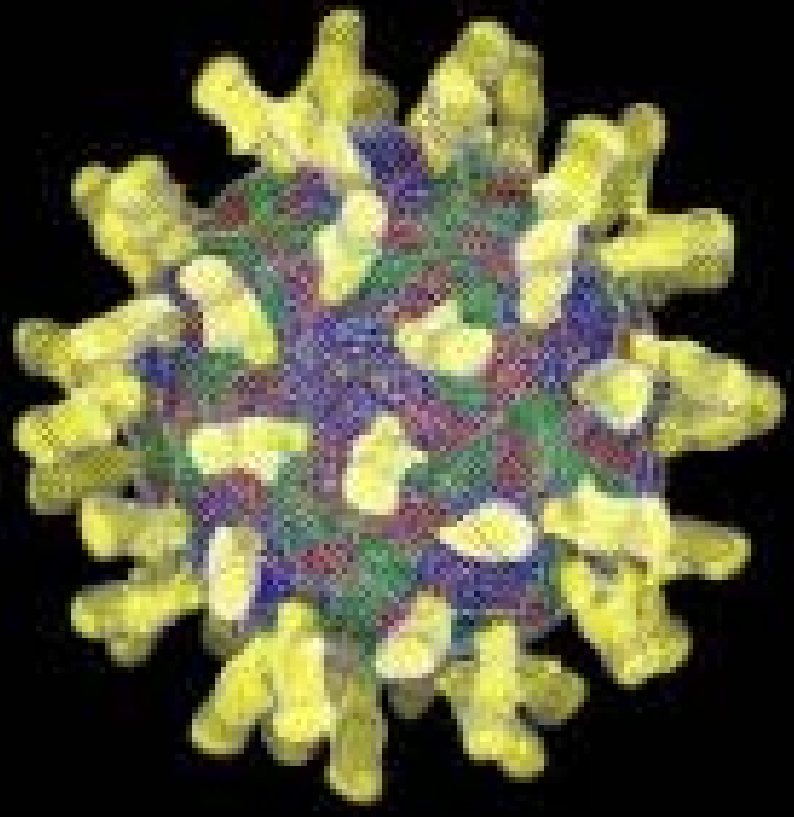
Future HCV Treatment:

Interferon-sparing Combination DAA therapy



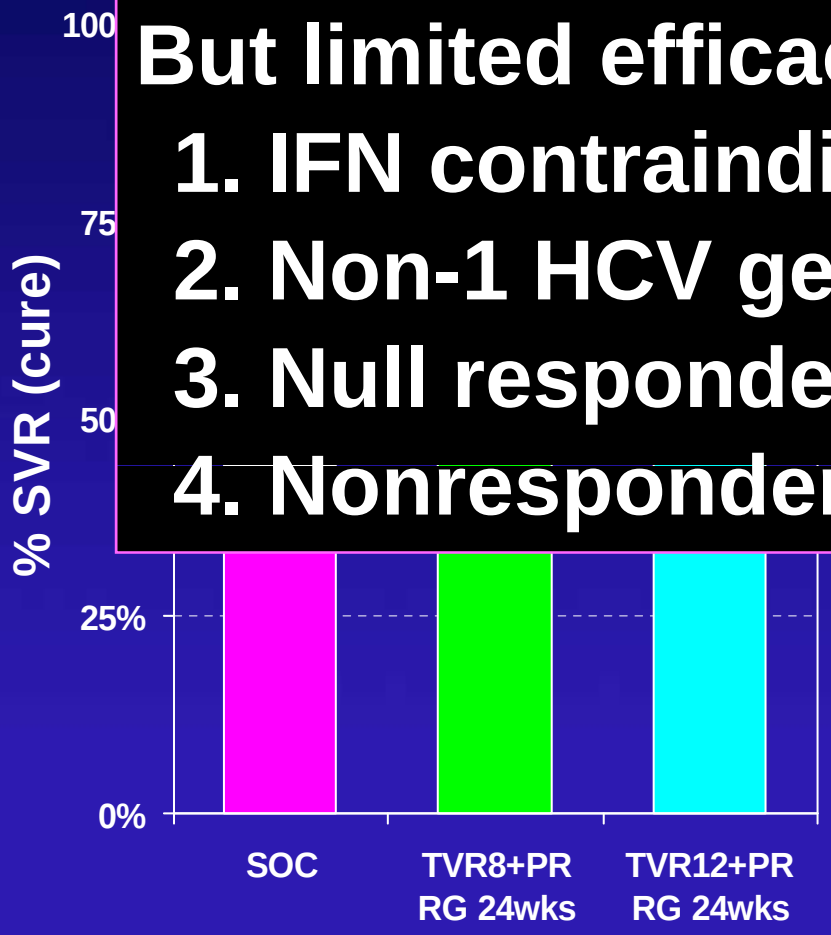
Ed Gane
NZ Liver Transplant Unit

Protease Inhibitor plus Peg-IFN/RBV
Triple Therapy in Treatment-Naïve Gt1

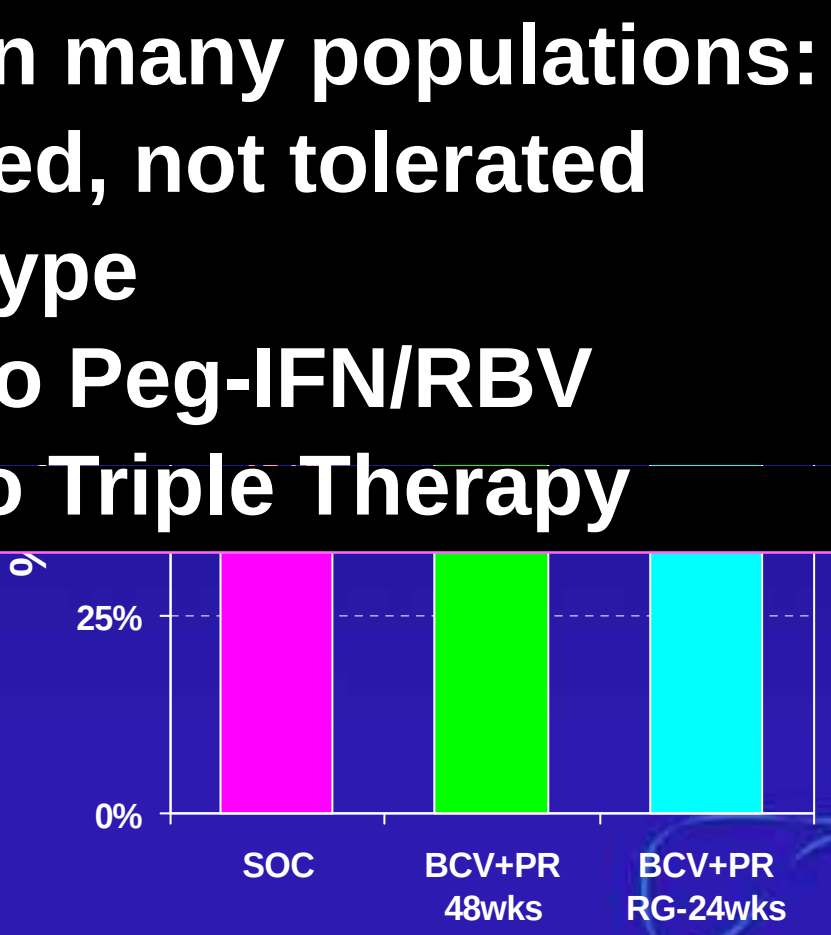
Triple Therapy ➡ new Standard-of-Care

But limited efficacy in many populations:

1. **IFN contraindicated, not tolerated**
2. **Non-1 HCV genotype**
3. **Null responders to Peg-IFN/RBV**
4. **Nonresponders to Triple Therapy**



Jacobson I, et al. *Hepatology* 2010; 52: 427A



Poordad F, et al. *Hepatology* 2010; 52: LB4

What about Combining two Direct Antivirals?

The INFORM-1 Study
Combination therapy with a nucleoside polymerase (RG7128) and protease inhibitor (danoprevir) in HCV

EJ Gane, SK Roberts, CA Stedman, PW Angus, B Ritchie, R Elston, D Ipe, PN Morcos, I Najera, T Chu, MM Berrey, WZ Bradford, NS Shulman, PF Smith

Auckland Clinical Studies, Auckland, New Zealand; The Alfred, Melbourne, Australia: Christchurch Clinical Studies, Christchurch, New Zealand; Austin Hospital, Heidelberg, Australia; Royal Adelaide Hospital, Adelaide, Australia; Roche Palo Alto LLC, Palo Alto, CA; Pharmasset, Inc., Princeton, NJ; Intermune, Inc., Brisbane, CA, USA

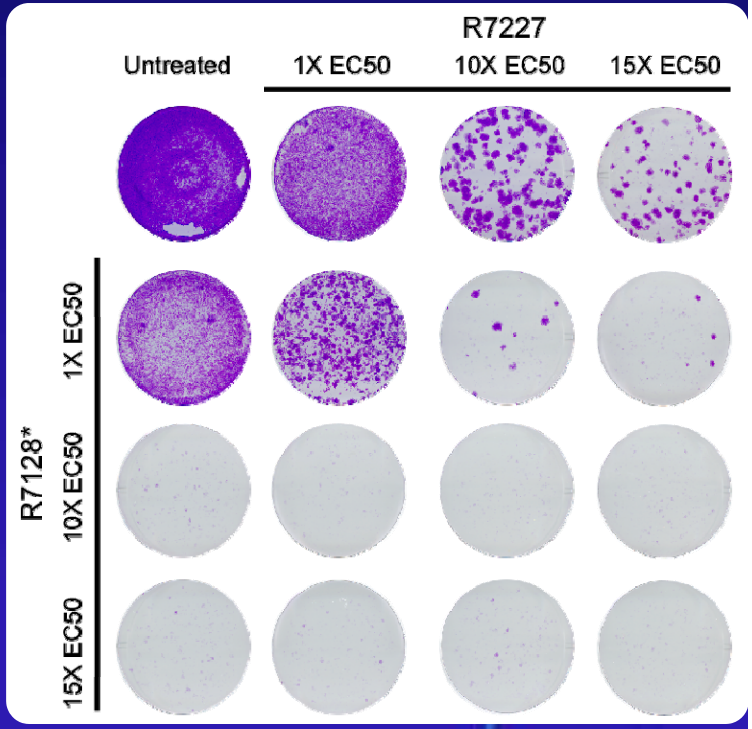
Gane E, et al. *Lancet* 2010; 376: 1467-75

Will adding Polymerase Inhibitor to the Protease Inhibitor prevent resistance?

- **Different mechanisms of action:**
  - » RG7128 is a Nucleoside Polymerase inhibitor
  - » Danoprevir is an NS3/4A protease inhibitor
  - ➡ No cross-resistance
- ***in vitro* Replicon Model**
  - » No resistance

