Changing Direction Towards More Effective HCV Treatment

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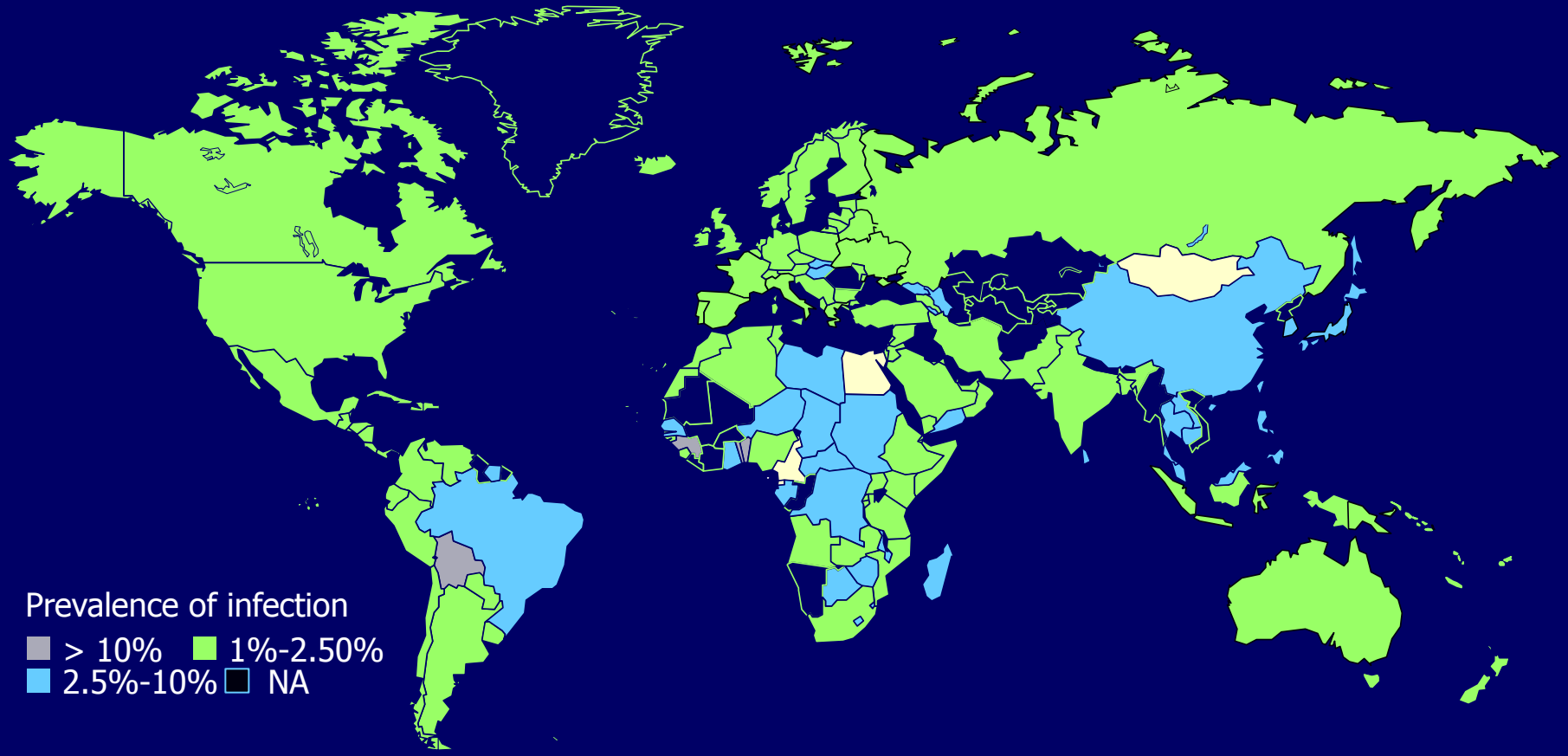
The most common disease in the world…

HCV infects almost 200 million people worldwide

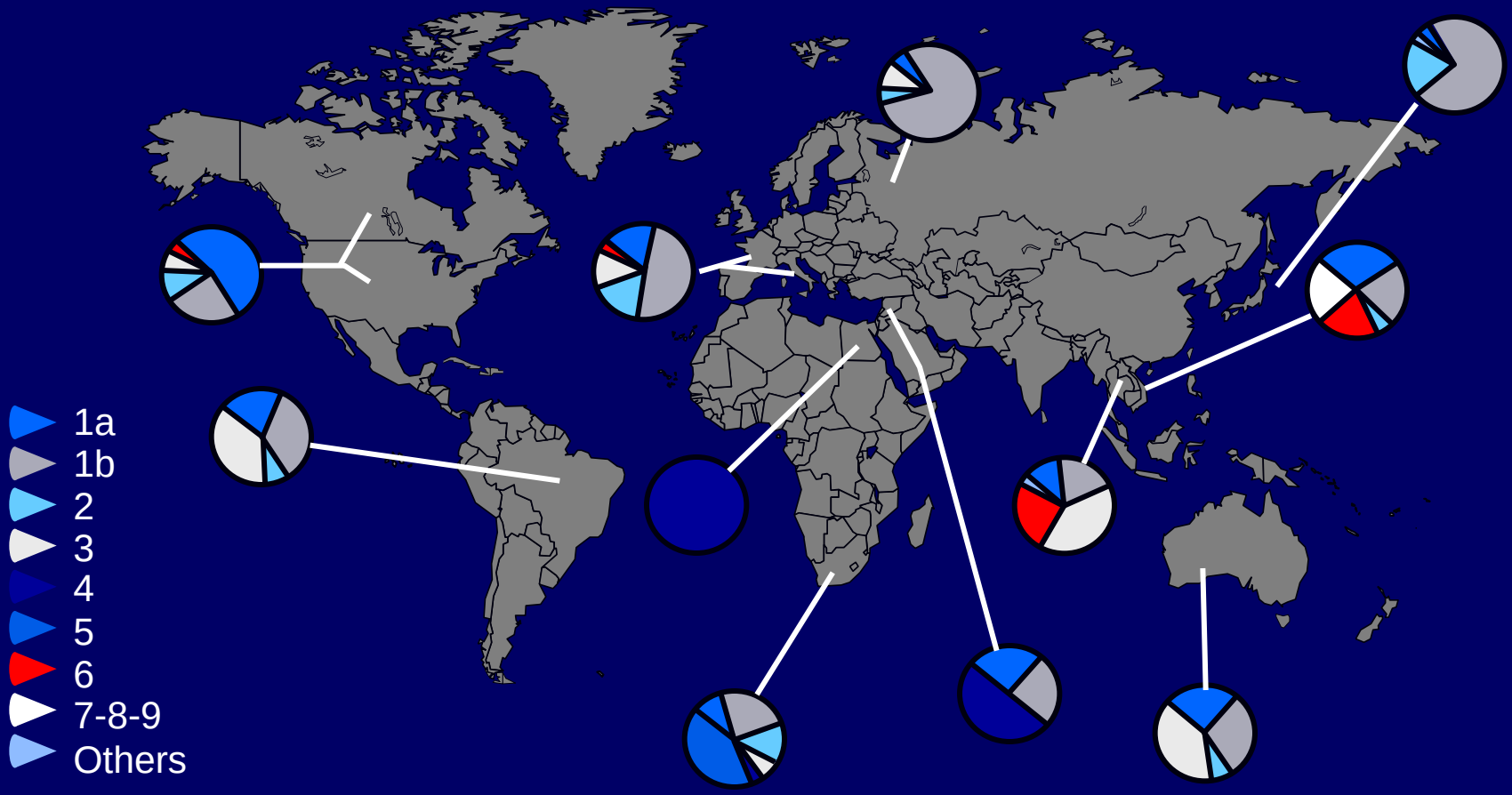
Estimated 170 Million Persons With HCV Infection Worldwide

- 3-4 million newly infected each year worldwide



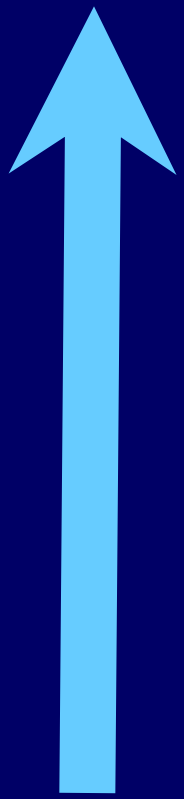
World Health Organization 2008. Available at: http://www.who.int/ith/es/index.html. Accessed October 28, 2009.

