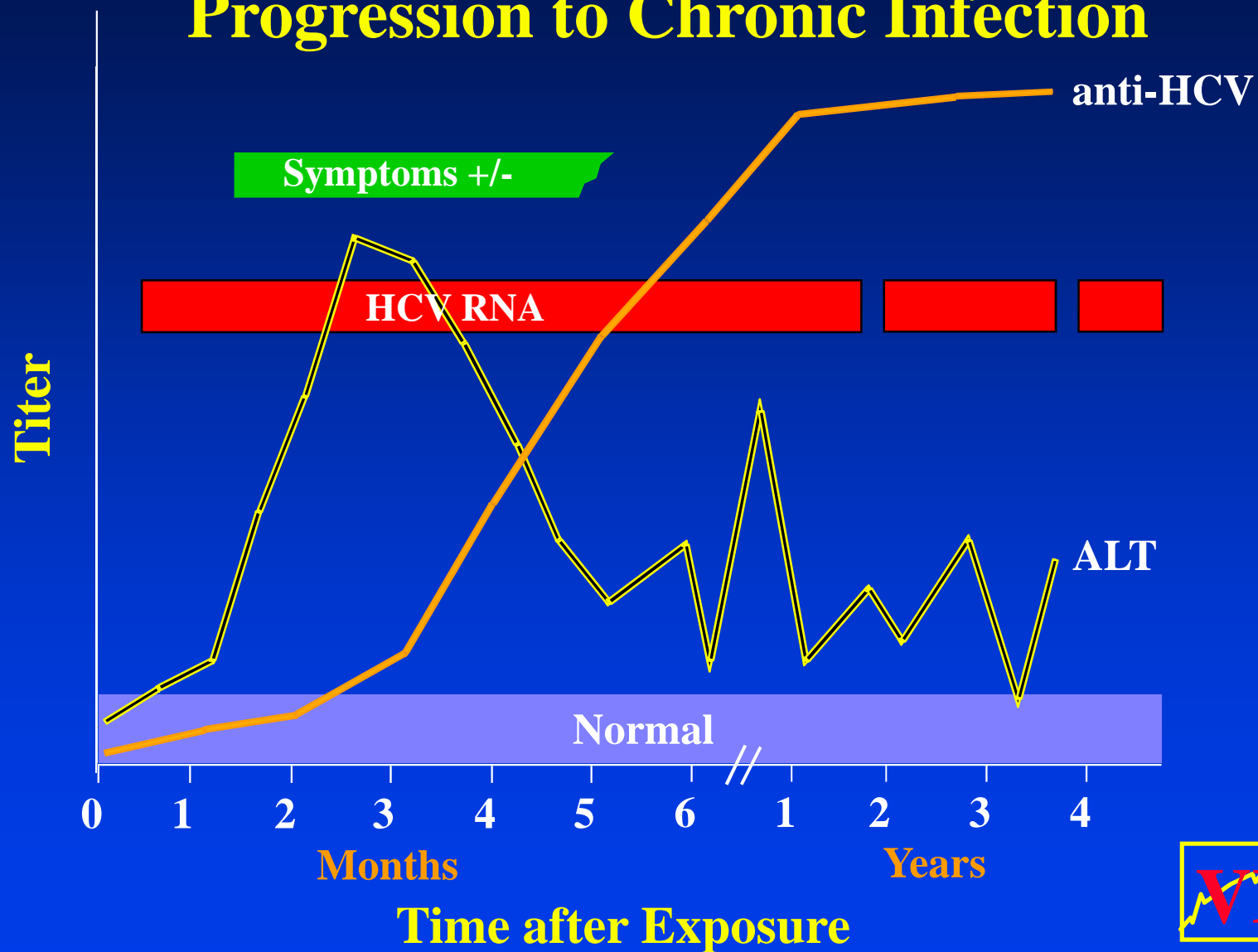
Hepatitis C – Diagnosis

RNA testing

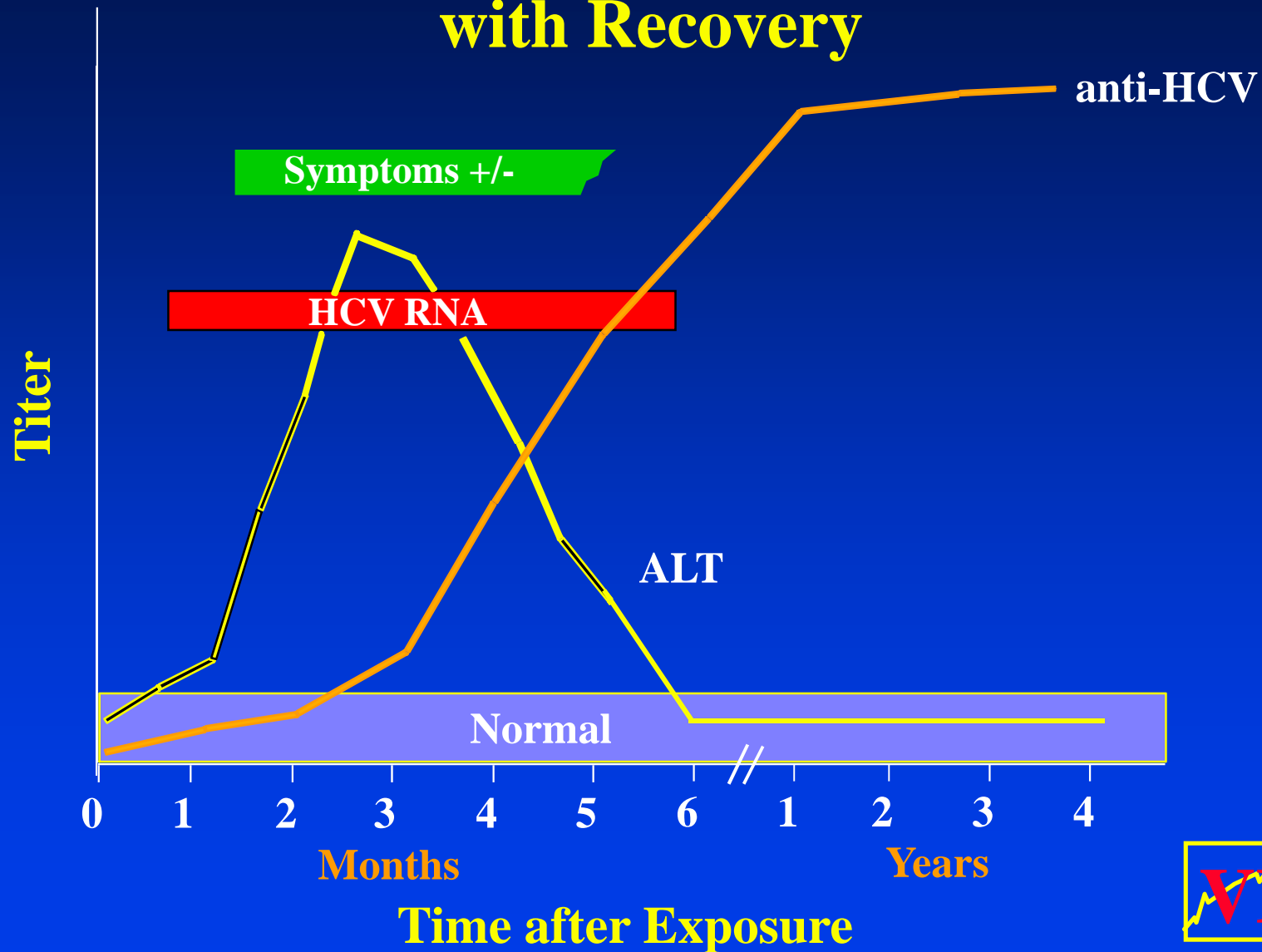
- HCV-RNA (PCR)
 - directly detects virus
 - qualitative (yes or no) is standard to determine viraemia
 - If detected ask lab to do subsequent HCV Viral load and genotype
 - quantitative (Viral load =measures amount of virus in IU/ml)
 - *Used pre treatment to predict response to therapy*
 - *Used on treatment for stopping rule*