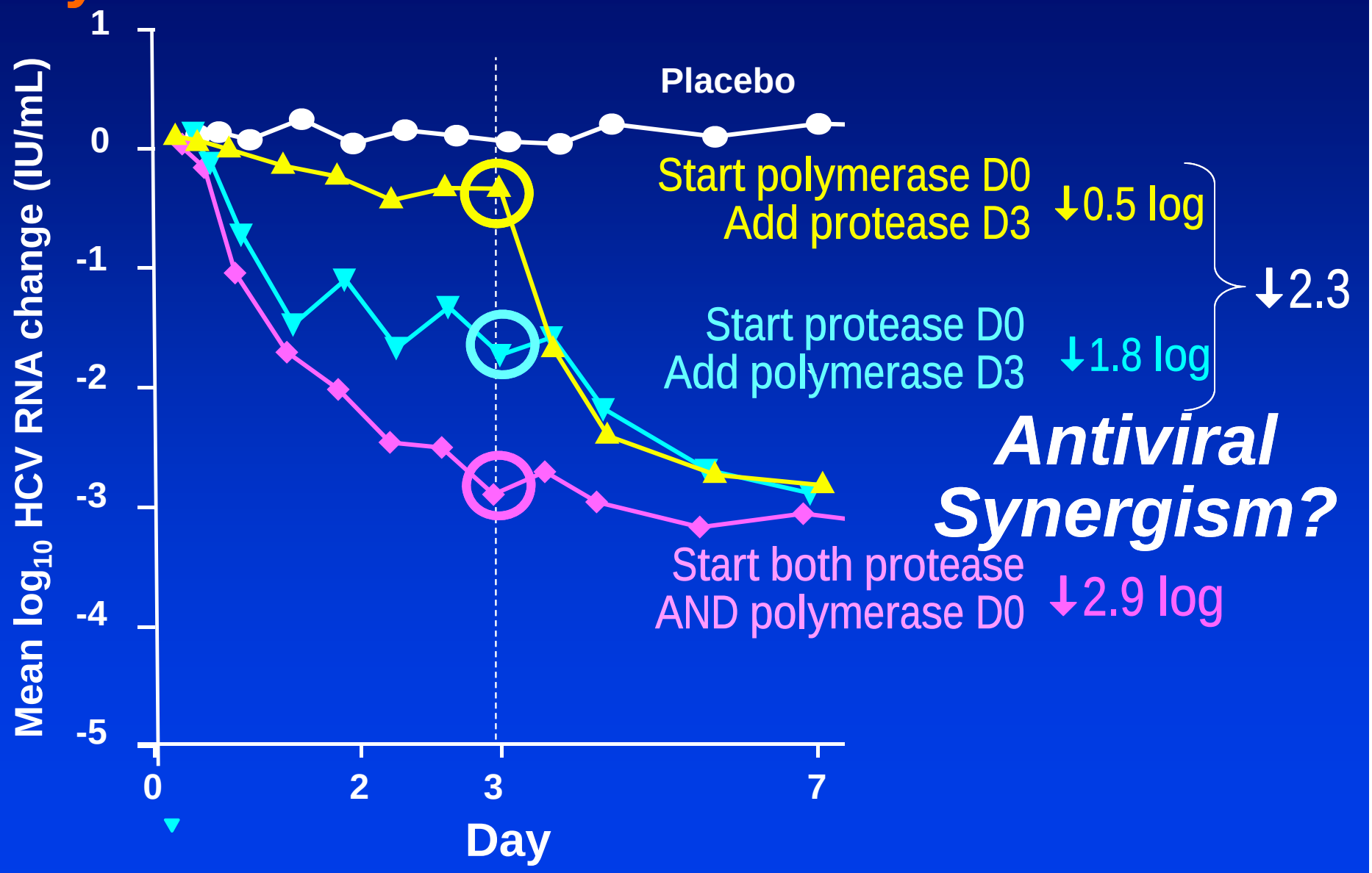
Tan. AASLD 2008; A 1885

- **In the INFORM-1 Study**
  - – 74 pts treated for 14 days
  - – No viral breakthrough
  - – No resistance mutations in NS3 or NS5B regions

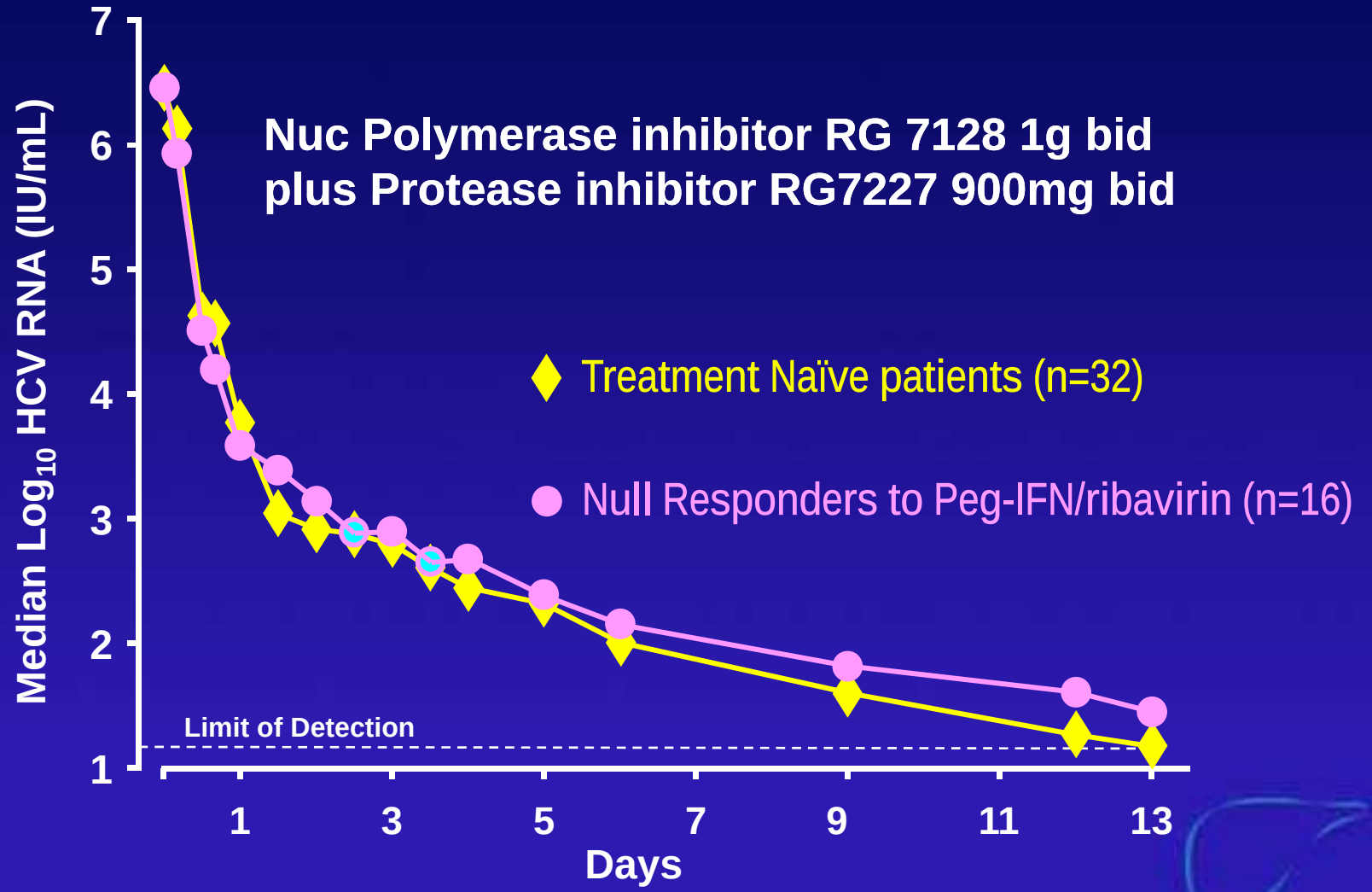


Gane E, et al. *Lancet* 2010; 376: 1467-75

Will combining protease inhibitor with polymerase inhibitor better than either alone?

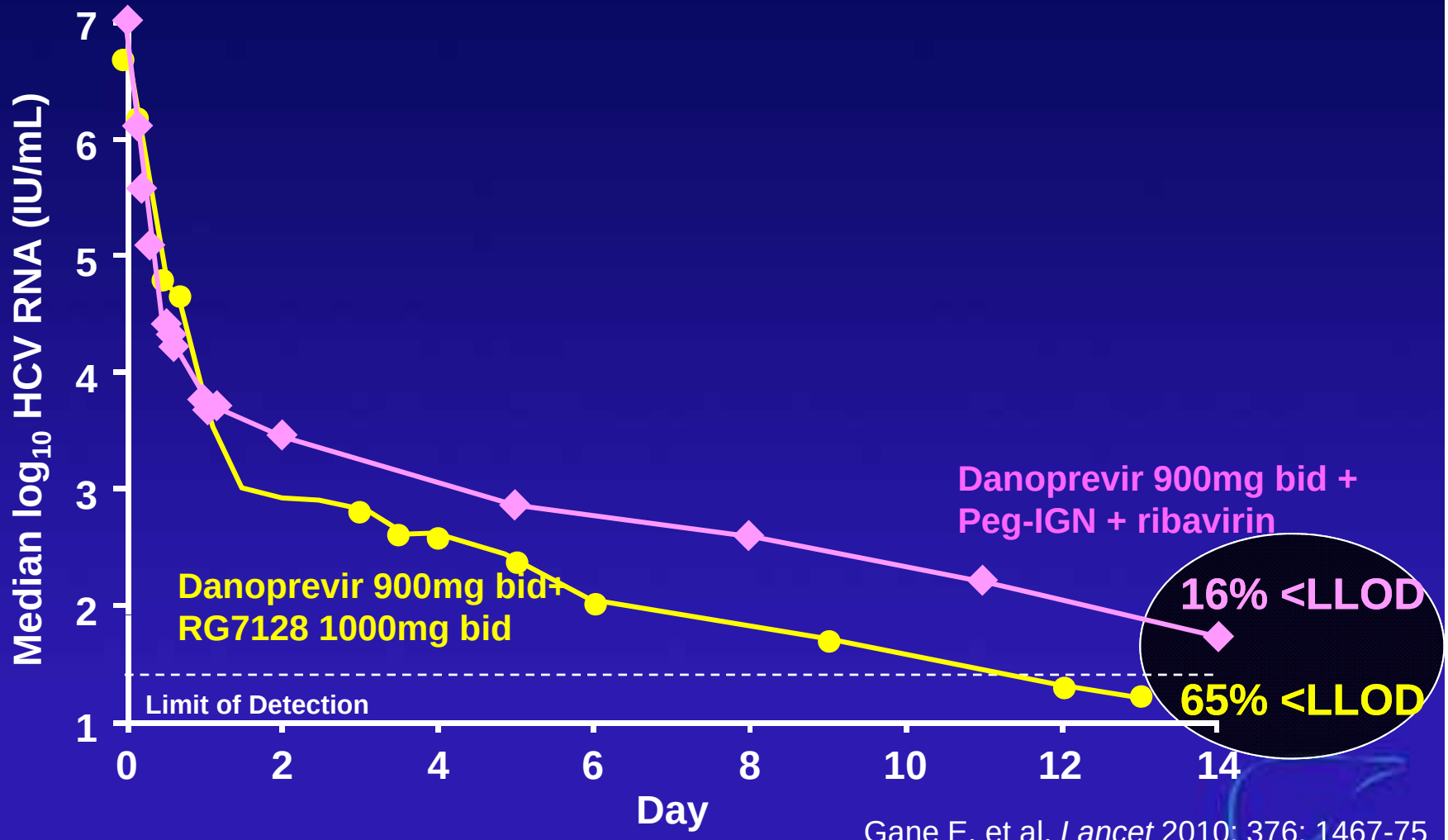


Will adding a combination DAA be as effective in previous nonresponders?



Gane E, et al. *Lancet* 2010; 376: 1467-75

Will Protease plus Polymerase inhibitor be better than Protease plus Peg-IFN/RBV?

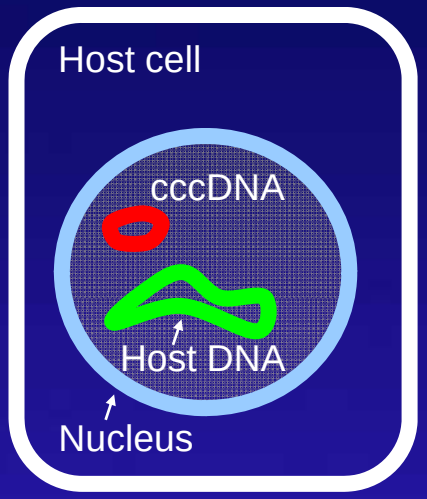


Gane E, et al. *Lancet* 2010; 376: 1467-75

Forestier et al. *J Hepatol* 2009;50: A1847

Will Combination Direct Acting Antiviral agents cure HCV without IFN?