Worldwide Distribution of HCV Genotypes



Zein N. Clin Microbiol Rev. 2000;13:223-235. Reproduced with permission.
http://cmr.asm.org/cgi/content/full/13/2/223?view=long&pmid=10755999

The Increasing Challenge of HCV Disease Burden



Hepatocellular carcinoma (HCC)

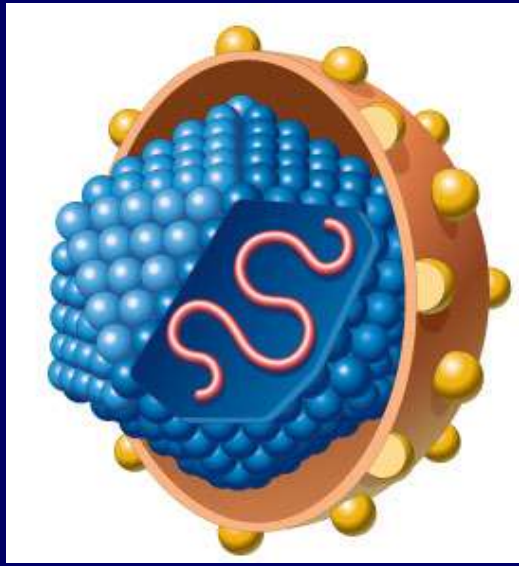
End-stage liver disease

HCV-related cirrhosis

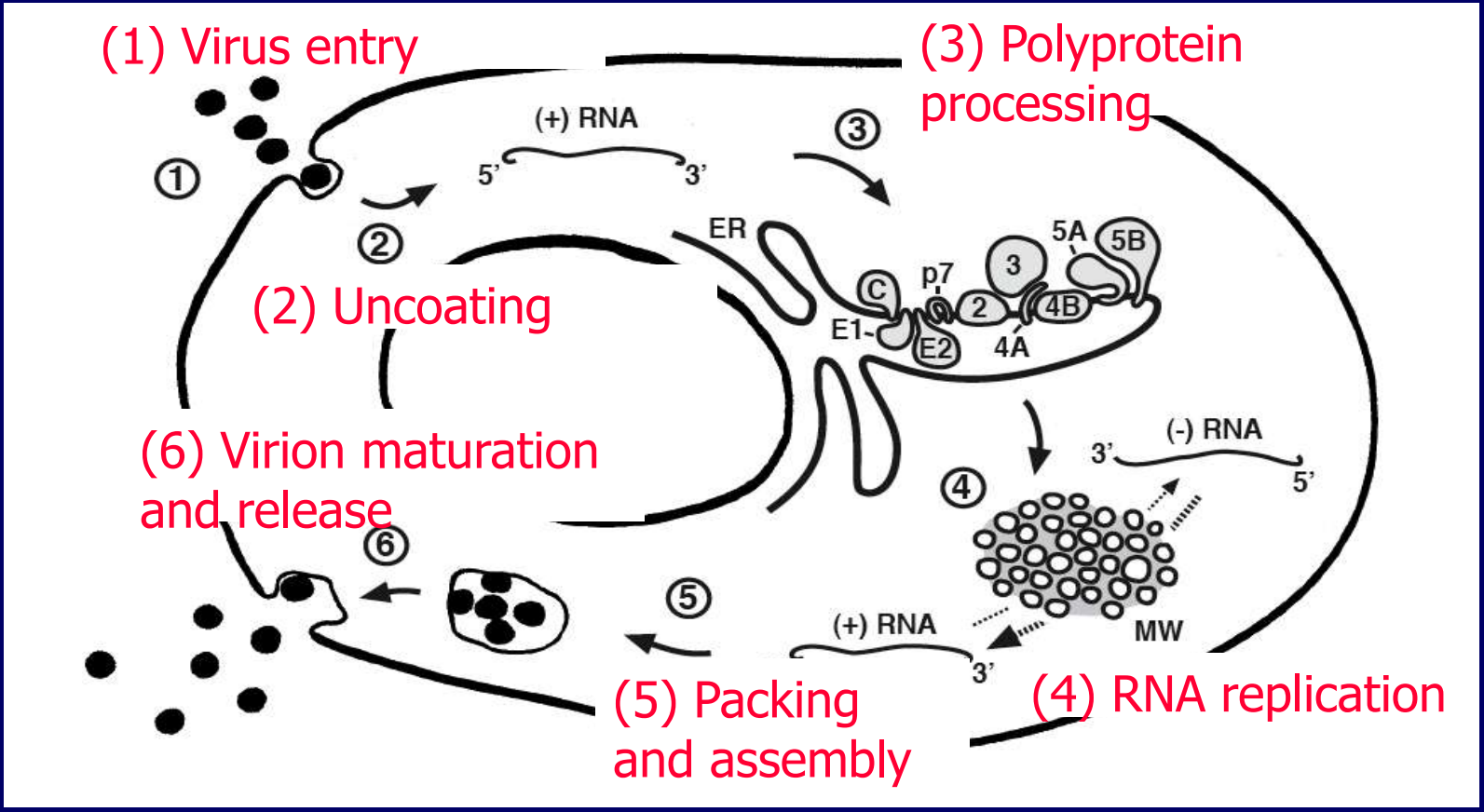
Virology of Hepatitis C

- HCV is a small, enveloped single stranded RNA virus in the Flaviviridae family

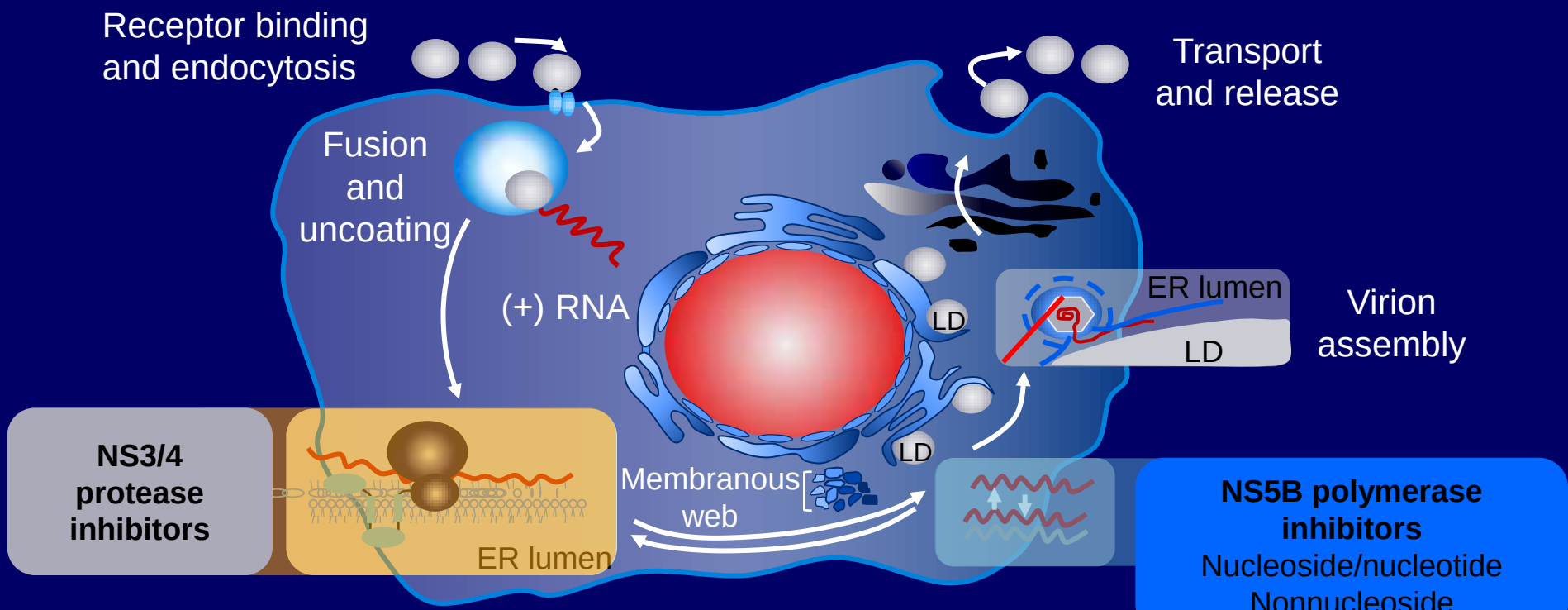
- There are six major genotypes and more than 100 subtypes