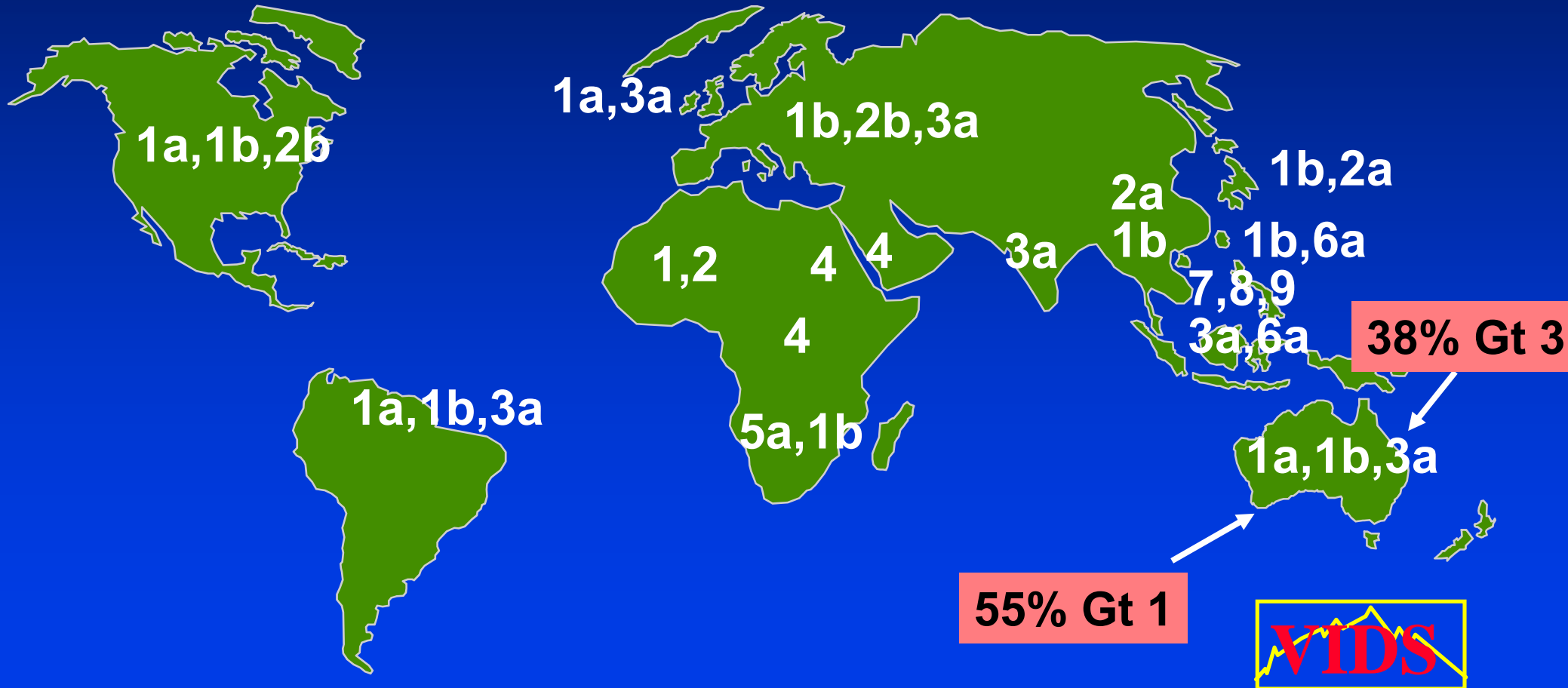
Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



Serologic Pattern of Acute HCV Infection with Recovery



Hepatitis C Virus Genotypes World View



Myth # 4

- If I have hepatitis C I will inevitably end up with liver failure or liver cancer



HCV Infection

50-85% chronic

15-50% resolve

60-70% abnormal ALT

30-40% normal ALT

10-20% cirrhosis

Slow progression

1-5% HCC

20% decompensate at 5 yrs



Myth # 5

- There is no treatment for hepatitis C

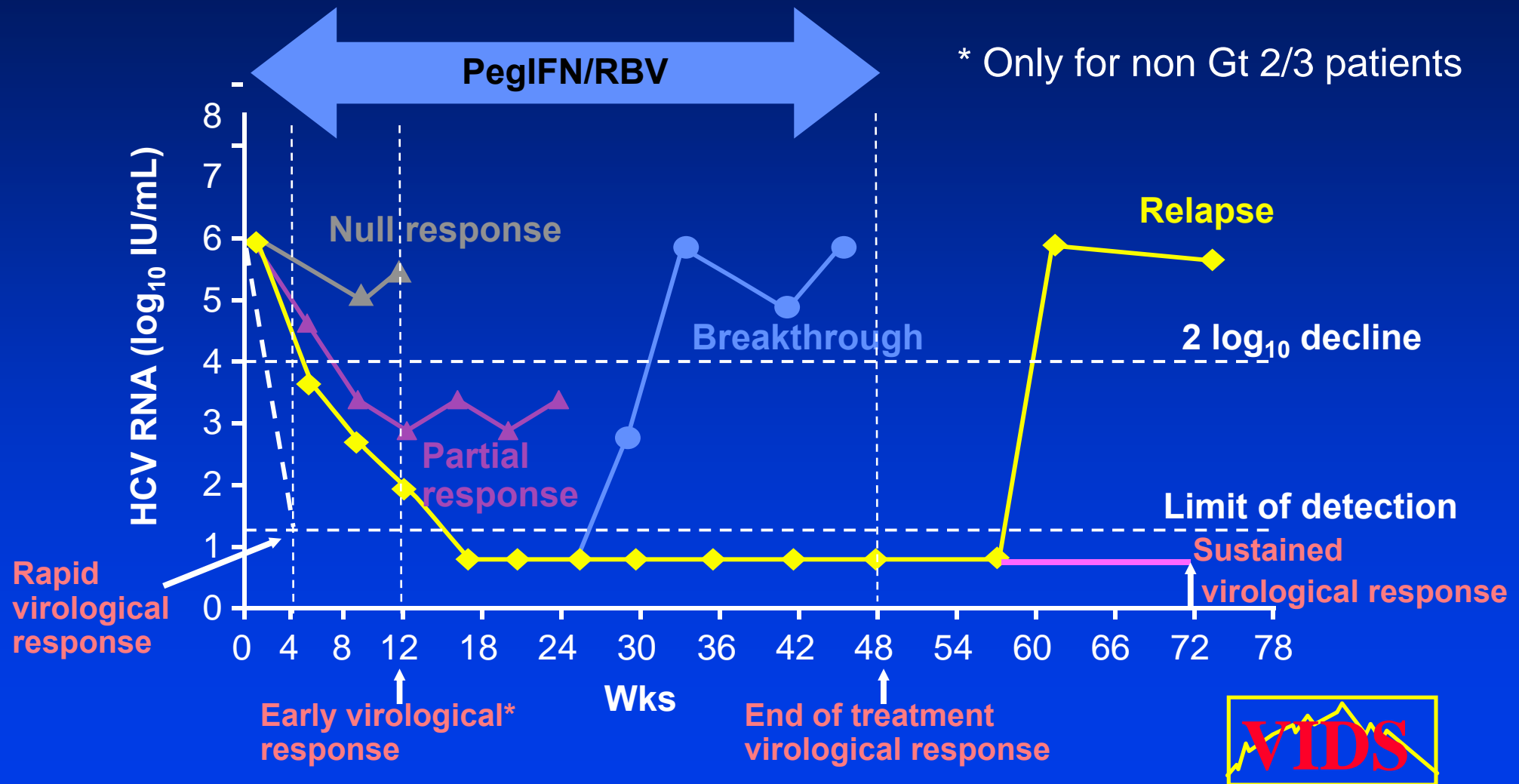


Reasons for treatment

- Prevent disease progression
- Prevent transmission
 - Individual
 - Patient to partners and family
 - Mother to child
 - HCW
 - IDUs
 - Public health level
- Symptoms
 - Inconsistent response
- “Get rid of infection”
 - Reminder of past behaviours