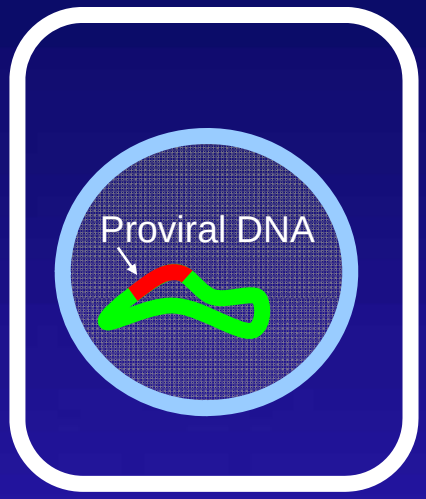
HBV



TREATMENT

Lifelong suppression of HBV replication[1]

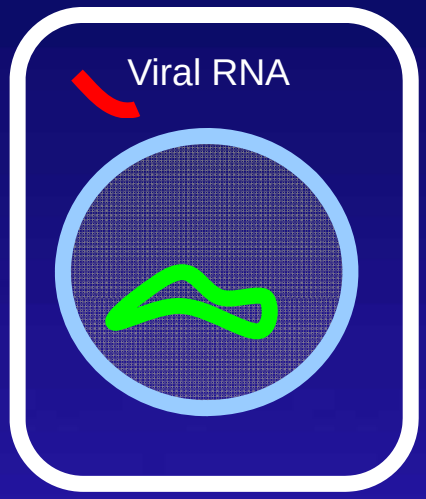
HIV



TREATMENT

Lifelong suppression of HIV replication[2]

HCV



TREATMENT

No reservoir of infection

↓

HCV clearance

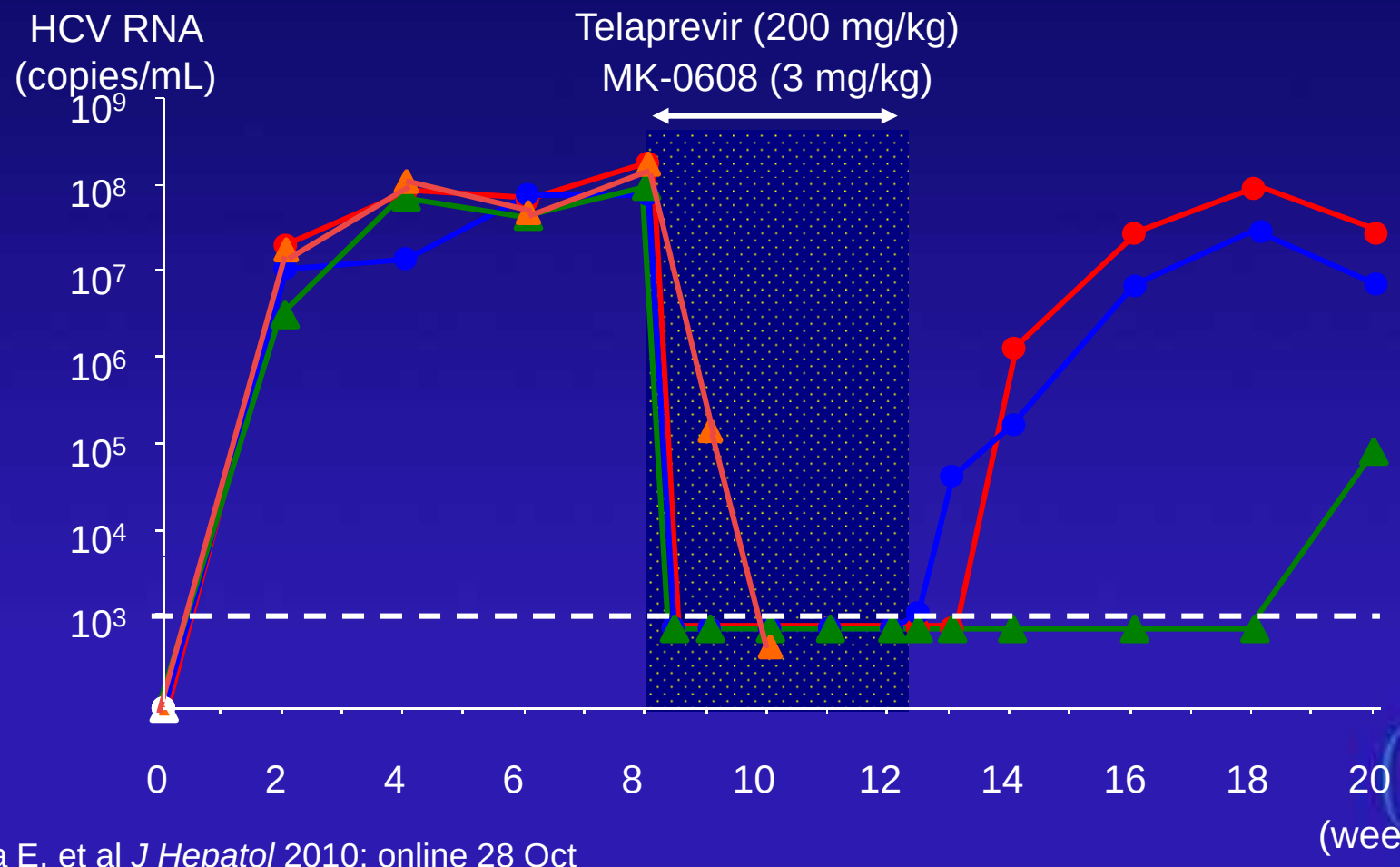
↓

CURE

1. Pawlotsky JM. *J Hepatol* 2006;44:S10-S13;
2. Siliciano JD, Siliciano RF. *J Antimicrob Chemother* 2004;54:6-9;

Will Combo DAAs cure HCV without IFN?

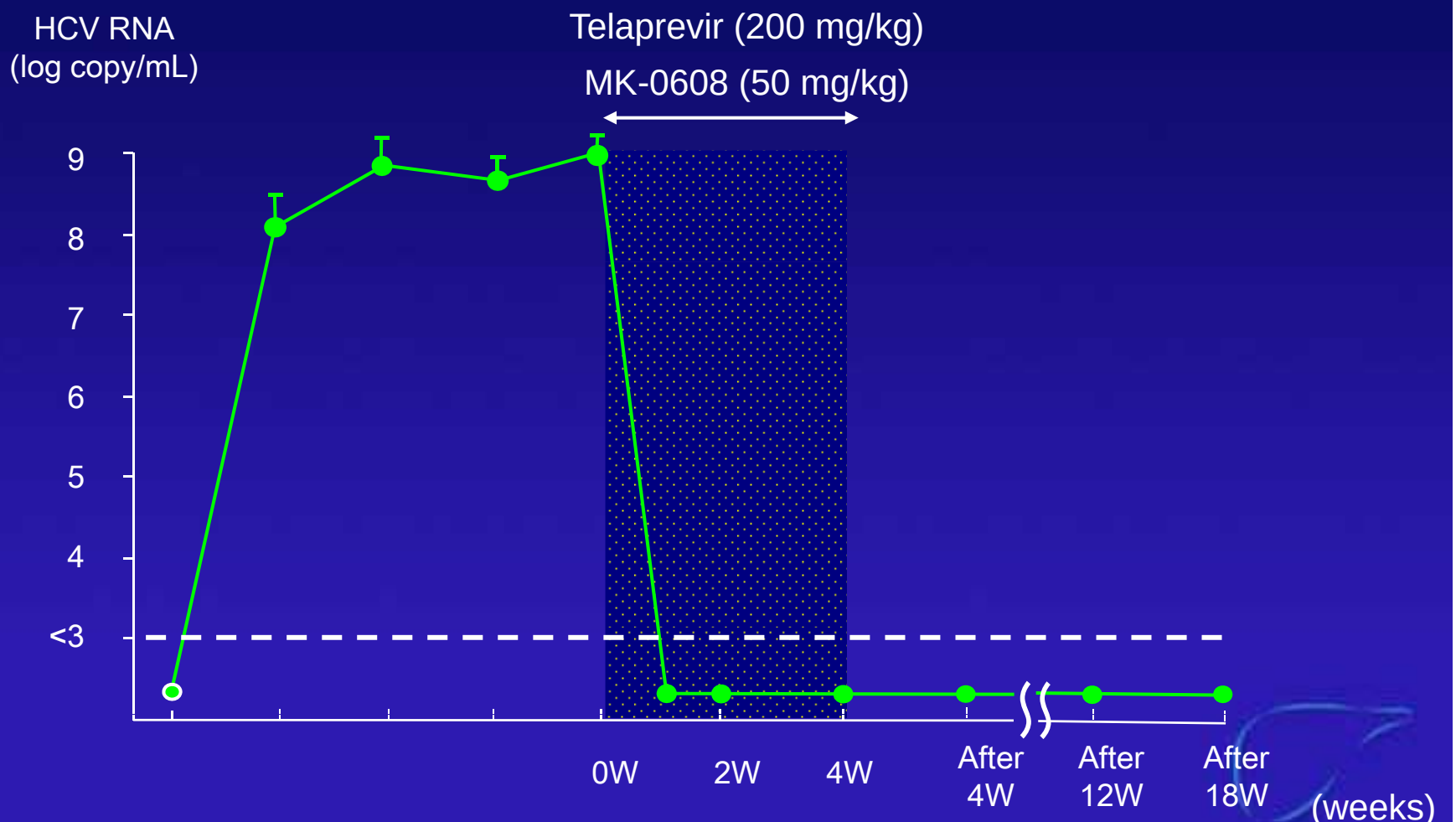
- Human hepatocyte chimeric mice infected with Gt1b
- Telaprevir plus low-dose Nuc polymerase inhibitor MK-0608 prevents rebound in 4/4 mice



Ohara E, et al *J Hepatol* 2010; online 28 Oct

Will Combo DAAs cure HCV without IFN?

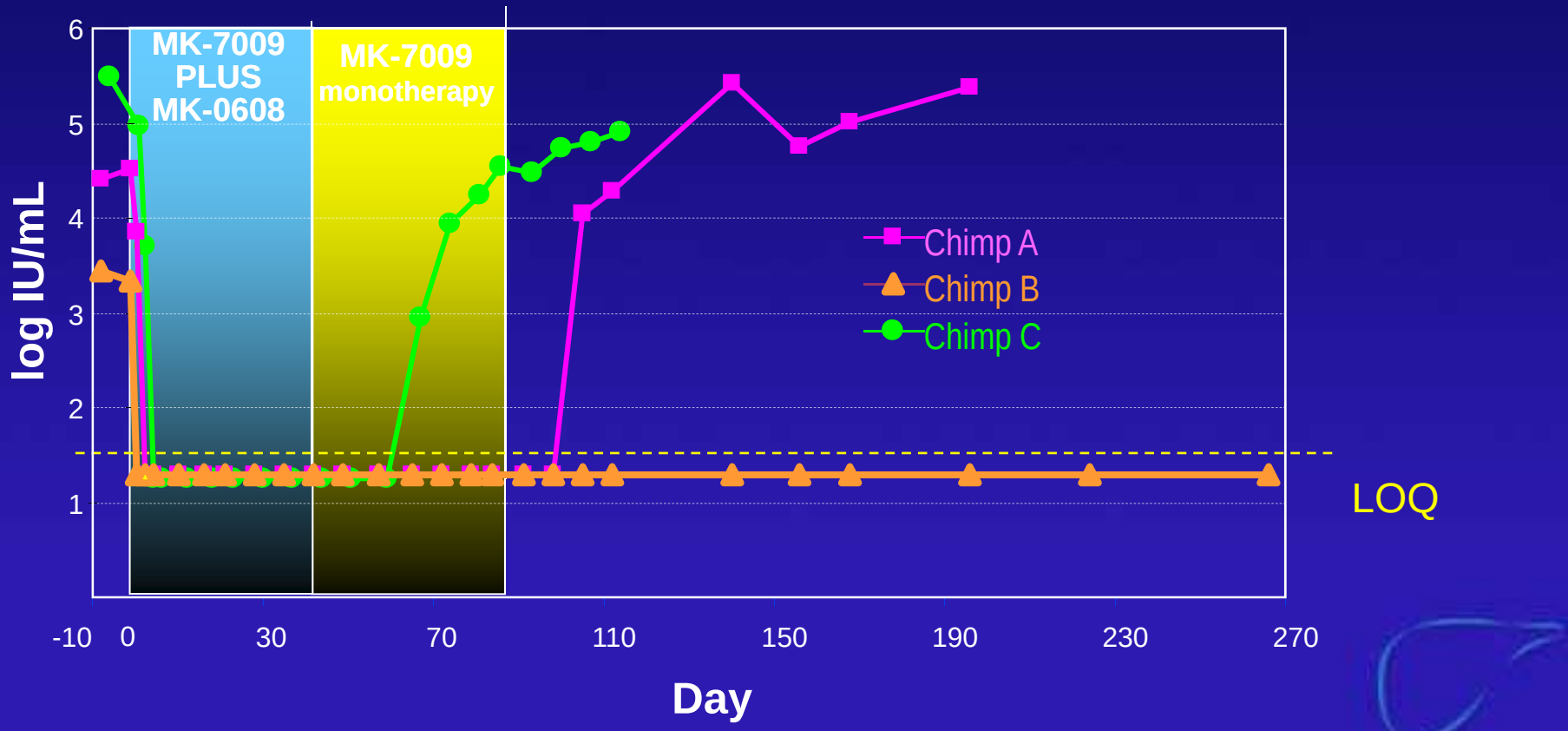
- 28 days Telaprevir plus **high-dose** MK-0608 **eradicates HCV infection** in 5/5 mice



Ohara E, et al *J Hepatol* 2010; online 28 Oct

Will Combo DAAs cure HCV without IFN?

- 35 days MK-7009 (protease inhibitor) plus MK-0608 (Nuc polymerase) **eradicates HCV** in 1/3 chimps



Merck On File

What duration of combination DAA will be needed to eradicate HCV in patients?