HCV life cycle

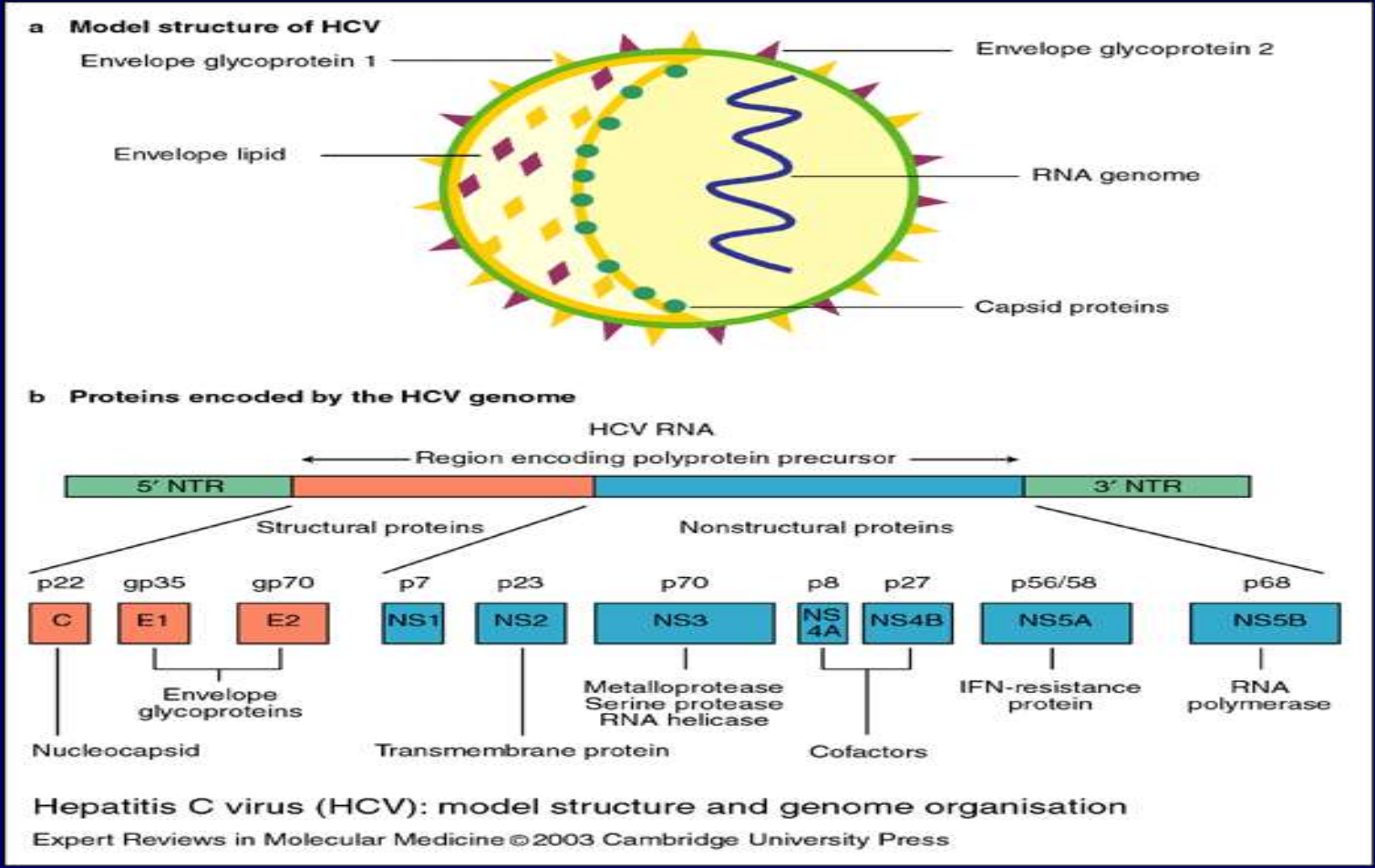


HCV Life Cycle and DAA Targets



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

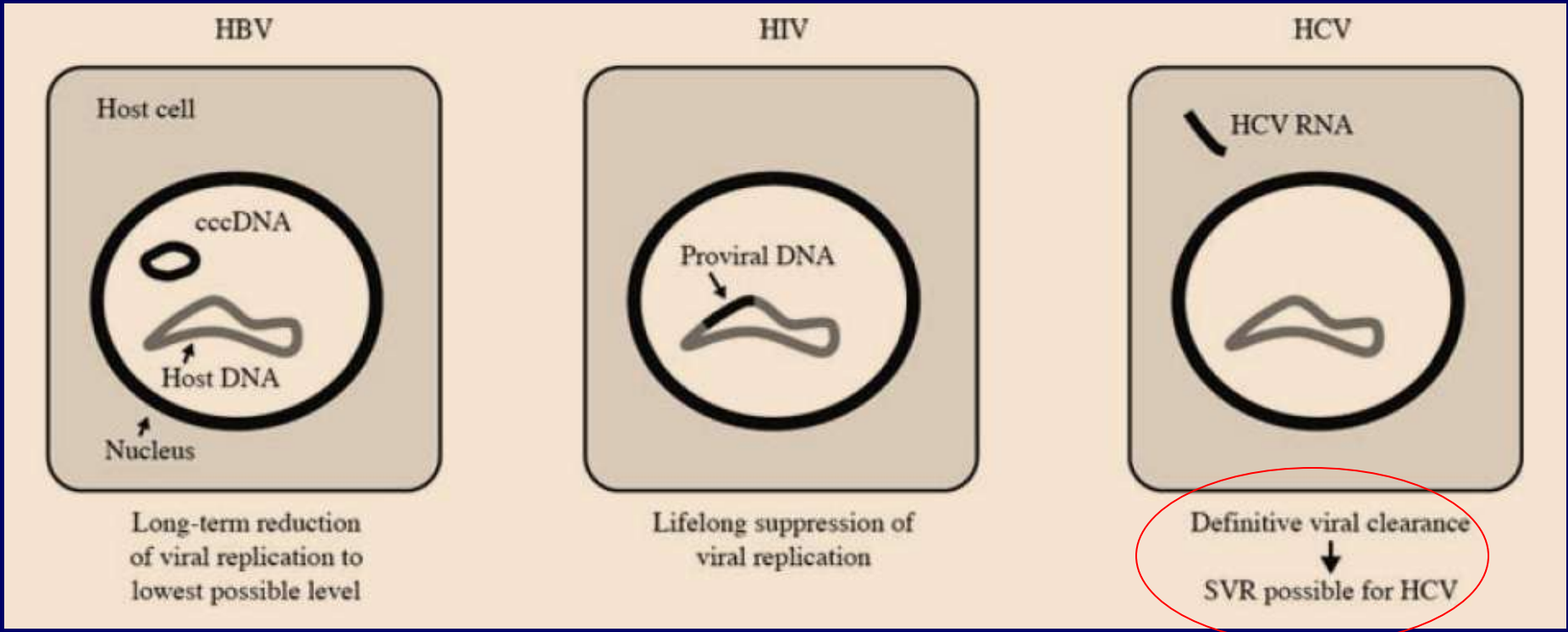
HCV genome



Hepatitis C virus (HCV): model structure and genome organisation

IS HCV A CURABLE DISEASE?