Virologic Responses/Monitoring



Sustained Virological Response: Potential Benefits

- Decreased risk of cirrhosis or decompensation ²
- Decreased risk of hepatocellular carcinoma ¹
- Improved survival ³
- Decreased infectivity
- Improved quality of life: more productive, fewer days off work, less likely to work shorter hours ⁴

1. Mazella, *et al. J Hep* 1996. 2. Serfaty L, *et al. Hepatology*

1998; 27: 1435–40., 3. Niederau C, *et al. Hepatology* 1998;

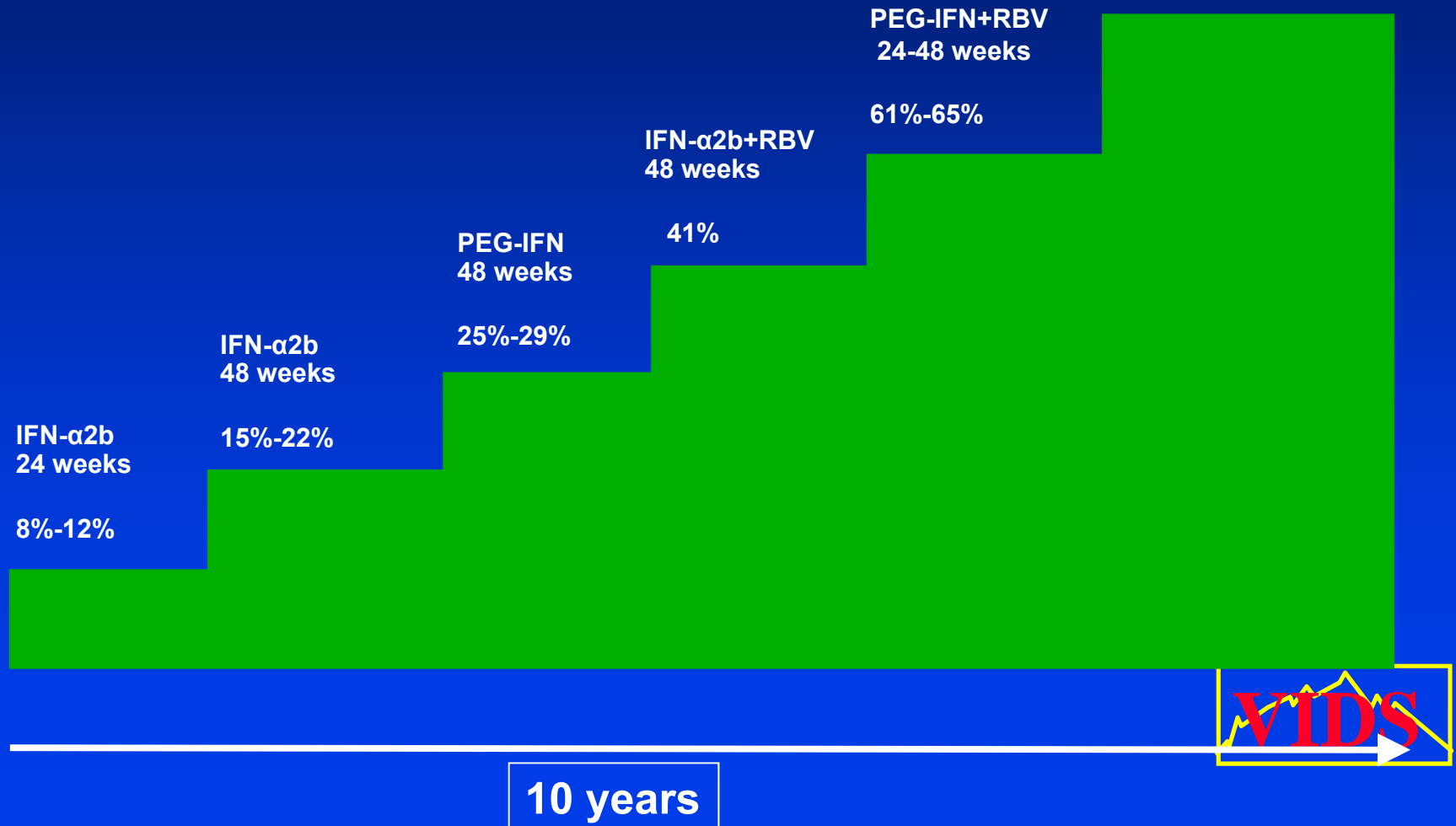
28: 1687–95. 4. McHutchinson JG, *et al. J. Hepatol* 2001; 34: 140–47.