- Typical HCV patient:
  - »Baseline VL = 10^6 virions/ml
  - »Total Body Water = 15 litres
  - »Total viral burden = 10^{11} virions

➡ Eradication *(<1 virus)* =11 log reduction

- Combination R7128/R7227:
  - »1st Phase: ~3.5 Logs in 1.5 days
  - » 2nd Phase: ~1 log per week

➡ **Duration of Therapy 8-10 wks**

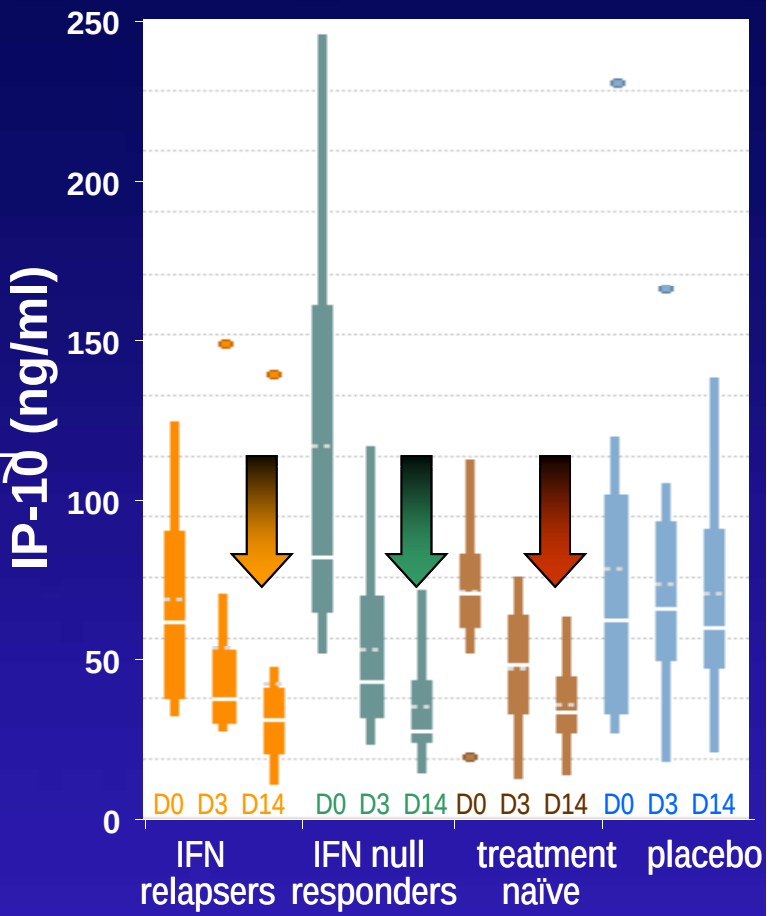
Will Combo DAAs cure HCV without IFN?

- HCV impairs immune response
  - »NS3/4A inhibits TLR-3 signaling and IRF-3 translocation
    - restored by protease inhibitors
  - »NS5A inhibits PKR activation and induces IL8 production

Sklan *Gastro & Hepatol* 2009;6:217-227

- **HCV increases IP-10 levels**
  - ⇨exhausts endogenous IFN
  - »rapidly normalise with DAA

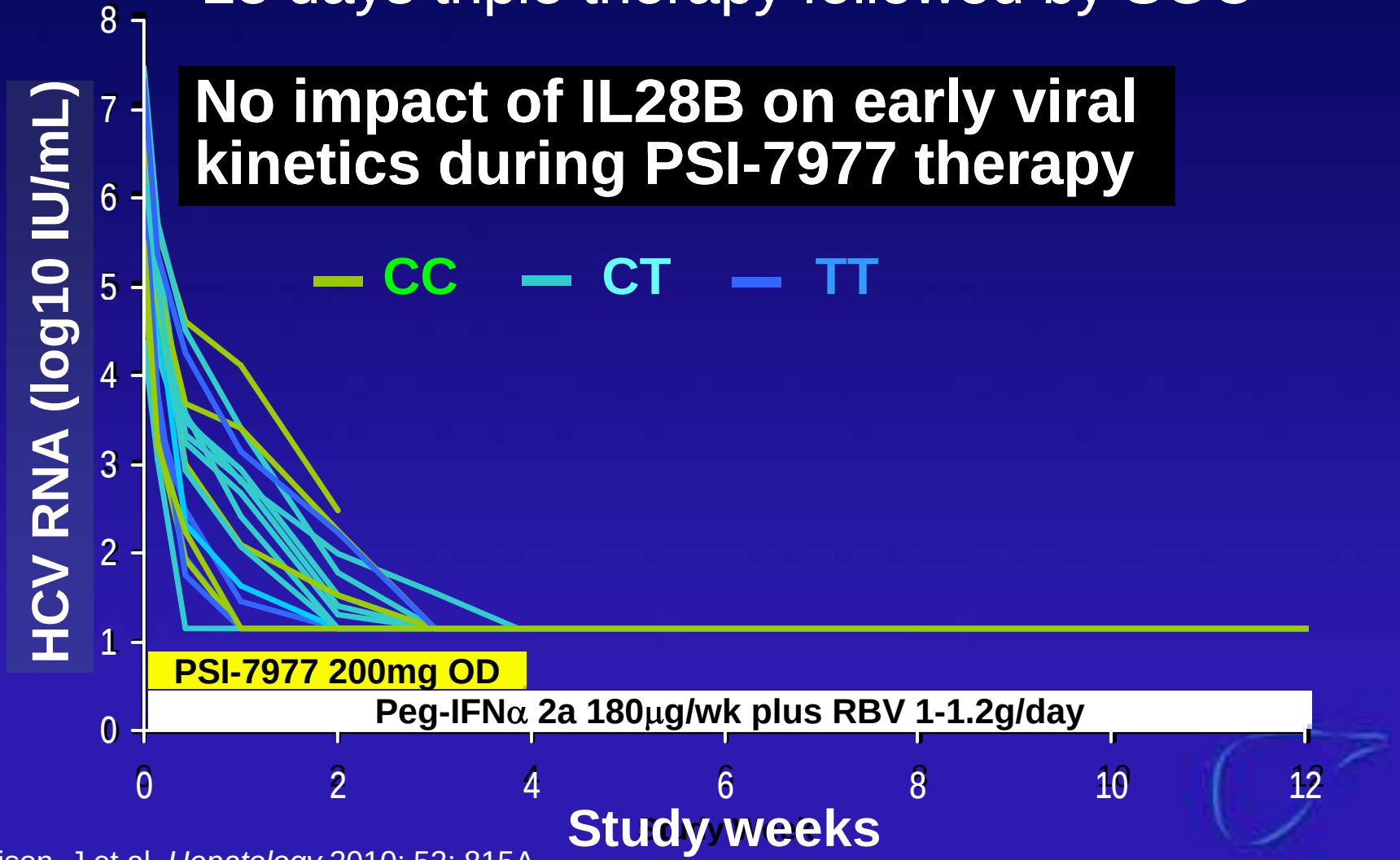
Gane *Lancet* 2010; 376: 1467-75



- **Will profound viral suppression reconstitute host immunity?**

Will IL28B influence response to DAA?

- Phase 2a study of PSI7977 200mg OD
  - »28 days triple therapy followed by SOC



McHutchison, J et al. *Hepatology* 2010; 52: 815A

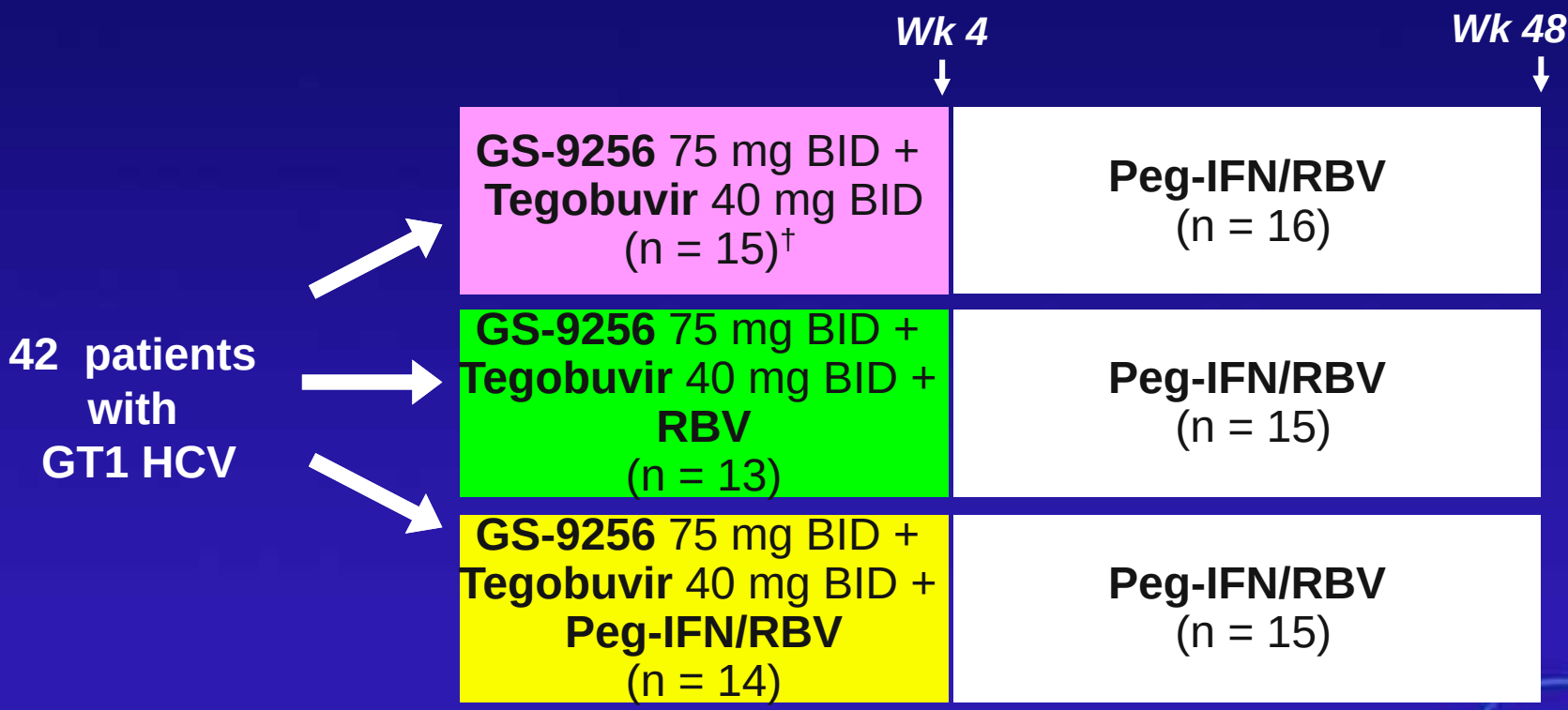
Planned Combination DAA trials in HCV GT1 Infection

DAA (1) NS3/4a Protease	DAA (2) NS5B Polymerase
NS3 protease inhibitor (Telaprevir)	Nonnucleoside NS5B inhibitor (VX-222)
NS3 protease inhibitor (GS9256)	Nonnucleoside NS5B inhibitor (GS9190)
NS3 protease inhibitor (BI201335)	Nonnucleoside NS5B inhibitor(BI297127)
NS3 protease inhibitor (ABT-450)	Nonnucleoside NS5B inhibitor (ABT-072)
NS3 protease inhibitor (ABT-450)	Nonnucleoside NS5a inhibitor
NS3 protease inhibitor (MK-7009)	Nonnuc polymerase inhibitor (MK-3281)
NS3 protease inhibitor (BMS650032)	NS5a inhibitor (BMS-790052)