Different Virus Replication Strategies: Different Treatment Goals

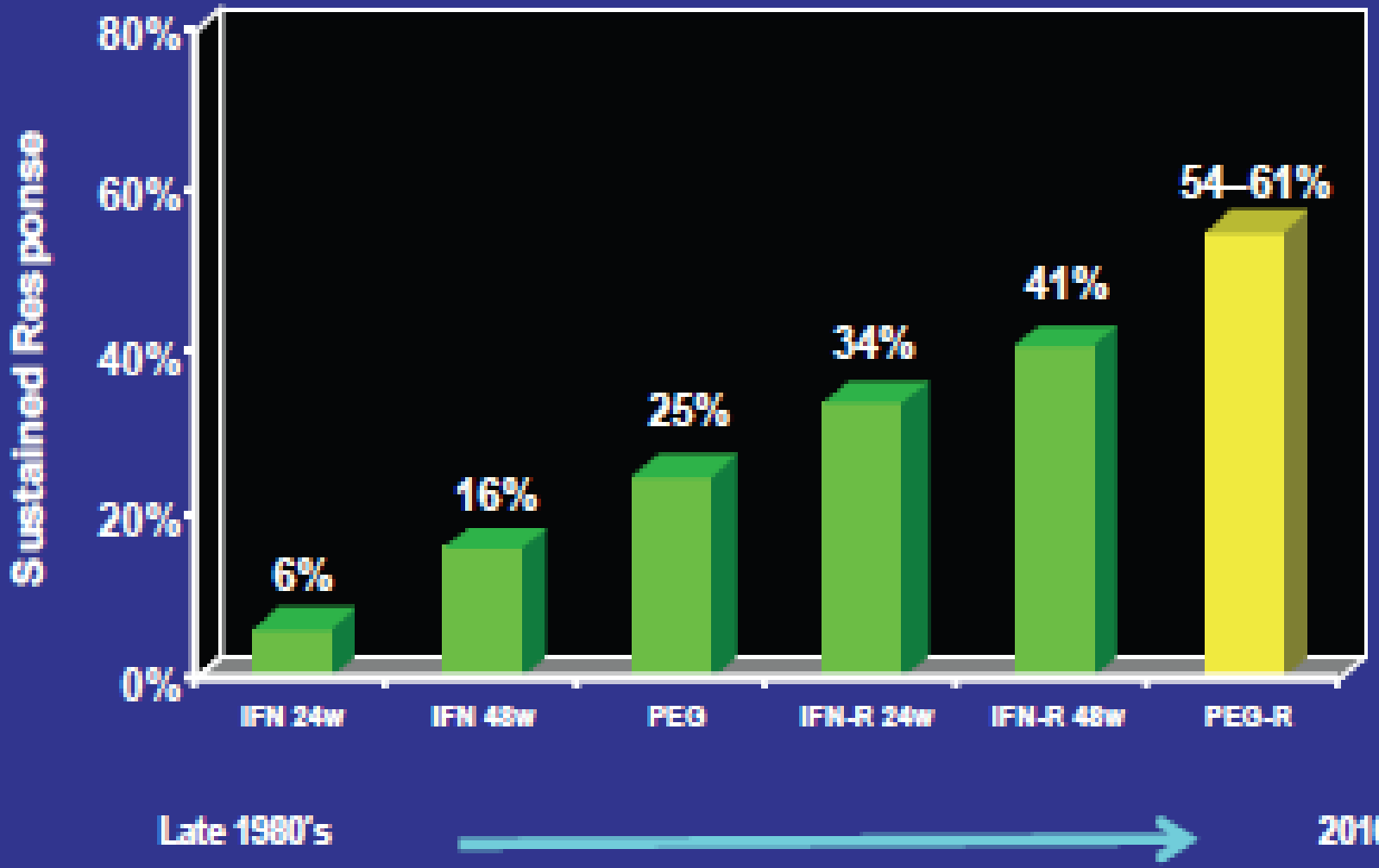


HCV Treatment Goals

- Goal of therapy to attain SVR and hence Prevent complications and death from HCV infection

Is this goal achievable by the currently available treatment strategies?

Current HCV Therapy: 2010

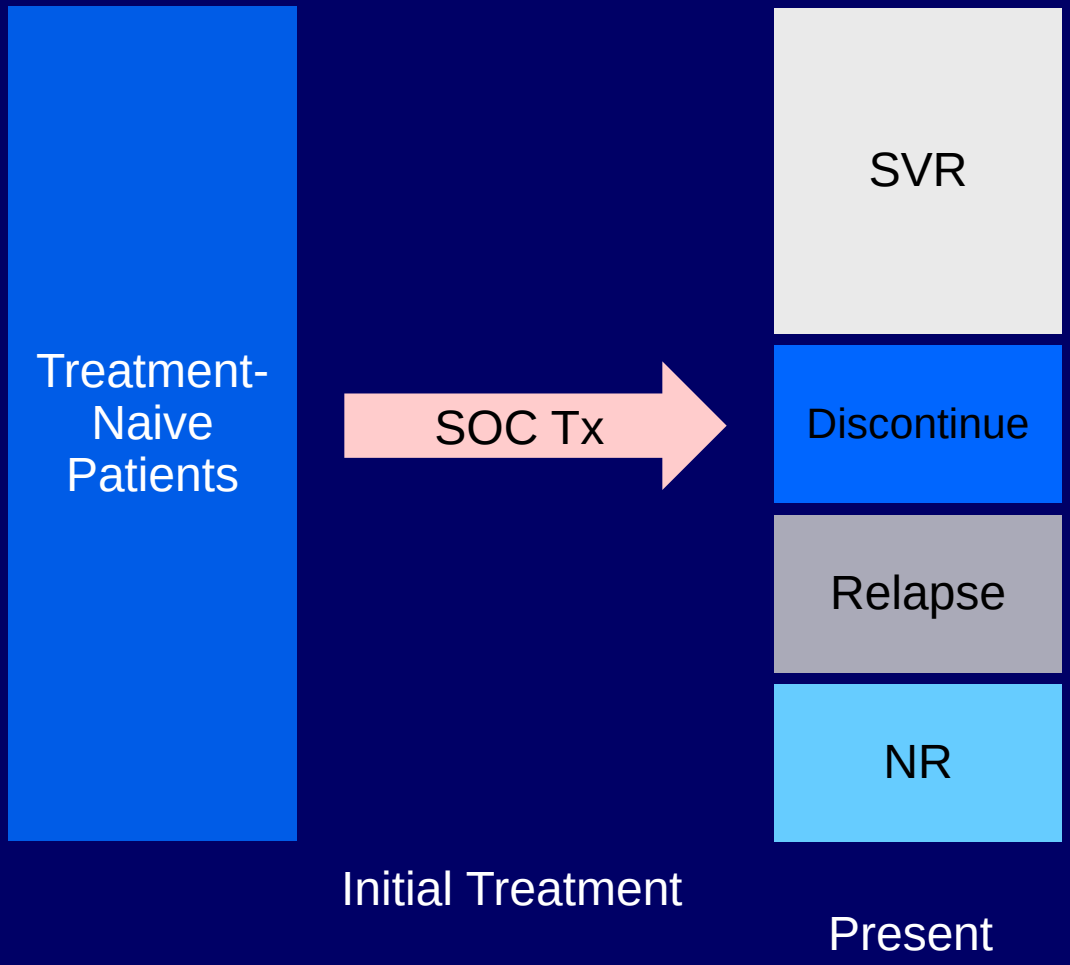


Reality Check:
Assessing the Present to Anticipate the Future

- Combination therapy with peg-INF + RIBA ,The ability of achiving SVR has improved significantly.
- However, more than half of all patients with Chronic HCV Genotypes 1 or 4 still don't achieve SVR ,in addition IFN is contraindicated in a significant proportion of patients due to concomitant diseases and other circumstances.

Zuezem 2009

The Reality of Current 48-Wk Standard-of-Care HCV Therapy



How can we find our Way in the Maze???