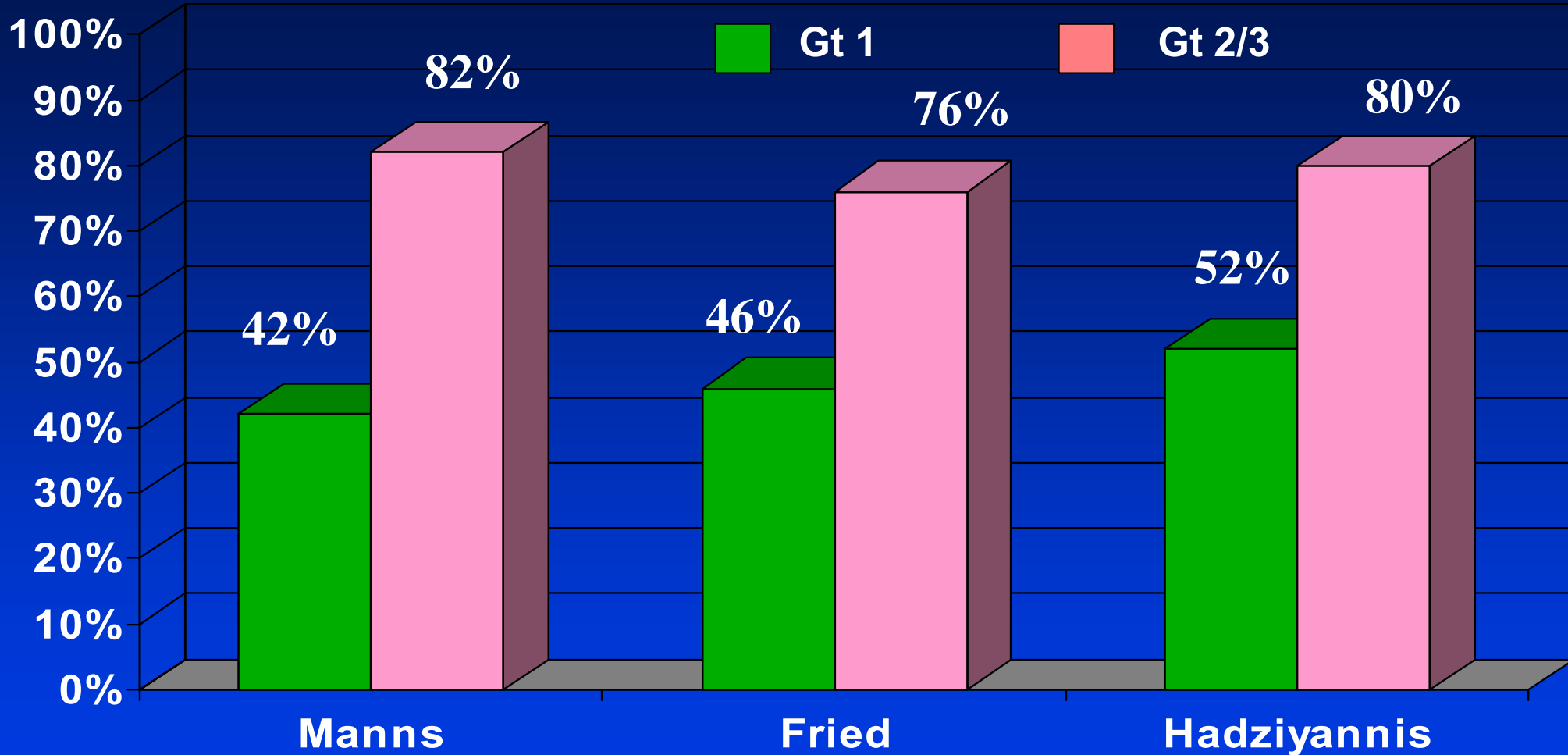
Hepatitis C treatment progress

Sustained Virological Response

Directly acting antivirals
(Protease inhibitors)



PEG/RBV and Effect of Genotype



Manns Lancet 2001, Fried N Eng J Med 2002,
Hadziyannis Ann Intern Med 2004



α Interferon - Side Effects

- Flu-like symptoms
- Fatigue
- Neuropsychiatric (esp depression, irritability)
- CNS (esp. sleep disturbance, concentration)
- Mouth ulcers
- Myelosuppression
 - *neutrophils*
 - *platelets*
- Induction of autoimmune disease
 - *thyroid disease*
 - *psoriasis*
- Hair loss (50%)
- Injection site reactions



Ribavirin - Side Effects

- Haemolysis
 - *usually mild*
 - *contraindicated if significant cardiac or respiratory disease*
- Teratogenicity
 - *both partners must use adequate contraception*
- Cough
- Rash



Suitability for therapy

- Absolute Contraindications
 - Severe current psychological instability
 - Chaotic injecting drug use (daily or greater)
 - Decompensated liver disease
 - Severe cytopenias (usually cirrhotics)
 - Pregnancy
- Relative contraindications
 - High alcohol intake (>3 standard drinks /day)
 - Patient ambivalence
 - No social support
 - Autoimmune disorders



Acute Hepatitis C-studies

	Jaundice	IDU-acquired	Baseline ALT	Duration infection* / diagnosis**	SVR (ITT)
Jaeckel 2001 (n=44)	68%	N=8 (18%)	885	13 weeks* (4 – 16)	98%
Kamal 2004 (n=40)	3%	N=0 (0%)	570	12 weeks**	80% (PEG) 85% (PEG/RBV)
Santantonio 2005 (n=16)	47%	N=2 (13%)	1019	12 weeks**	94%
Broers 2005 (n=14)	14%	N=11 (79%)	800	6 weeks** (1-50)	57% (88% PP)
De Rosa 2006 (n=19)	16%	N=14 (74%)	627	4 weeks** (0 – 16)	74%
Weigand 2006 (n=89)	62%	N=20 (22%)	599	11 weeks* (2 – 21)	71% (89% PP)
Kamal 2006a (n=129)	22%	N=12 (9%)	644	10 weeks* (8 – 11)	88%
Kamal 2006b (n=102)	23%	N=9 (9%)	642	13 weeks*	80%



Myth # 6

- A liver biopsy is required to access treatment



Section 100 Criteria

- 18 years or older
- Compensated liver disease
- Documented chronic HCV
 - Repeatedly anti-HCV +
 - and/or
 - RNA +
- Not pregnant or breastfeeding
- Both partners using effective contraception

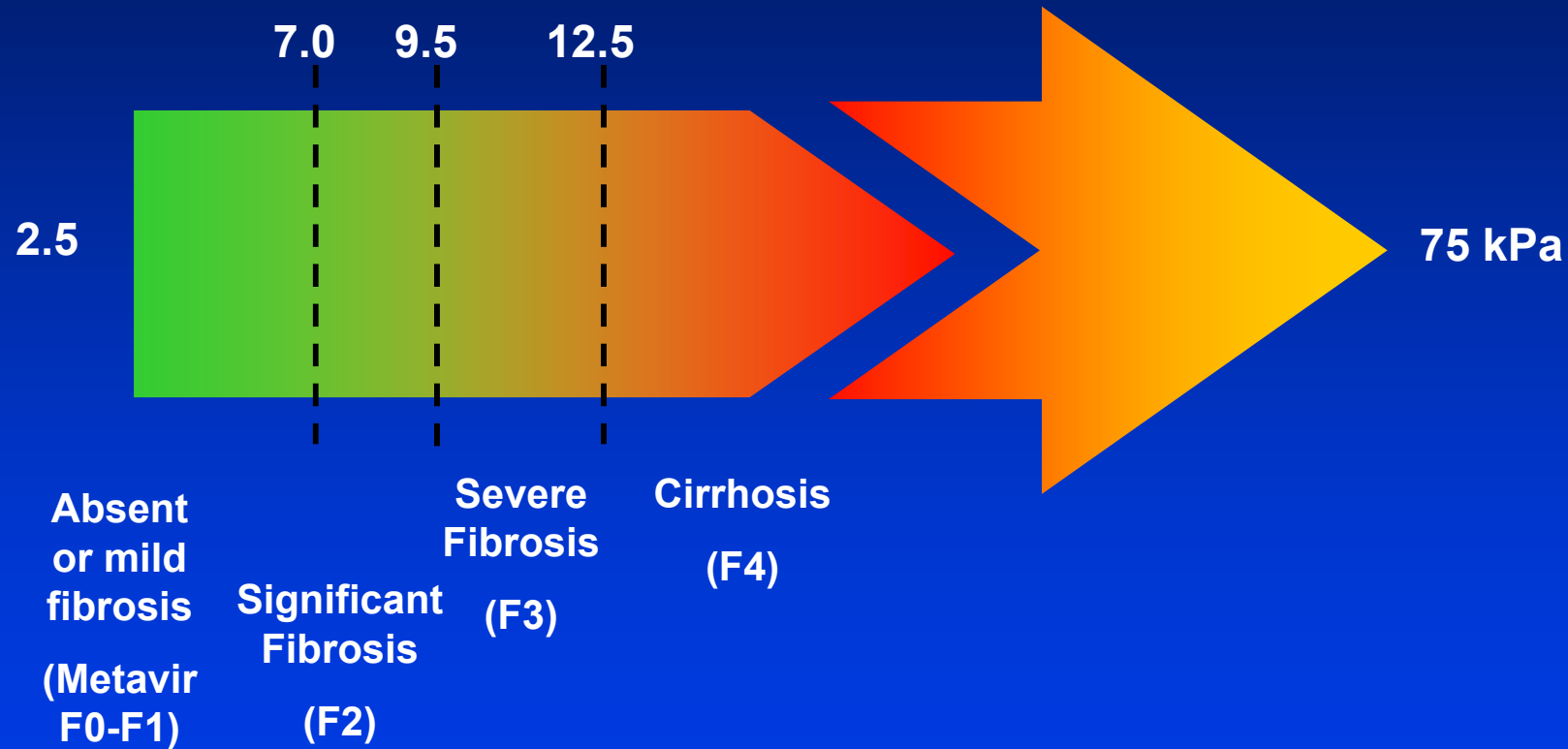
- ❖ Requirement for liver biopsy removed April 2006
- ❖ Requirement for abnormal ALT removed April 2005
- ❖ Retreatment allowed since 2009