1. Most include arms ± Ribavirin
2. All shorten duration from 48 wks⇨ 12 wks

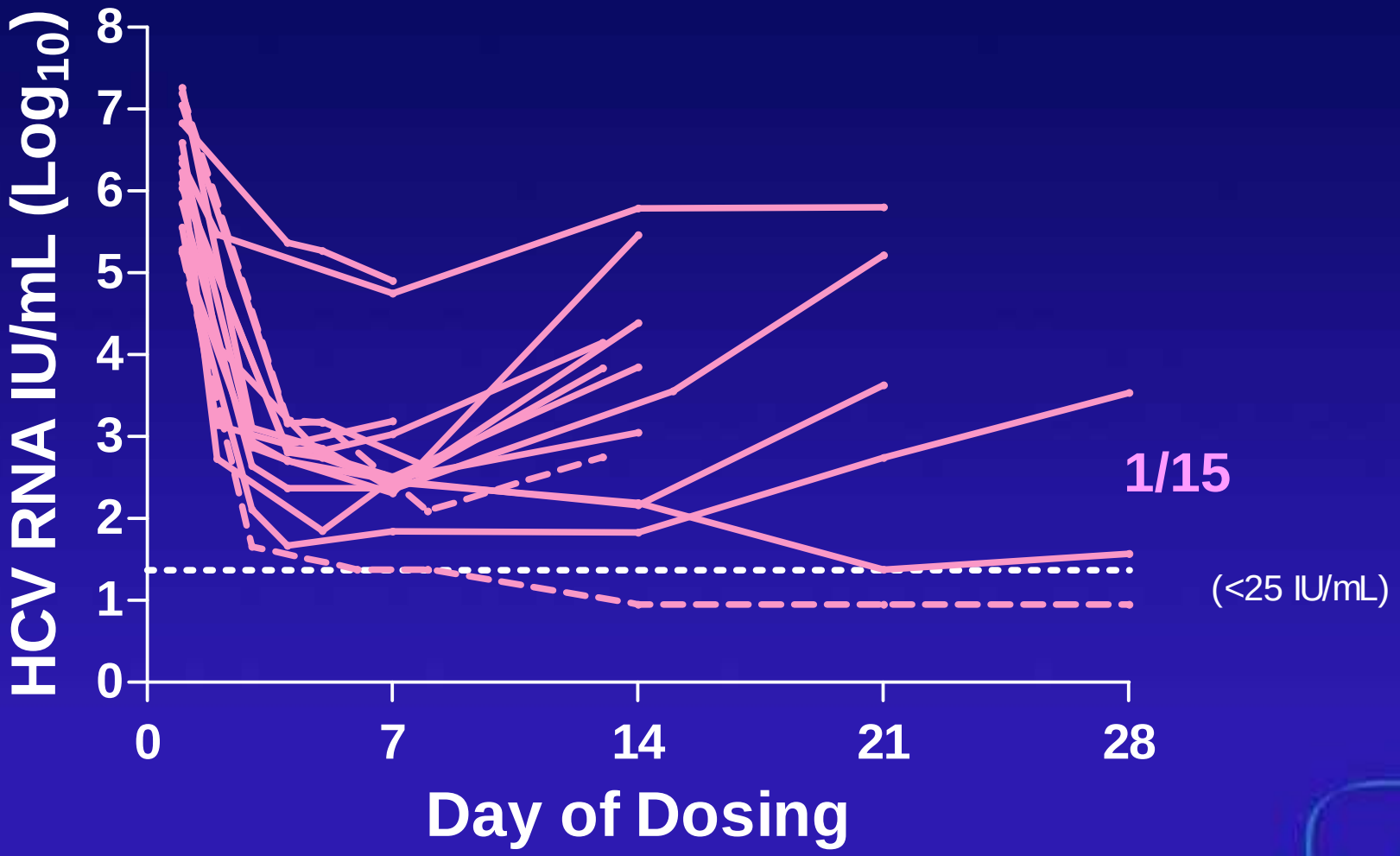
NS3 protease inhibitor GS-9256 plus Non-Nuc NS5B inhibitor Tegobuvir

- Open-label, randomized, placebo-controlled phase IIa trial in treatment-naive HCV GT 1



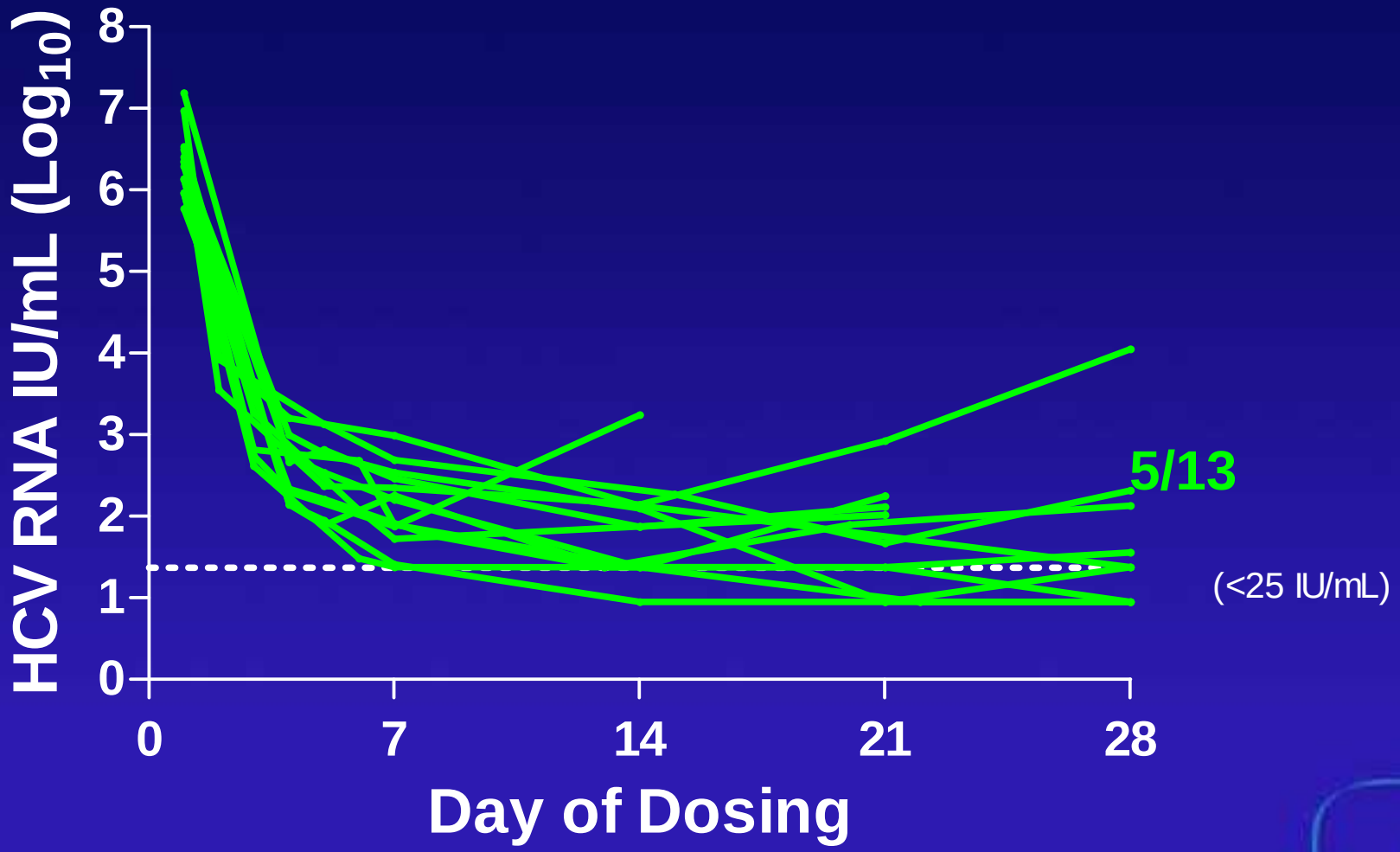
Zeuzem S, et al. *Hepatology* 2010; 52: LB-1.

Antiviral Response
GS-9256 + tegobuvir (Arm 1)



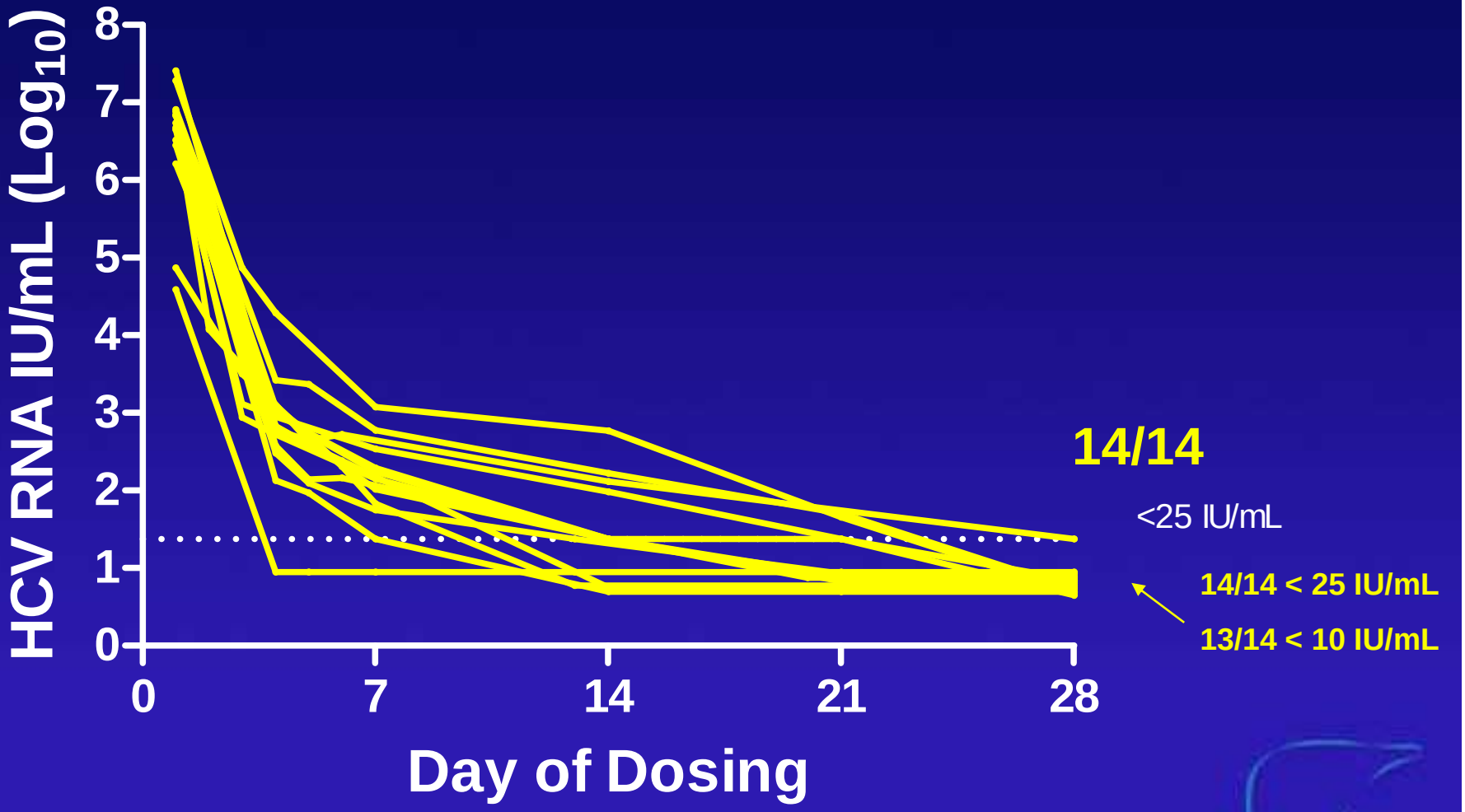
Zeuzem S, et al. *Hepatology* 2010; 52: LB-1.

Antiviral Response
GS-9256 + tegobuvir + RBV (Arm 2)



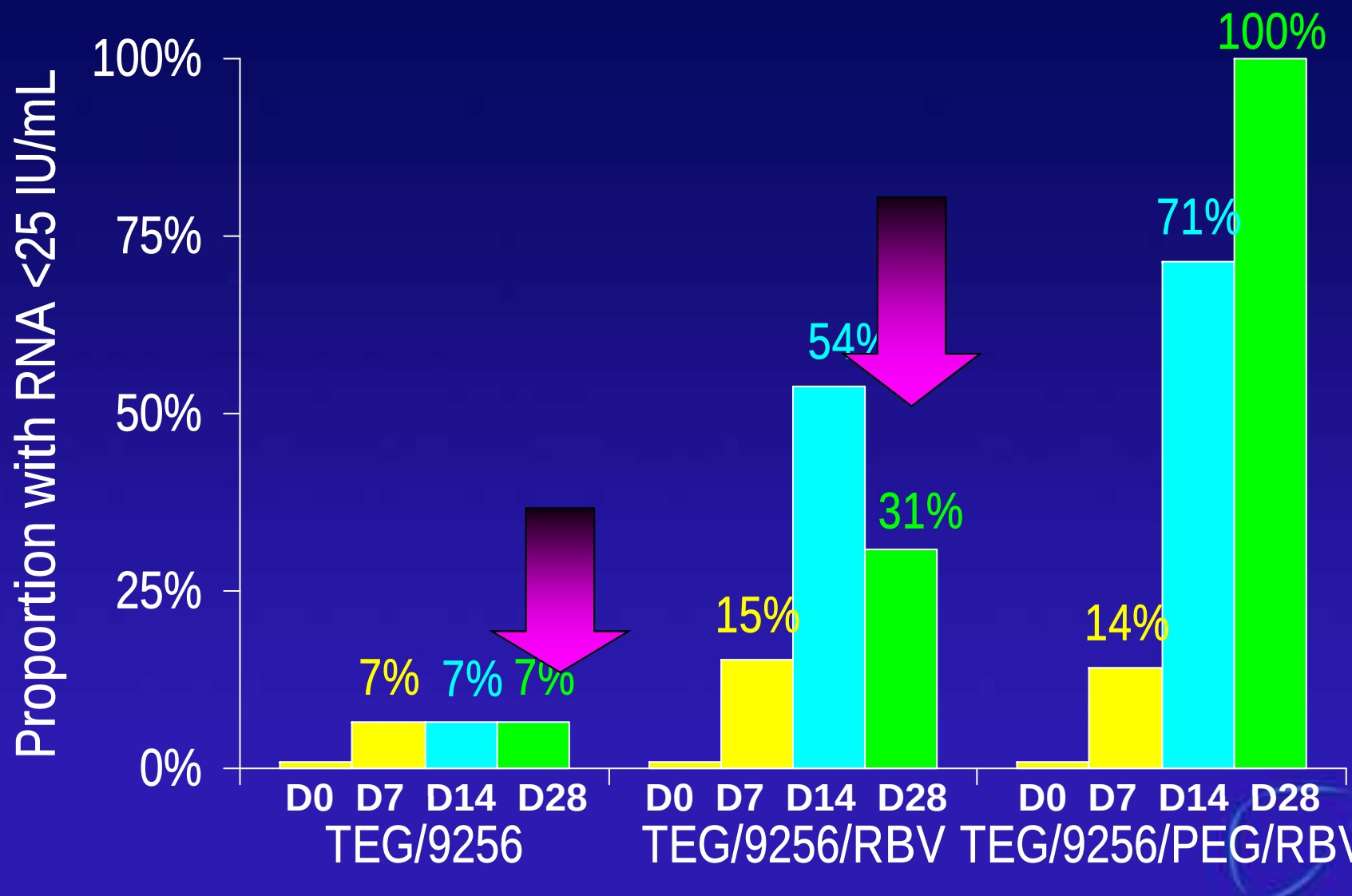
Zeuzem S, et al. *Hepatology* 2010; 52: LB-1.