Finding Our Way in the Maze

Changing Direction Toward More Effective Treatment

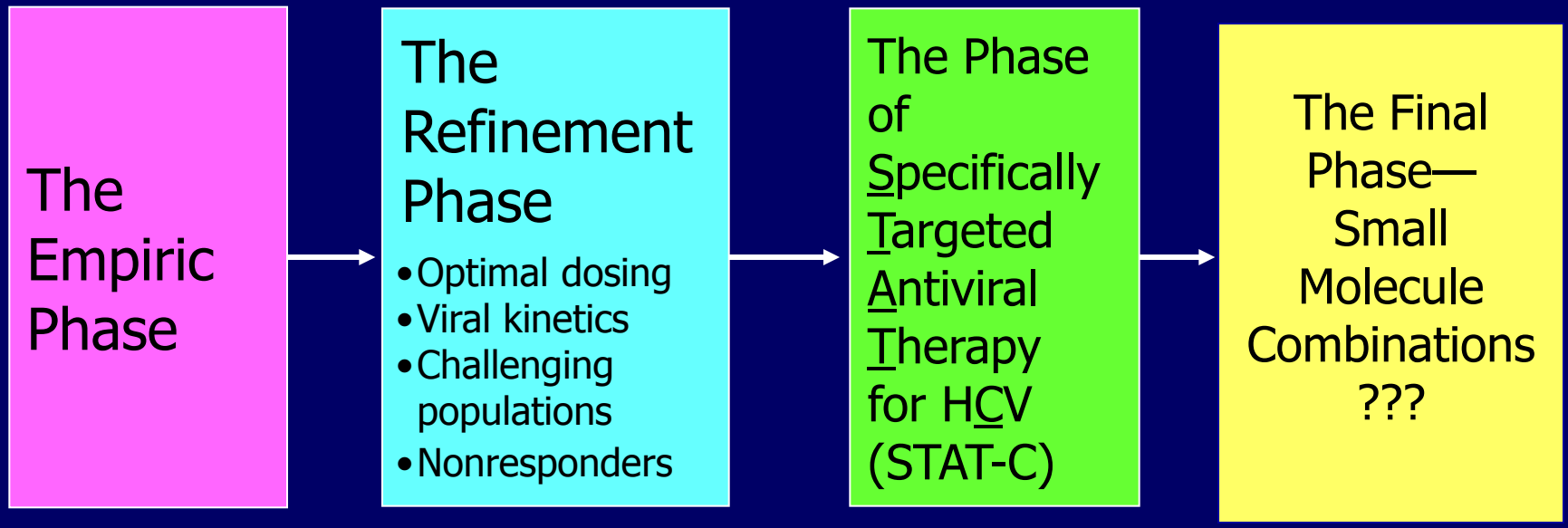
Think more like
virologists
than
hepatologists
or gastroenterologists

- The exploding Knowledge of the HCV lifecycle and structural features of HCV proteins, obtained by replicative cell culture systems, has spurred the development of many promising direct-acting antiviral agent(DAA),previously known as “specifically Targeted Antiviral Therapy For HCV” (STAT-C) compounds

Moradpour 2007

what is the current status of drug development?

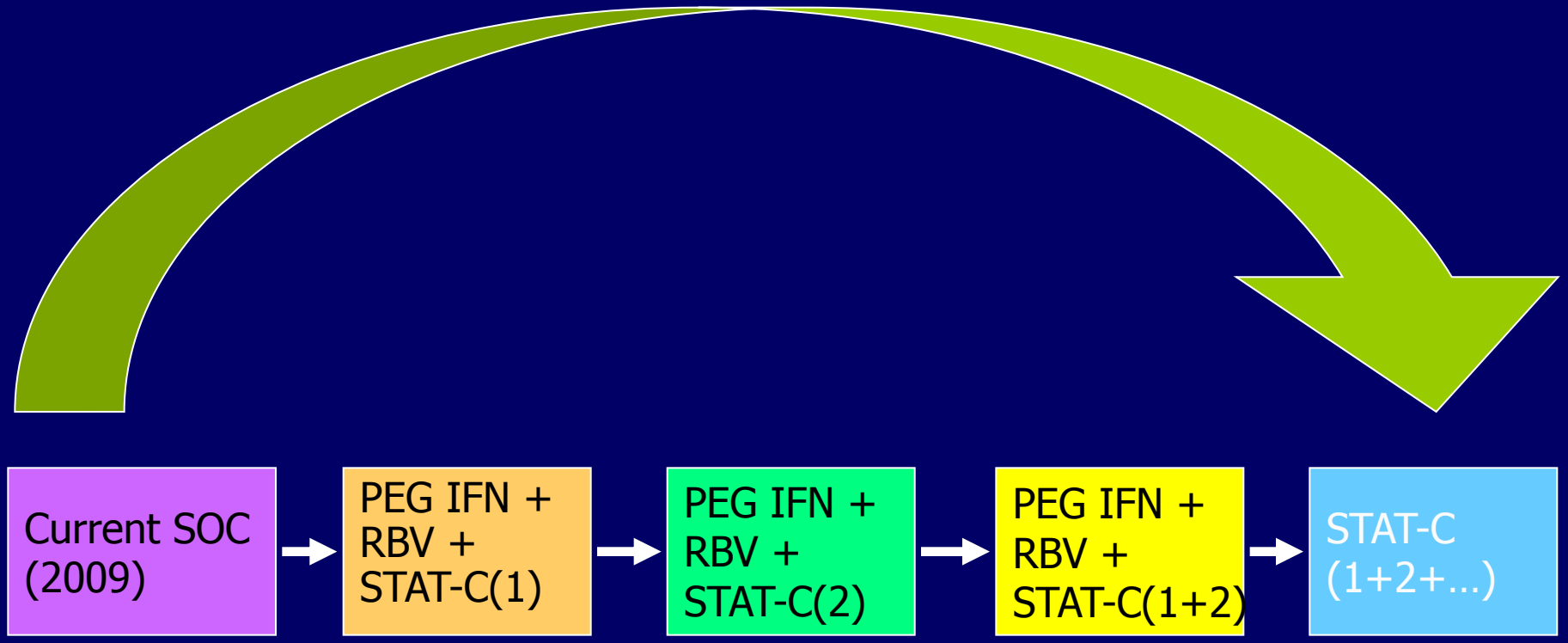
Phases in the Evolution of Anti-HCV Therapy



Weisberg IW, et al. *Current Hepatitis Reports.* 2007;6:75-82. Graphic courtesy of Dr. Ira Jacobson.

- After almost a decade with no change in treatment, the addition of the direct HCV antiviral agents to our treatment regimen is a tremendous step forward for patients with hepatitis C

Can We Leapfrog Ahead?



Graphic courtesy of Dr. Ira Jacobson.

Treating HCV in the Next 5 Years

↑ Opportunities

- Cure more patients
- Shorter duration of therapy

↑ Challenges

- Increased toxicity
- Increased complexity
- Increased costs
- Mandate to prevent resistance

Finding Our Way in the Maze: Changing Direction Toward More Effective Treatment

Future treatment paradigms in HCV treatment

- The classes of DAAs *offer a range of compounds targeting different sites of the HCV life cycle.*

The principle of DAA targeting :

1. The four HCV structural proteins
2. Six non-structural protiens
3. HCV specific RNA structures
4. Host factors

Emerging Anti-HCV Therapies

Specifically Targeted Antiviral Therapy for HCV

Enzyme Inhibitors

- Polymerase
- Protease
- NS5A

Genome Sequence-Based

- RNA interference

Other

IFN and RBV modifications
- Albinterferon, omega IFN, PEG IFN lambda (IL-29)
- Taribavirin (viramidine)

Immune approaches
- Therapeutic vaccines
- Toll-like receptor agonists
- Hepatitis C immune globulin
- Monoclonal antibodies

Targeting cellular factors
- Cyclophilin antagonists
- Nitazoxanide

Abbreviations: HCV, hepatitis C virus; IFN, interferon; PEG IFN, peginterferon; RBV, ribavirin.
Graphic courtesy of Dr. Ira Jacobson.

- The direct HCV antiviral agents are characterized as the first major breakthrough in HCV treatment since the introduction of ribavirin.
- These direct antivirals may generate sustained virologic response (SVR) rates of approximately 85% among some genotype 1 subgroups, if used optimally.

Classes of DAAs

- Protease inhibitors
- Nucleoside polymerase inhibitors
- Nonnucleoside polymerase inhibitors
- NS5A inhibitors
- others

DAAs 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 polymerase inhibitors		IDX184 PSI-7977 RG7128	
NS5A inhibitors	A-831 PPI-461	BMS-790052 BMS-824393 CF102	

Activity of DAAs by HCV Genotype

Agent	Potential Activity
Protease Inhibitors	
Boceprevir[1,2]	1, 2
Telaprevir[3,4]	1, 2
BI 201335[5]	1, 2?
Danoprevir[6]	1, 2?
MK-5172[7]	1-6
TMC435[8]	1, 2, 4, 5, 6
Vaniprevir[9]	1, 2?

1. Poordad F, et al. AASLD 2010. Abstract LB-4. 2. Pawlotsky JM, et al. Gastroenterology. 2011[epub ahead of print]. Abstract 820. 3. Jacobson IM, et al. AASLD 2010. Abstract 211. 4. Foster G, et al. EASL 2010. Abstract 57. 5. Sulkowski M, et al. EASL 2010. Abstract 1190. 6. Terrault N, et al. AASLD 2010. Abstract 32. 7. Petry A, et al. AASLD 2010. Abstract 807. 8. Fried M, et al. AASLD 2010. Abstract LB-5. 9. Manns MP, et al. AASLD 2010. Abstract 82.