Transient Elastography (FibroScan®)



Fibroscan



Castera et al. *J Hepatol* 2008



Advantages of FibroScan®

- Simple
- Quick
- Reproducible
- Instant result

- For the first time
 - Ongoing prospective follow up of patients to monitor for fibrosis progression
 - Allow for widespread screening for hepatic fibrosis in patient populations at risk of liver disease



Myth # 7

- Hepatitis C is incurable



Durability of SVR

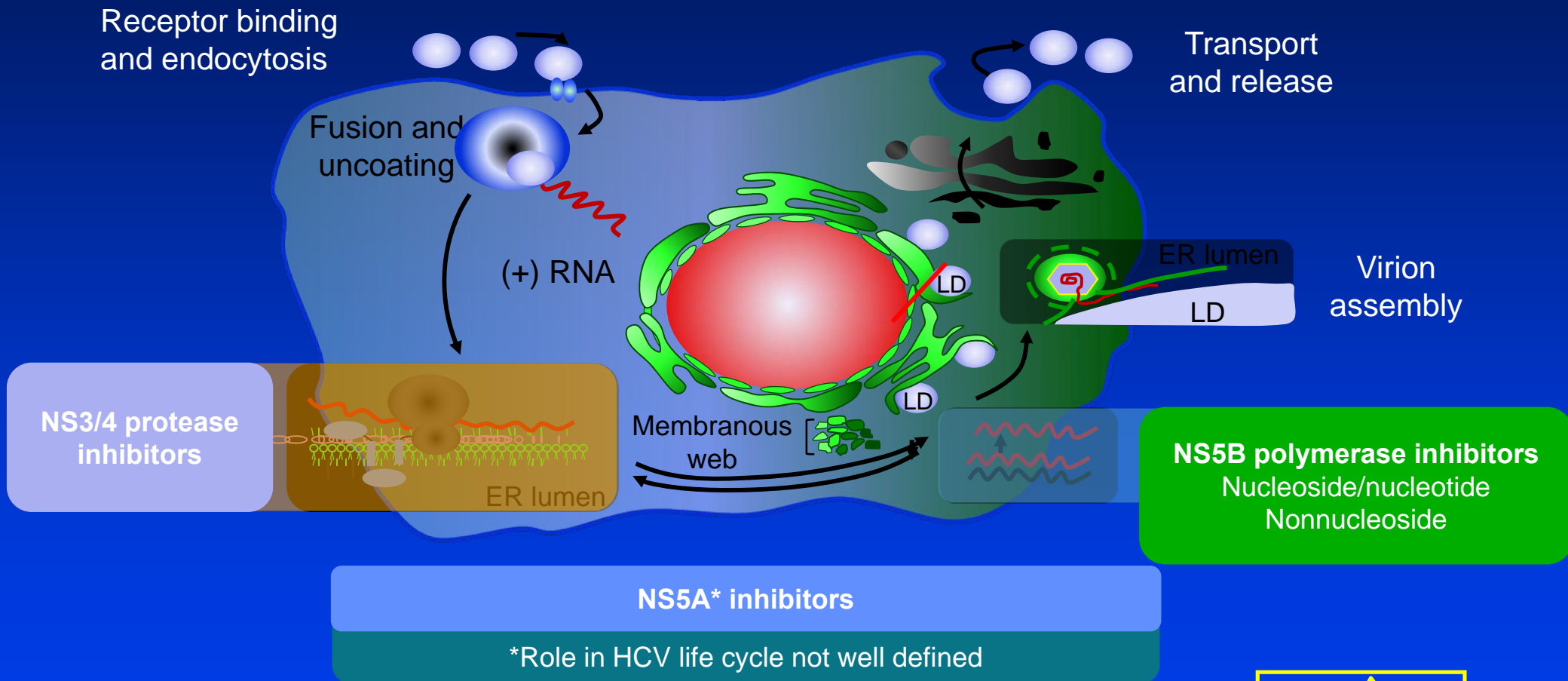
- 155 patients with SVR
- Long term follow up
- Median duration 65 months (range 13-86)
- 147 (98 %) had at least one HCV RNA after SVR
- 137 (91%) at least 3 times
- No patient had HCV RNA by PCR on any sample



Looking Further Into the Crystal Ball of HCV Therapy



HCV Life Cycle and DAA Targets



Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

DAAAs in Clinical Development

	Phase I	Phase II	Phase III
Protease Inhibitors	ABT-450 ACH-1625 GS 9451 MK-5172 VX-985	BMS-650032 CTS-1027 Danoprevir GS 9256 IDX320 Vaniprevir	BI 201335 Boceprevir* Telaprevir * TMC435
Nonnucleoside polymerase inhibitors	BI 207127 IDX375	ABT-333 ABT-072 ANA598 BMS-791325 Filibuvir Tegobuvir VX-759 VX-222	
Nucleoside/tide polymerase inhibitors		IDX184 PSI-7977 RG7128	
NS5A inhibitors	A-831 PPI-461	BMS-790052 BMS-824393 CF102	

Strategies

- Adding one or two DAAs to Pegylated interferon and ribavirin
- All oral DAA combination using drugs to inhibit different steps of life cycle
 - Interferon free
 - Like HIV



Boceprevir and Telaprevir

- Both potent inhibitors of HCV NS3/4A protease
- Active only against Gt1
- Both being tested in combination with standard-of-care pegIFN alfa-2/RBV in phase III studies in chronic HCV infection