Antiviral Response
GS-9256 + tegobuvir + PegIFN/RBV (Arm 3)



Zeuzem S, et al. *Hepatology* 2010; 52: LB-1.

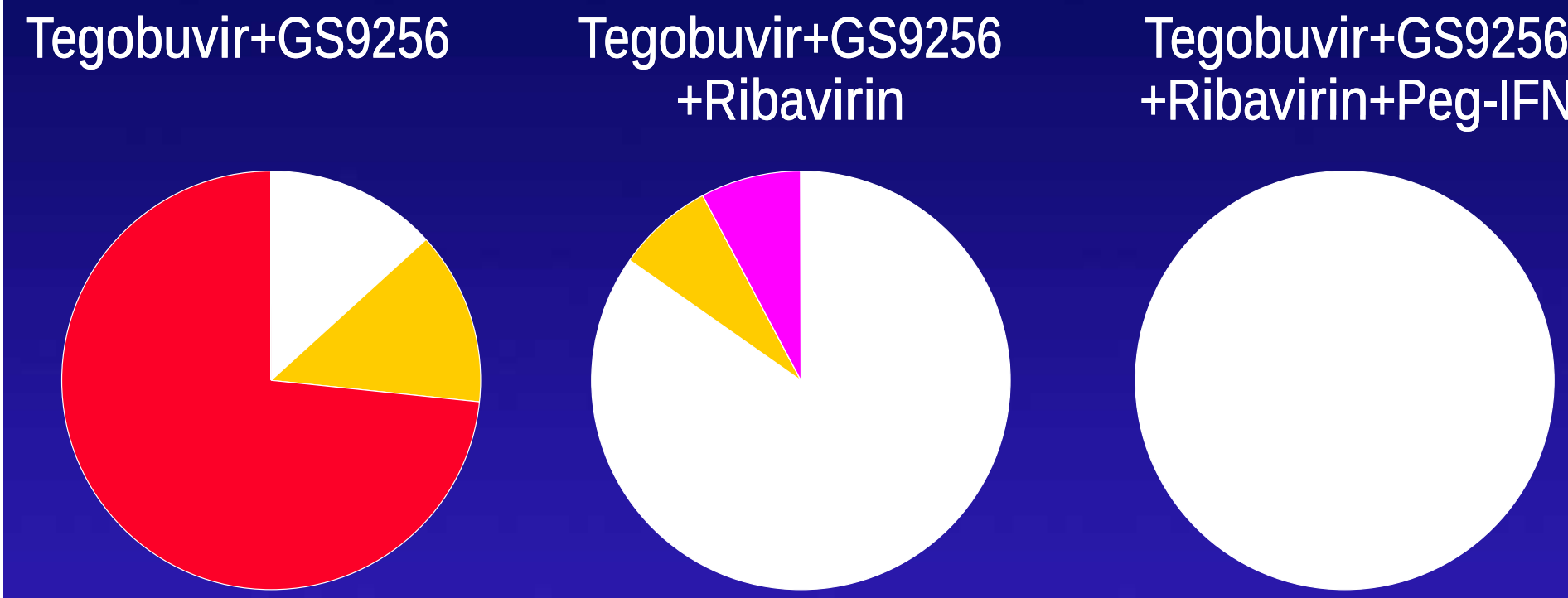
Tegobuvir + GS-9256
Week 4 Interim Analysis



Zeuzem S, et al. *Hepatology* 2010; 52: LB-1.

Tegobuvir + GS-9256 in HCV GT1 Resistant mutations

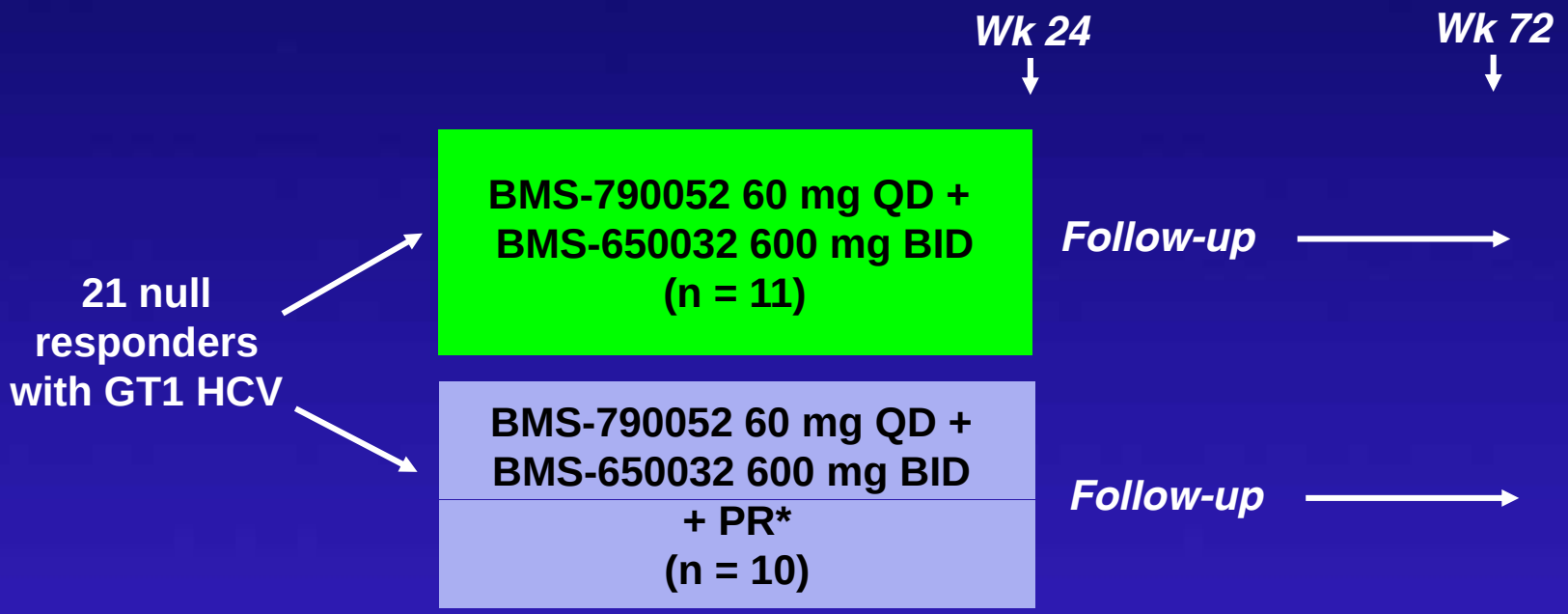
- Population sequencing for NS3 and NS5b



Zeuzem S, et al. *Hepatology* 2010; 52: LB-1.

NS3 protease inhibitor BMS-650032 plus NS5A inhibitor BMS-790052

- Open-label, randomized, placebo-controlled phase IIa trial in HCV GT 1 prior null-responders

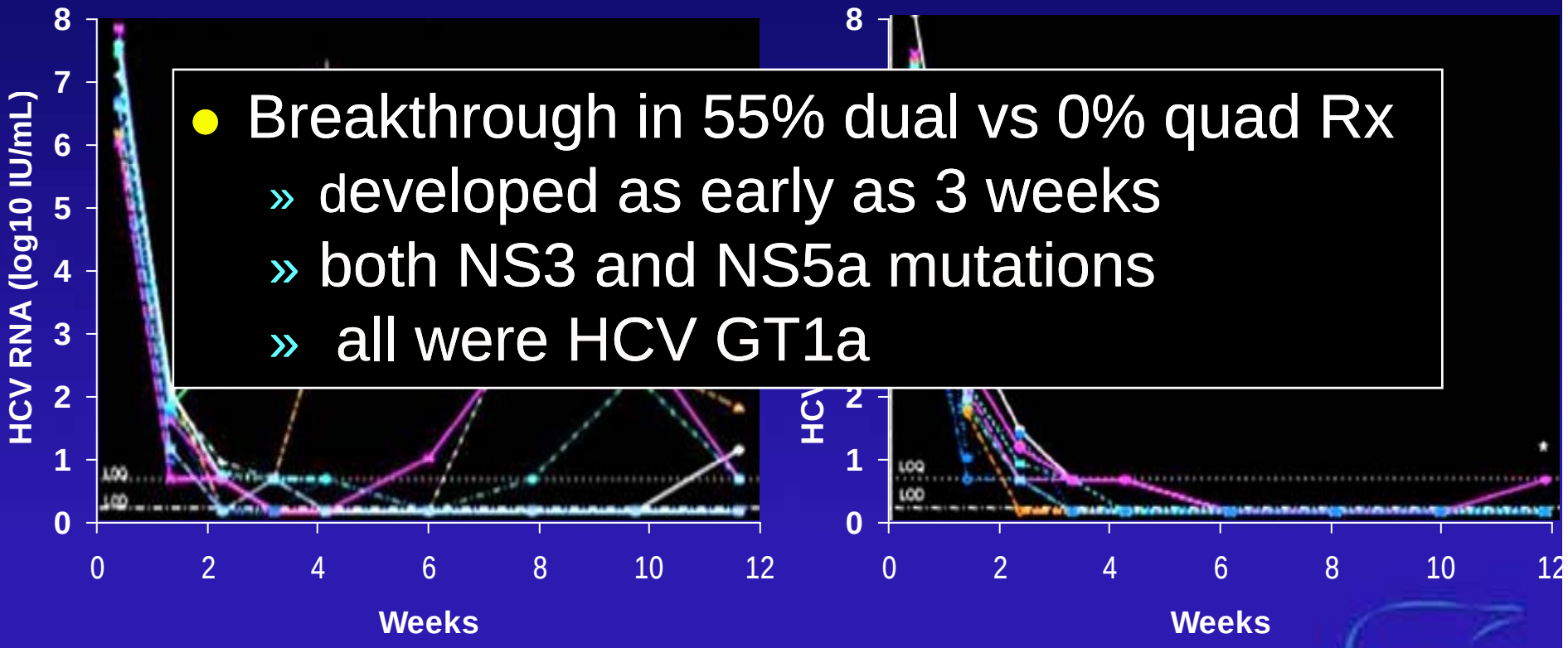


Lok A, et al. *Hepatology* 2010; 52: 877A. Abstract LB-8.