Activity of DAAs by HCV Genotype

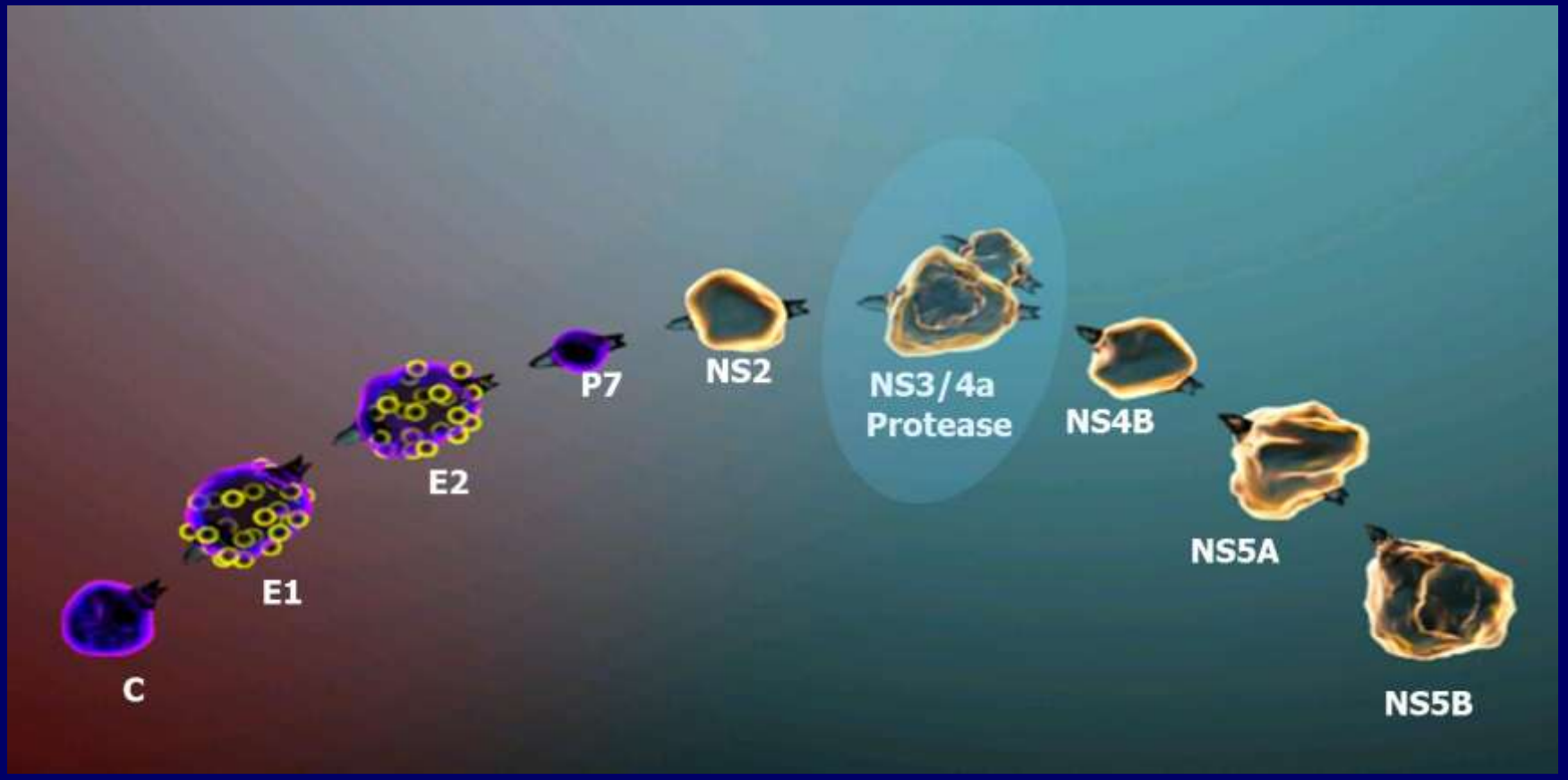
Agent	Potential Activity
Polymerase Inhibitors	
Nonnucleoside	
ANA598[1]	1
Filibuvir[2]	1
Nucleoside	
IDX184[3]	1-4 (5, 6?)
RG7128[4]	1-6
NS5A Inhibitors	
BMS -790052[5]	1+ (not fully pangenotypic)

1. Lawitz E, et al. AASLD 2010. Abstract 31. 2. Jacobson I, et al. EASL 2010. Abstract 2088. 3. Standring DN, et al. EASL 2009. Abstract 91. 4. Jensen DM, et al. AASLD 2010. Abstract 81. 5. Pol S, et al. EASL 2010. Abstract 1189.

Potential antiviral genomic targets

NS3/4a Cleaves Nonstructural Proteins from the Polypeptide Chain[1,2]

Viral Replication Initiated

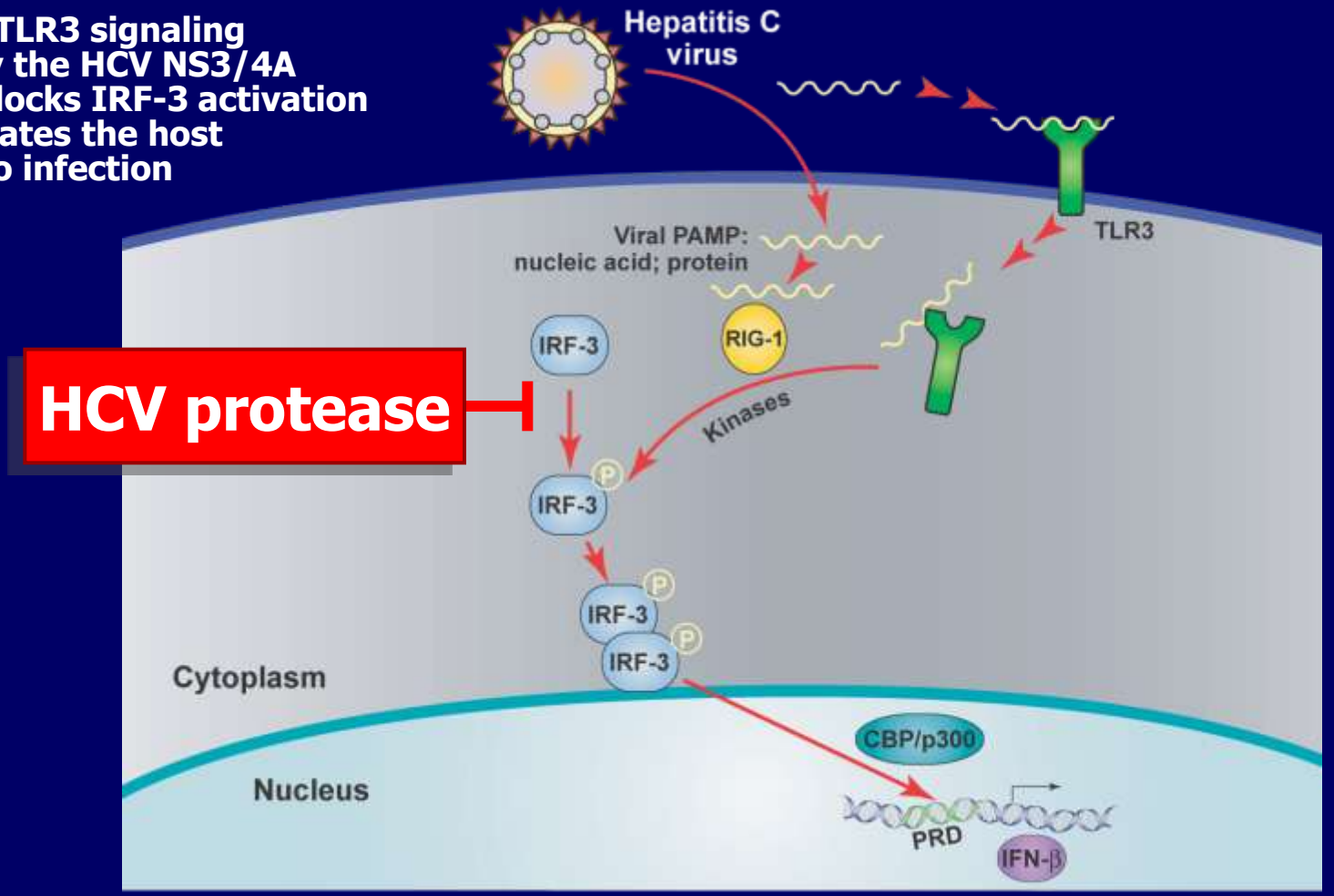


Graphic courtesy of Dr. M. Sulkowski.