Boceprevir

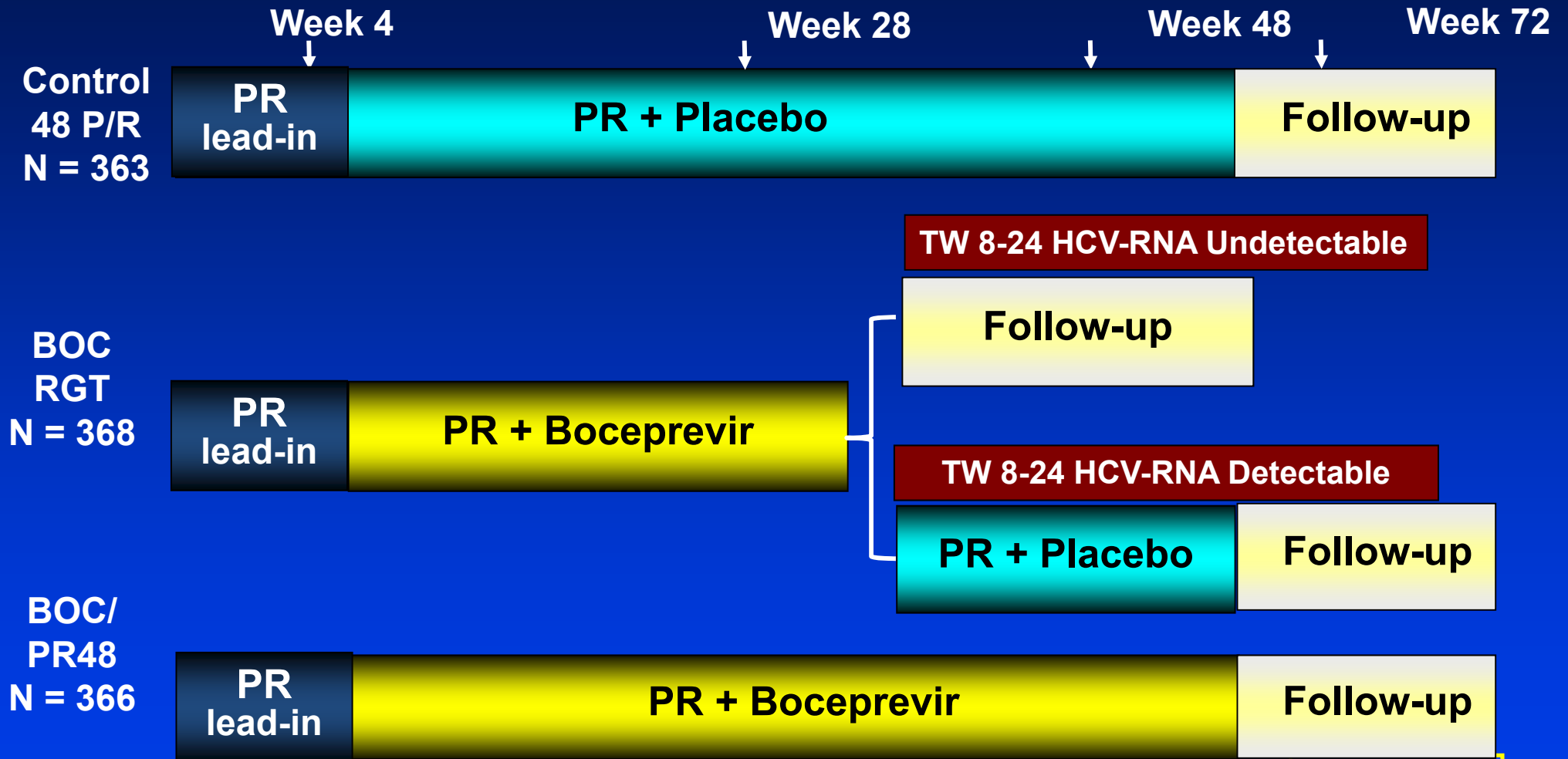
- SPRINT-2: naive GT1
- RESPOND-2: nonresponder GT1 (partial and relapsers)

Telaprevir

- ADVANCE: naive GT1
- ILLUMINATE: response-guided therapy in naive GT1
- REALIZE: nonresponder GT1 patients (null, partial and relapsers)



SPRINT 2: Study Design



SPRINT 2: SVR and Relapse Rates (ITT)

Cohort 1: Non African American

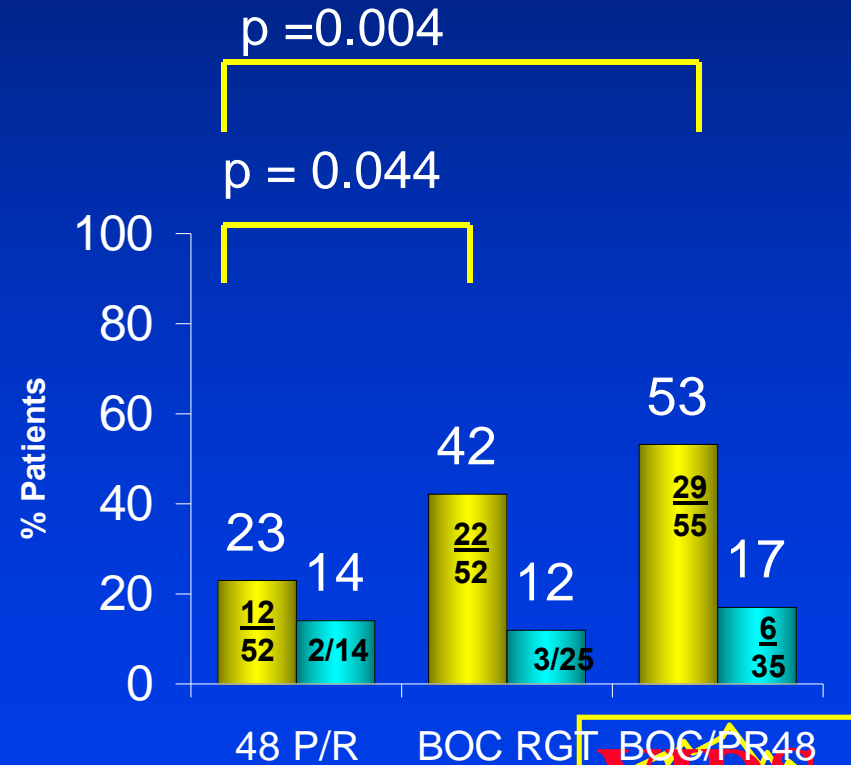
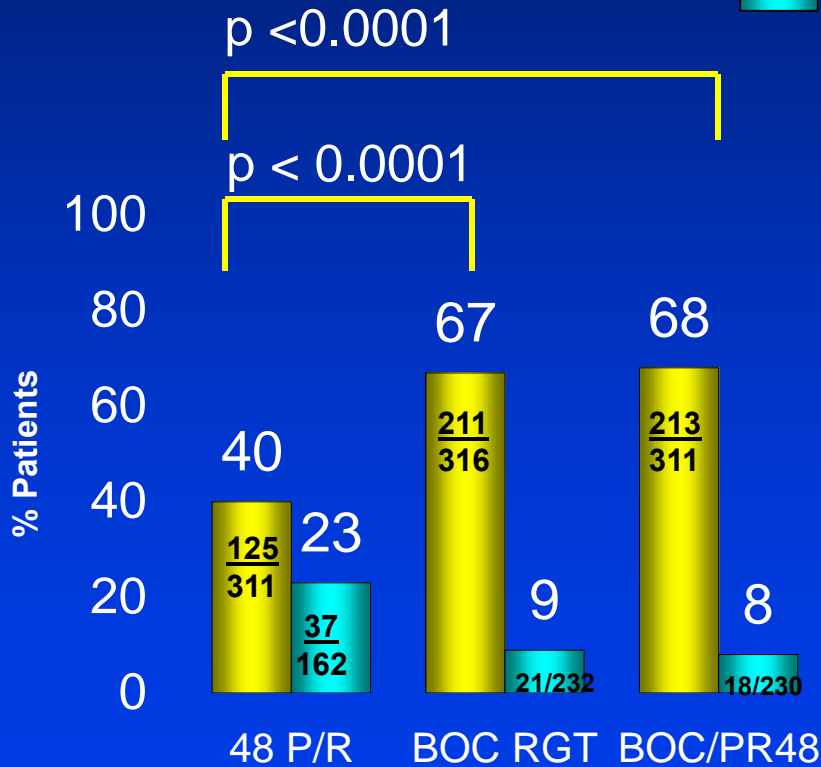