NS3 protease inhibitor BMS-650032 plus NS5A inhibitor BMS-790052

Group A
BMS-790052/BMS-650032

Group B: Peg-IFN+RBV+
BMS-790052/BMS-650032



- Breakthrough in 55% dual vs 0% quad Rx
  - » developed as early as 3 weeks
  - » both NS3 and NS5a mutations
  - » all were HCV GT1a

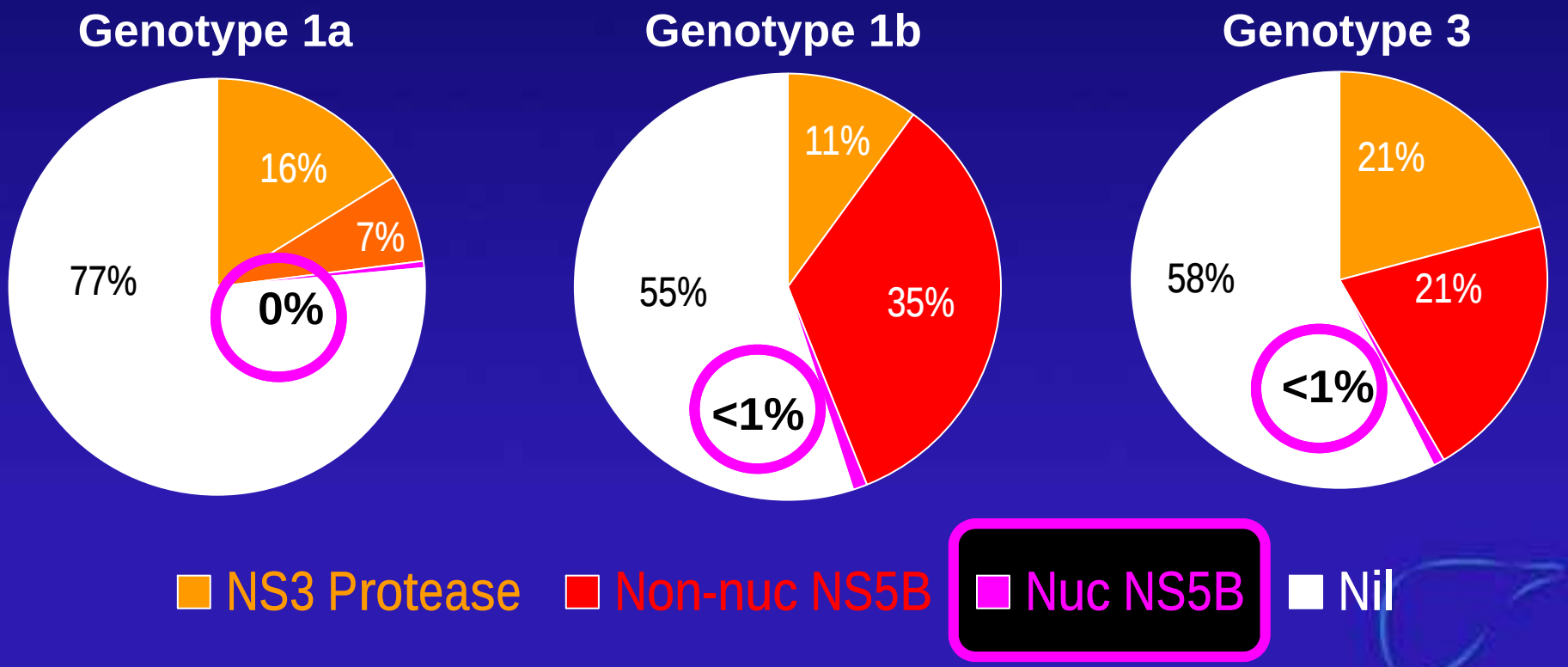
Lok A, et al. *Hepatology* 2010; 52: 877A. Abstract LB-8.

Potential Pitfalls for DAA Combinations

- Overlapping toxicities
- Drug-drug interactions (esp PIs, ritonivir)
- High pill burden ⇨non-adherence
- Reduced activity across target population
  - »Genotype 1a vs. 1b
  - »Genotypes 2 vs. 3
- Low barrier to resistance
  - »Low antiviral potency
  - »Low binding affinity for target
  - »Pre-existing single and double mutants

in vivo Resistance to DAAs
Prevalence in untreated population

- NS3 and NS5b sequences from 405 treatment-naïve pts, sequenced for known drug resistance mutations
- frequency of mutations ranged from 0.5-5%



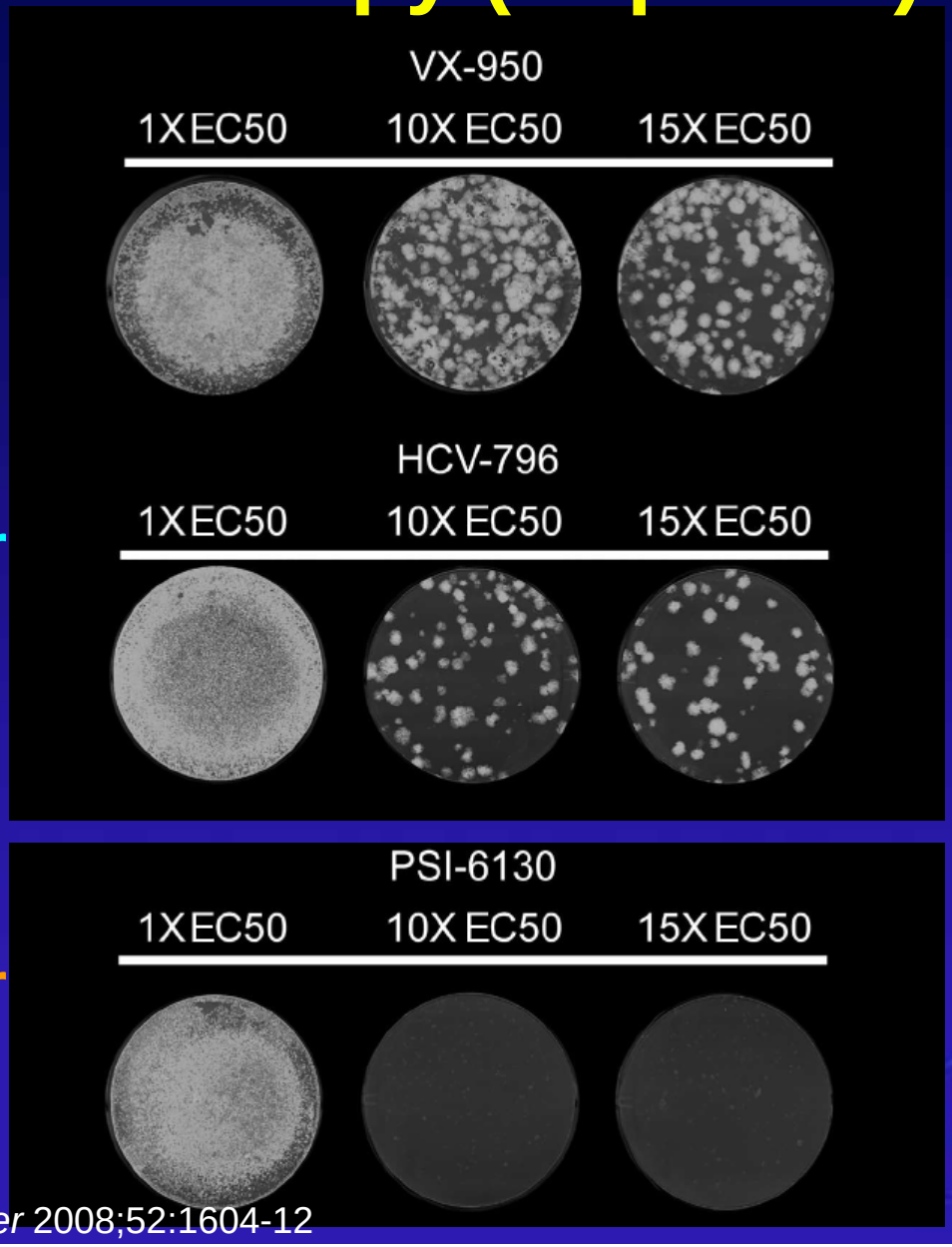
Gaudieri S, et al. *Hepatology* 2009; 49: 1069-82

in vitro Resistance to DAAs
14 Days Monotherapy (Replicon)

Protease Inhibitor

Nonnucleoside Polymerase inhibitor

Nucleoside Polymerase inhibitor



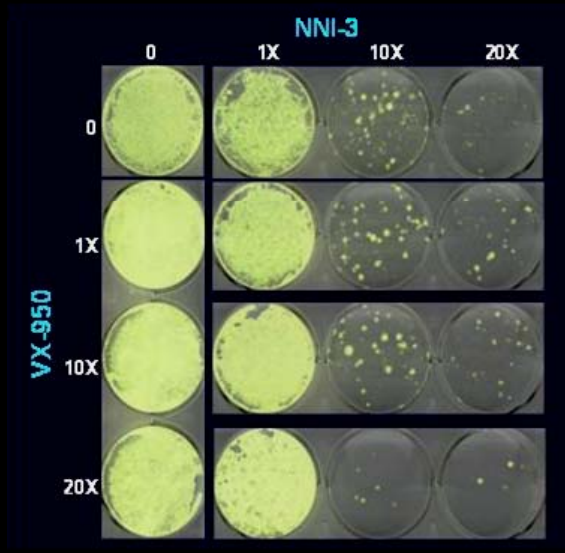
McCown *et al*. *Antimicrob Agents Chemother* 2008;52:1604-12

Purine Nucleoside analog (PSI-7977) plus NS5a inhibitor (BMS-790052)

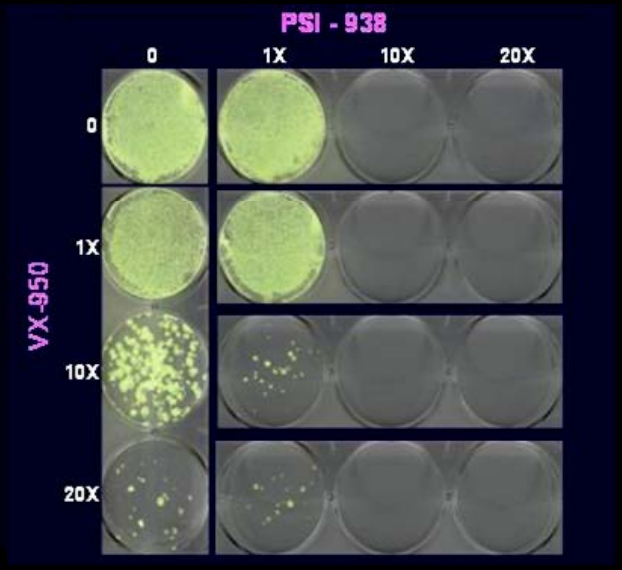
- Collaboration between Pharmasset and BMS
- Includes HCV Genotypes 1, 2, and 3
- 24 weeks duration⇨ SVR Endpoint
- Commence Q2 2011

Combining 2 Nucleoside NS5B inhibitors
in vitro Resistance to DAAs

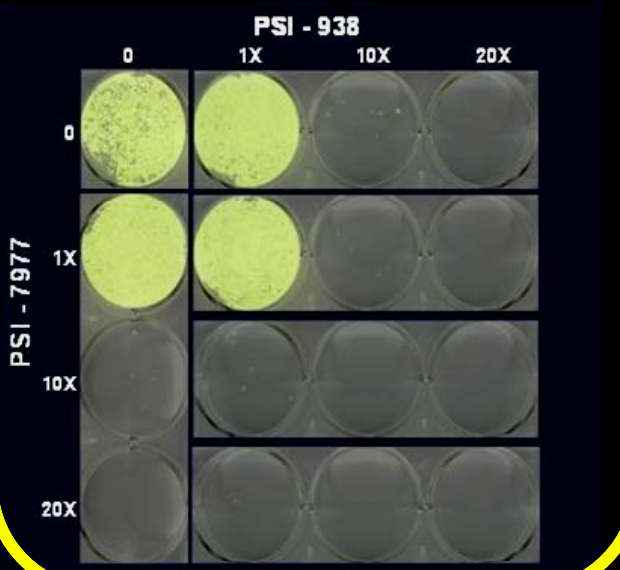
Protease inhibitor
+ Non-nuc NS5B



Protease inhibitor
+ Purine nuc NS5B



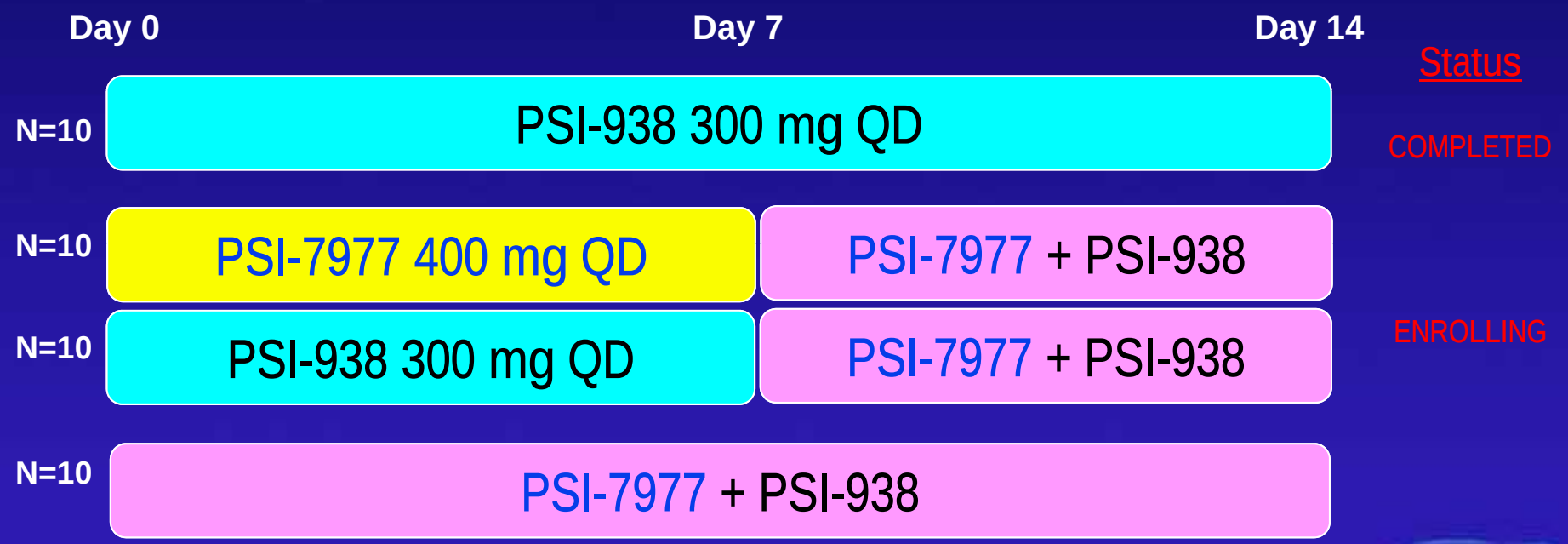
Pyrimidine nuc NS5B
+ Purine nuc NS5B



Zennou V, et al. *J Hepato* 2010; 52: S401: Abstract 1034.