1. Lindenbach BD, et al. *Nature*. 2005;436:933. 2. Lindenbach BD, et al. *Science.* 2005;309:623.

HCV Protease Interferes with IFN Signaling

RIG 1 and TLR3 signaling ablation by the HCV NS3/4A protease blocks IRF-3 activation and attenuates the host response to infection



IRF = interferon regulatory factor 3; PRD = positive regulatory domain; RIG 1 = retinoic acid-inducible gene-1; TLR3 = toll-like receptor 3.

Adapted from Gale M, et al. *Nature*. 2005;436:939. Reprinted with permission.

NS3-4A protease inhibitors

- The NS3-4A protease inhibitors cleavage the junctions between NS3/NS4A,NS4A/NS4B,NS4B/NS5A and NS5A/NS5B.

Mode of action:

- Imhibition of HCV replication .

Side effect:

- Selection of resistant mutant which is followed by viral break through so the recommendation is to use them with standard of care in order to reduce the frequency of development of resistance.

Generations of protease inhibtors

- 1 st generation:
- A-Telaprevir(VX-950)
- B-Boceprevir(SCH 503034)
- C-Ciluoprevir(BILN 2061)
- 2 nd Generation:
- A-Danoprevir(R2772)
- B-Vaniprevir(MK 7009)

- 3rd generation
- A-Narlaprevir (SCH 900518)
- B-BMS-650032
- C-PHX1 1766
- D- MK-5172
- E-TMC435

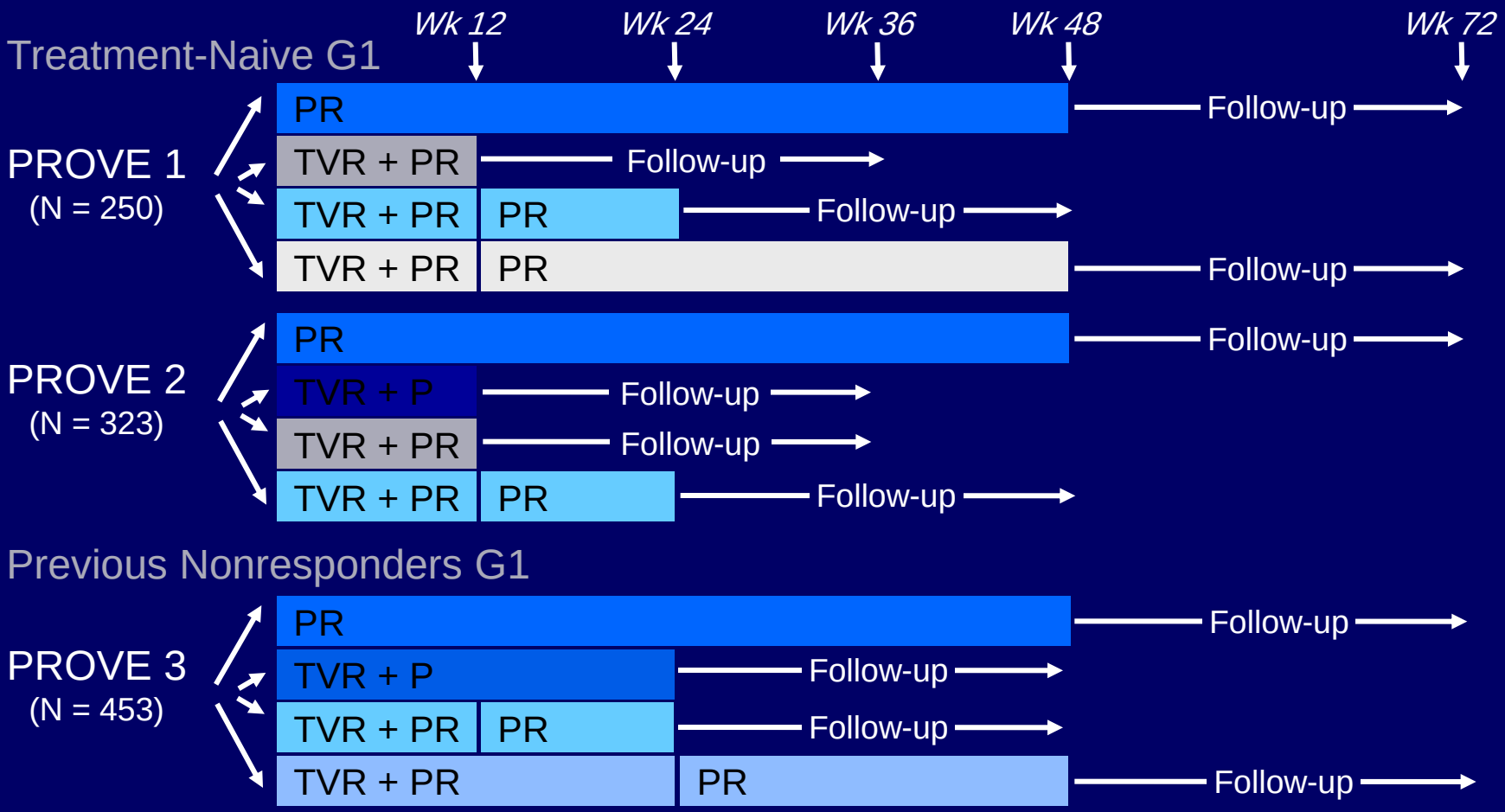
- Potenial advantages of these 2nd and 3rd generations protease inhibitors might be improved to tolerability, broader genotypic activity ,different resistance profiles,and/or improved pharmacokinitics to allow for once-daily dosage.
- MK-5172 which exhibit potent antiviral activity against variant carrying mutations .

- Telaprevir and different HCV genotype:

In genotypes 3 and 4 patients no significant antiviral activity was detectable .