SVR*



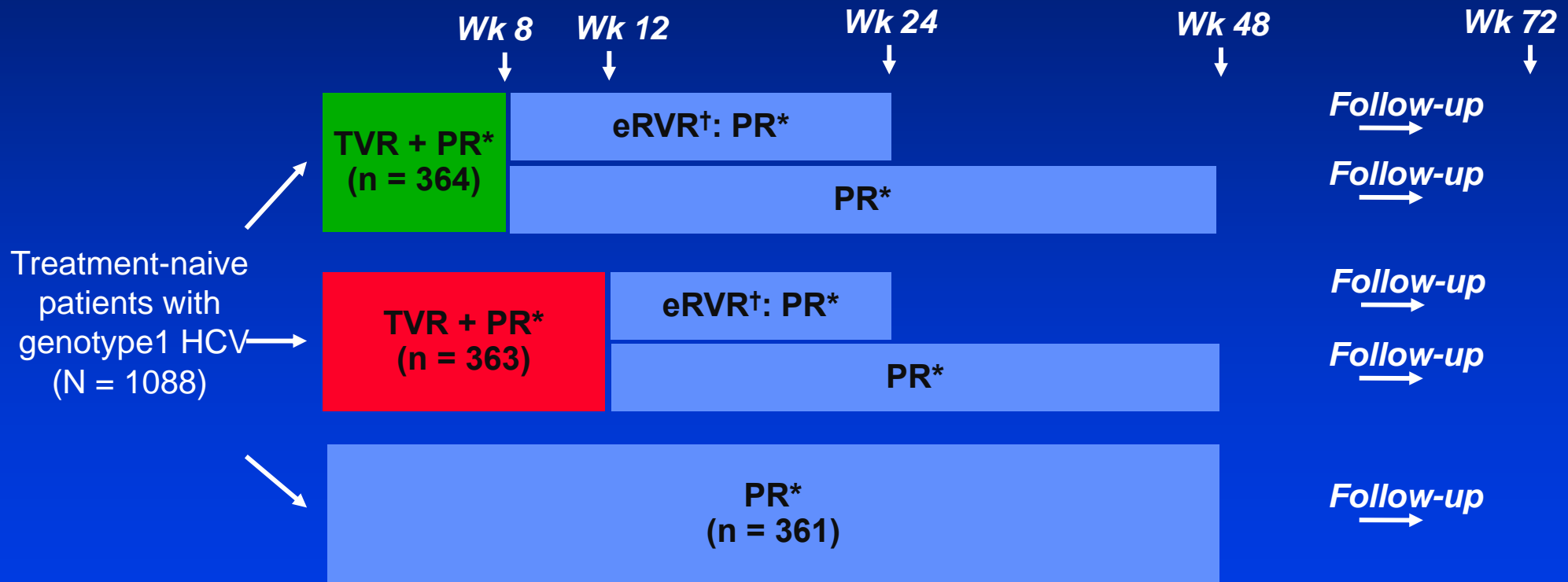
Relapse Rate

Cohort 2: African American



Phase III ADVANCE: Telaprevir + PegIFN/RBV in GT1 Tx-Naive Patients

- Randomized, placebo-controlled trial

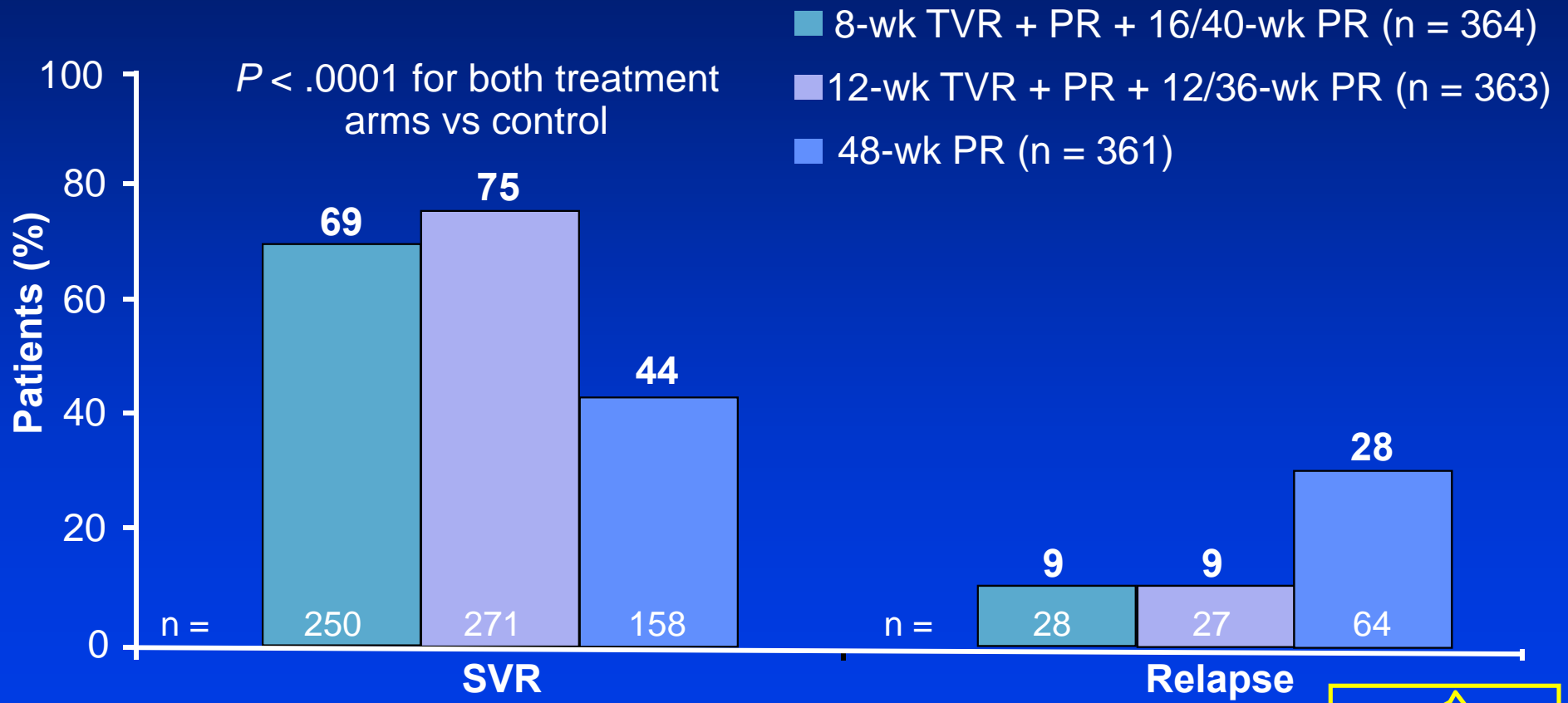


*TVR 750 mg q8h; pegIFN alfa-2a 180 µg/wk; weight-based RBV 1000-1200 mg/day.