PSI-7977 plus PSI-938 in HCV GT1

- **First combination of pyrimidine + purine Nucs**
  - »14 days in 40 HCV GT1
  - »Safety, PK, & viral kinetics Nuc combo



Current/Future Combination DAA trials in HCV GT1 Infection

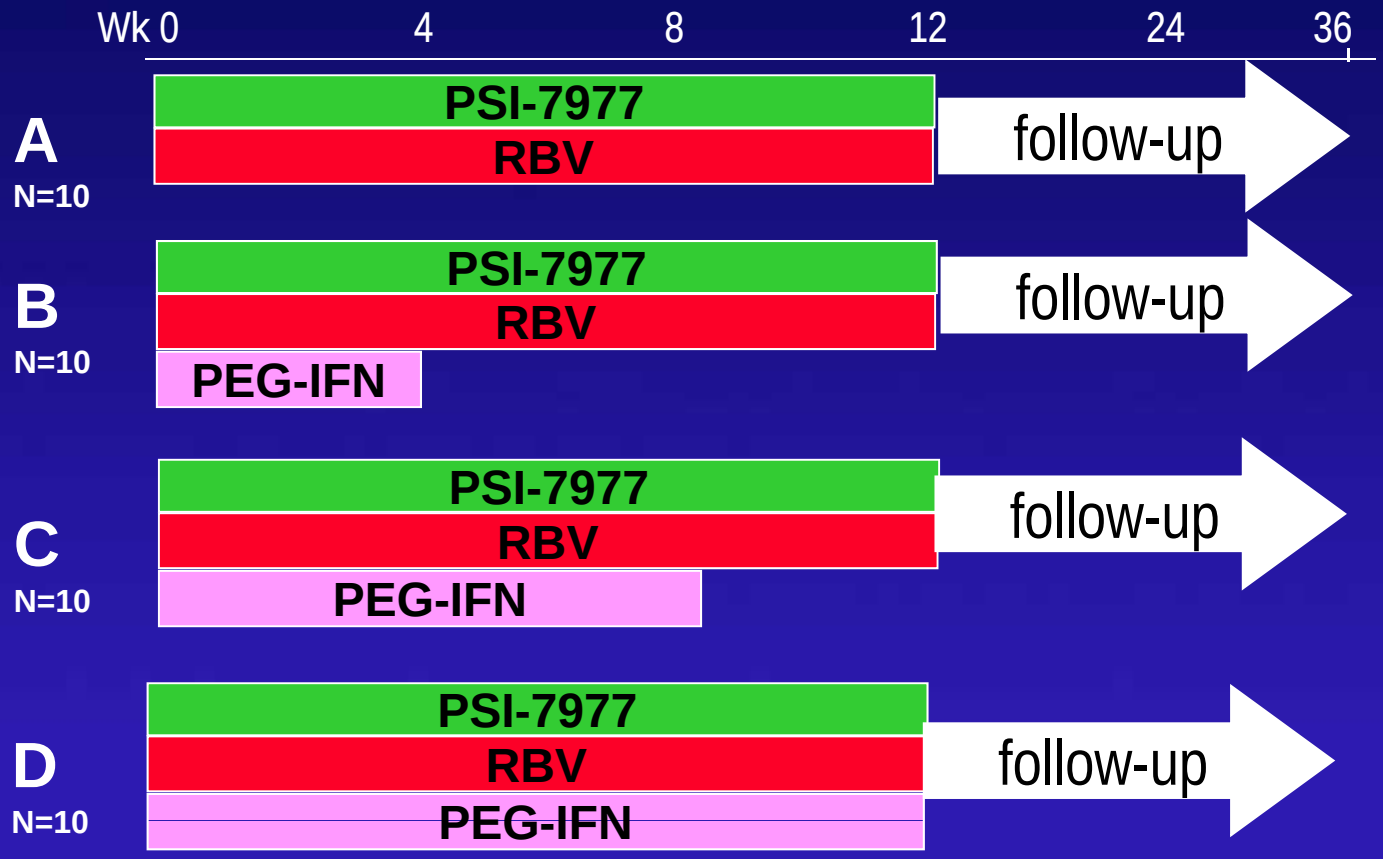
DAA (1)	DAA (2)
NS3 protease inhibitor (Telaprevir)	Nonnucleoside NS5B inhibitor (VX-222)
NS3 protease inhibitor (GS9256)	Nonnucleoside NS5B inhibitor (GS9190)
NS3 protease inhibitor (BI201335)	Nonnucleoside NS5B inhibitor(BI297127)
NS3 protease inhibitor (ABT-450)	Nonnucleoside NS5B inhibitor (ABT-072)
NS3 protease inhibitor (ABT-450)	Nonnucleoside NS5a inhibitor
NS3 protease inhibitor (MK-7009)	Nonnuc polymerase inhibitor (MK-3281)
NS3 protease inhibitor (BMS650032)	NS5a inhibitor (BMS-790052)
Pyrimidine Nuc NS5B inhibitor (RG7128)	NS3 protease inhibitor (Danoprevir)
Pyrimidine Nuc NS5B inhibitor (IDX184	NS3 protease inhibitor (IDX320)
Pyrimidine Nuc NS5B inhibitor (PSI-7977)	NS5a inhibitor (BMS-790052)
Pyrimidine Nuc NS5B inhibitor (PSI-7977)	Purine Nuc NS5B inhibitor (PSI-938)

Potential Combination DAA trials in HCV GT2/3 infection

DAA (1) Nuc Polymerase NS5B	DAA (2) Other
Pyrimidine nucleoside NS5B	Ribavirin
Pyrimidine nucleoside NS5B	NS5A inhibitor
Pyrimidine nucleoside NS5B	Cyclophillin Inhibitor
Pyrimidine nucleoside NS5B	Purine nucleotide NS5B

P7977-0523: IFN-sparing study in GT2/3

- **40 IFN-naïve** GT2/3 **pts (stratified HCV and** IL28B**)**
  - » 12 weeks PSI-7977 + RBV ± PEG
  - » SVR Primary Endpoint



- **Viral breakthrough ⇨ SOC rescue**

Combination Direct Acting Antivirals in HCV
Summary

- Combinations of potent DAAs with low barriers to resistance will fail without IFN/RBV because of rapid emergence of dual resistance
- IFN-free combination DAA regimen will require at least one with high barrier to resistance such as Nuc NS5B and Cyclophyllin B inhibitors
- Roles of both Ribavirin and IL-28B genotype in determining early response and relapse after IFN-free DAA therapy are still to be determined
- Further studies should include effects of rapid viral decline on innate and adaptive immunity

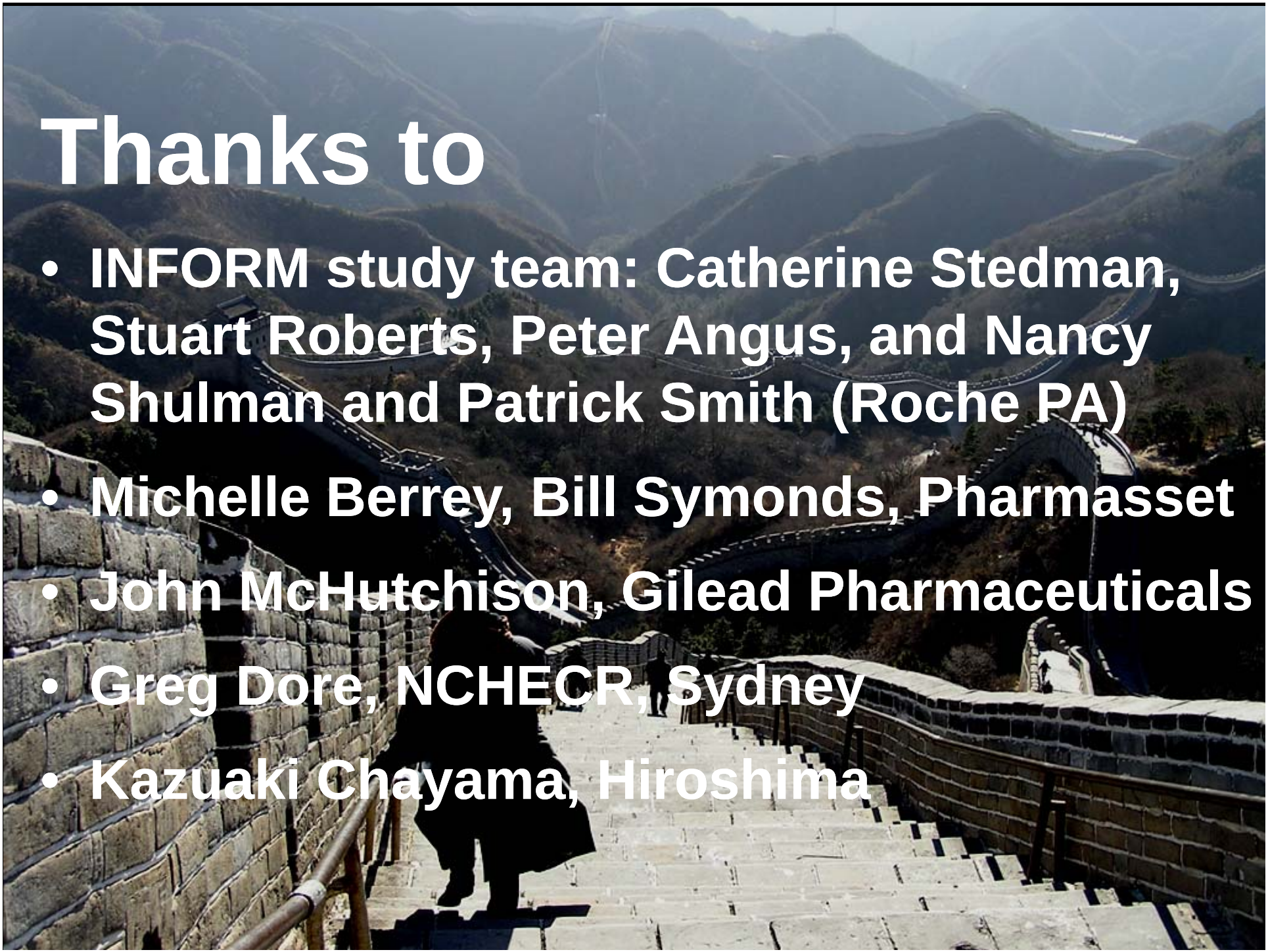
Combination Direct Acting Antivirals in HCV
Conclusion

- Combination DAAs should provide a short duration, IFN-free, oral regimen for all HCV+ patients including those unsuitable for, or nonresponders to current and future SOC

Better tolerated, more effective Rx

↑treatment uptake

↓global health burden



Thanks to

- INFORM study team: Catherine Stedman, Stuart Roberts, Peter Angus, and Nancy Shulman and Patrick Smith (Roche PA)
- Michelle Berrey, Bill Symonds, Pharmasset
- John McHutchison, Gilead Pharmaceuticals
- Greg Dore, NCHECR, Sydney
- Kazuaki Chayama, Hiroshima