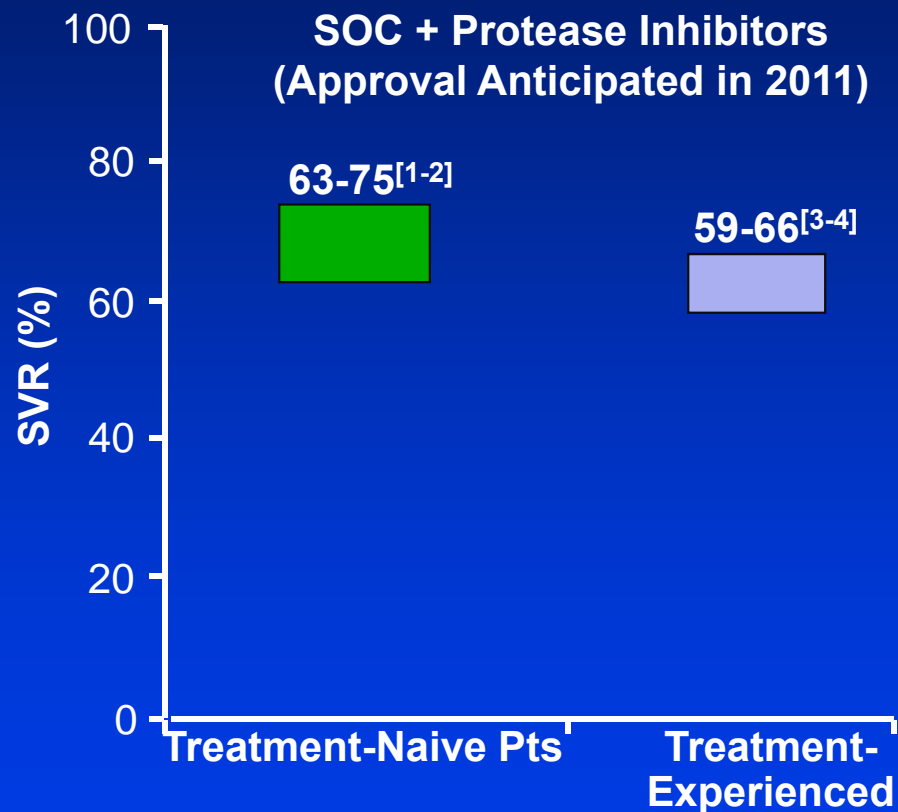
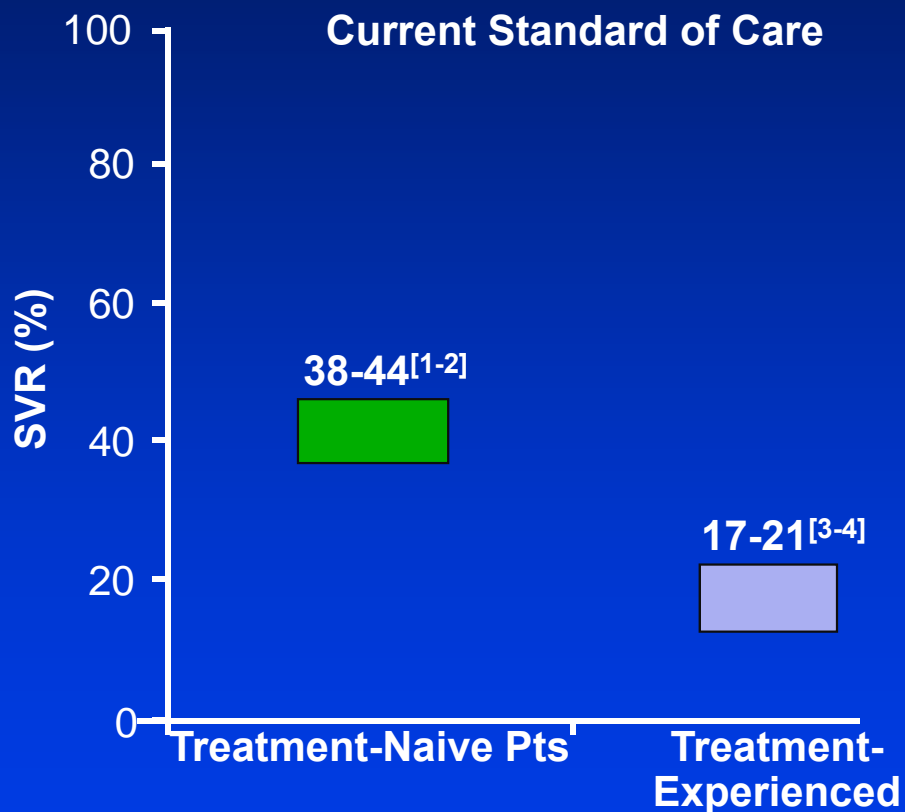
†eRVR: extended rapid virologic response = undetectable HCV RNA at Wks 4 and 12 (<25U/ml).



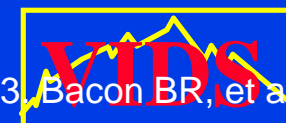
ADVANCE: Overall SVR and Relapse Rates



SVR Rates With BOC and TPV in GT1 Treatment-Naive and -Experienced Pts



1. Poordad F, et al. AASLD 2010. Abstract LB-4. 2. Jacobson IM, et al. AASLD 2010. Abstract 211. 3. Bacon BR, et al. AASLD 2010. Abstract 216. 4. Foster GR, et al. APASL 2011. Abstract 1529.

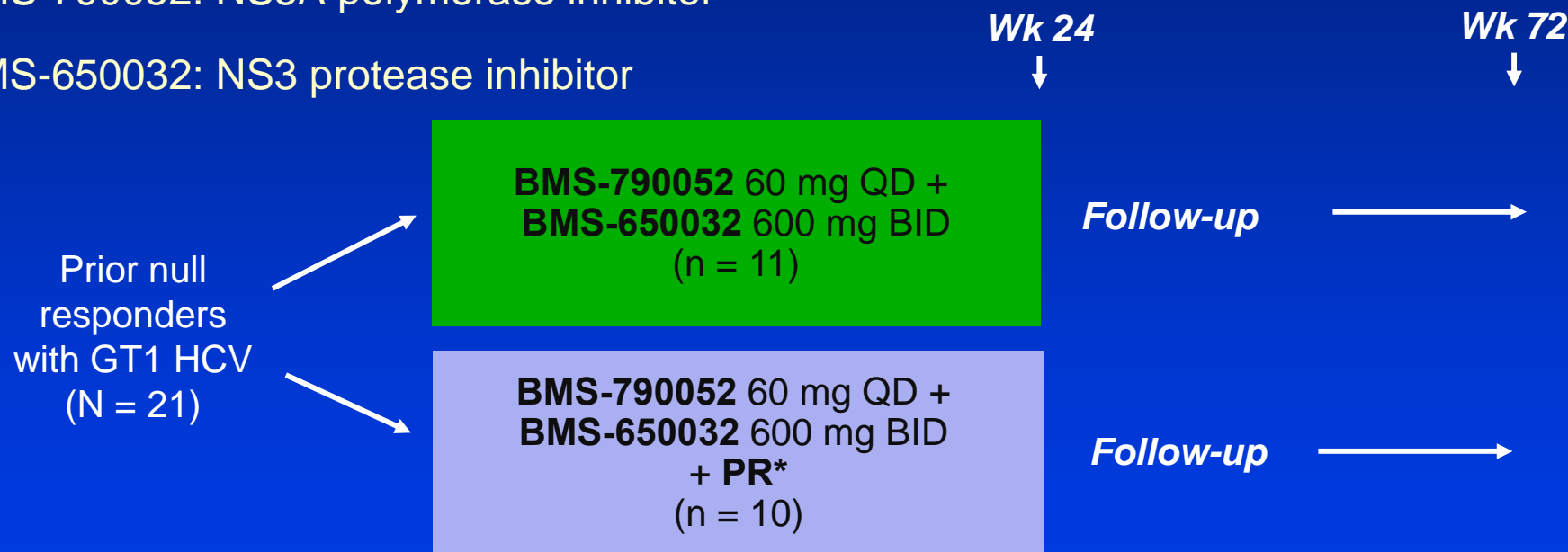




VIDS

BMS-790052 + BMS-650032 Alone or With PegIFN/RBV in GT1 Null Responders

- Open-label, randomized, placebo-controlled phase IIa trial
- BMS-790052: NS5A polymerase inhibitor
- BMS-650032: NS3 protease inhibitor



*PegIFN alfa-2a 180 µg/wk; weight-based RBV 1000-1200 mg/day.

Abstract #1356. Lok et.al.



Results

	Group A	Group B
% RVR	64	60
% eRVR (w4+12)	36	60
% cEVR	46	90
% ETR	46	100
% SVR12	36	100
% SRV24	36	90*

Abstract #1356. Lok et.al.



Please Refer !

Dr Tom Schultz
Shepparton Medical Centre
Melbourne University Rural Clinical School
49 Graham Street
Shepparton

Call 5823 3100 for appointment



Thank You