Benhamou 2010,Foster 2010

Phase II PROVE Studies: Telaprevir + PegIFN Alfa-2a ± RBV



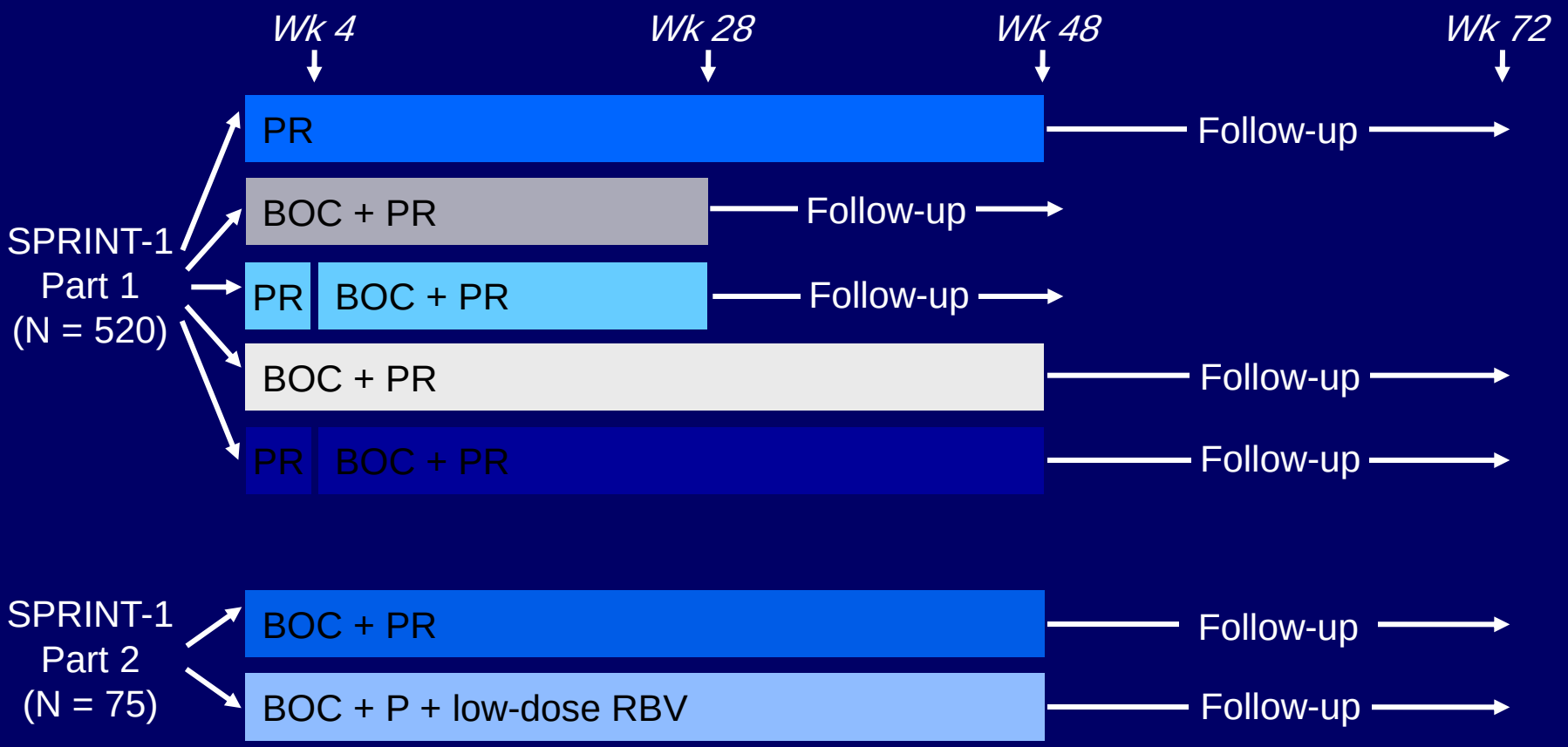
Peginterferon alfa-2a 180 µg/wk. Ribavirin 1000 or 1200 mg/day by weight.
Telaprevir 1250 mg on Day 1 then 750 mg every 8 hrs.

Overview of Phase II Efficacy Results: Telaprevir

- Phase II PROVE trials:
  - 12-wk TVR + 24/48-wk pegIFN alfa + RBV vs 48-wk SOC[1,2]
    - Significantly increased RVR and SVR rates, lower relapse rates
  - Proof of concept for SVR with 12 wk treatment
  - Importance of RBV as component of regimen
  - Low rates of breakthrough in treatment-naive patients
  - Promising results for relapsers and nonresponders

1. McHutchison J, et al. N Engl J Med. 2009;360:1827-1838.
2. Hézode C, et al. N Engl J Med. 2009;360:1839-1850.

Phase II SPRINT-1: Boceprevir + PegIFN Alfa-2b + RBV in Treatment-Naive G1



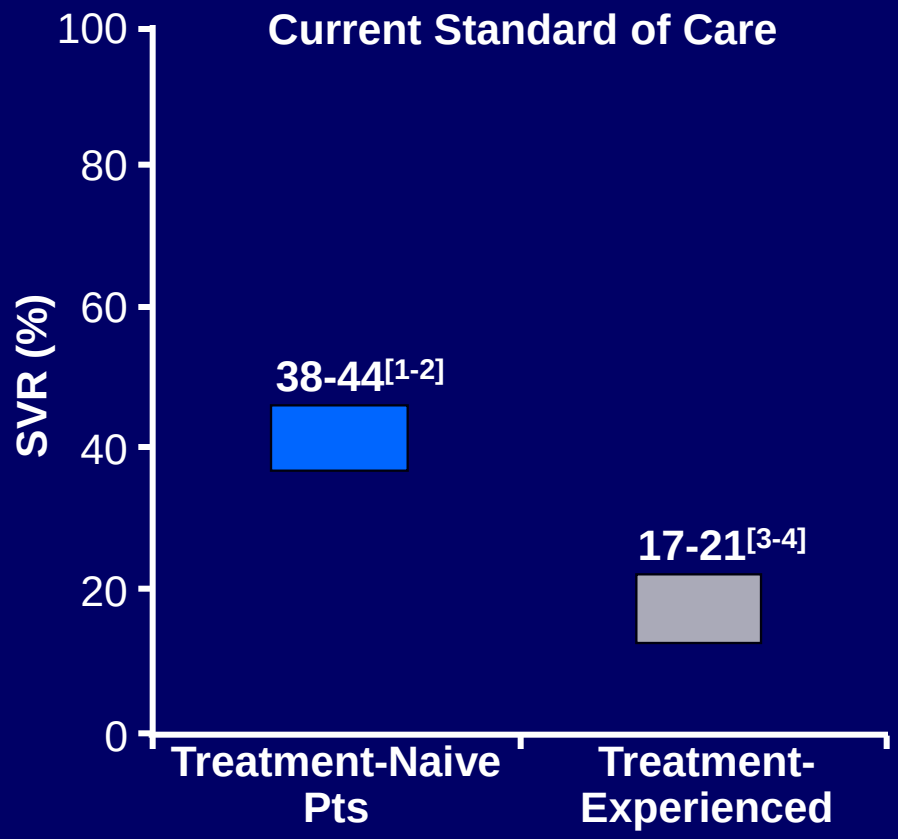
Peginterferon alfa-2b 1.5 µg/kg/wk. Ribavirin 800-1400 mg/day and low-dose ribavirin 400-1000 mg/day by weight. Boceprevir 800 mg every 8 hrs.

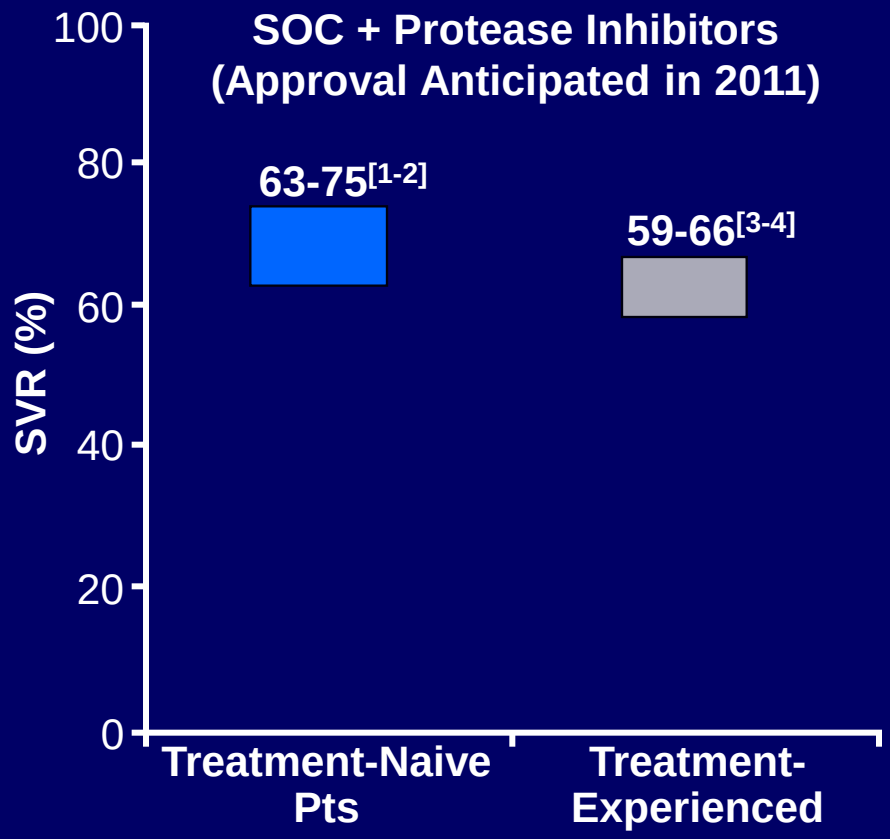
Overview of Phase II Efficacy Results: Boceprevir

- Phase II SPRINT-1 trial
  - Increased SVR rates (44-48 wks BOC + PR > 24-28 wks BOC + PR > SOC)
  - High rate of SVR after RVR with 24 wks of treatment
  - Lead-in dosing associated with less breakthrough and relapse
  - Significant SVR rates in null responders (as defined during lead-in phase)
  - Importance of full (vs low dose) RBV

Kwo P, et al. EASL 2009. Abstract 4.

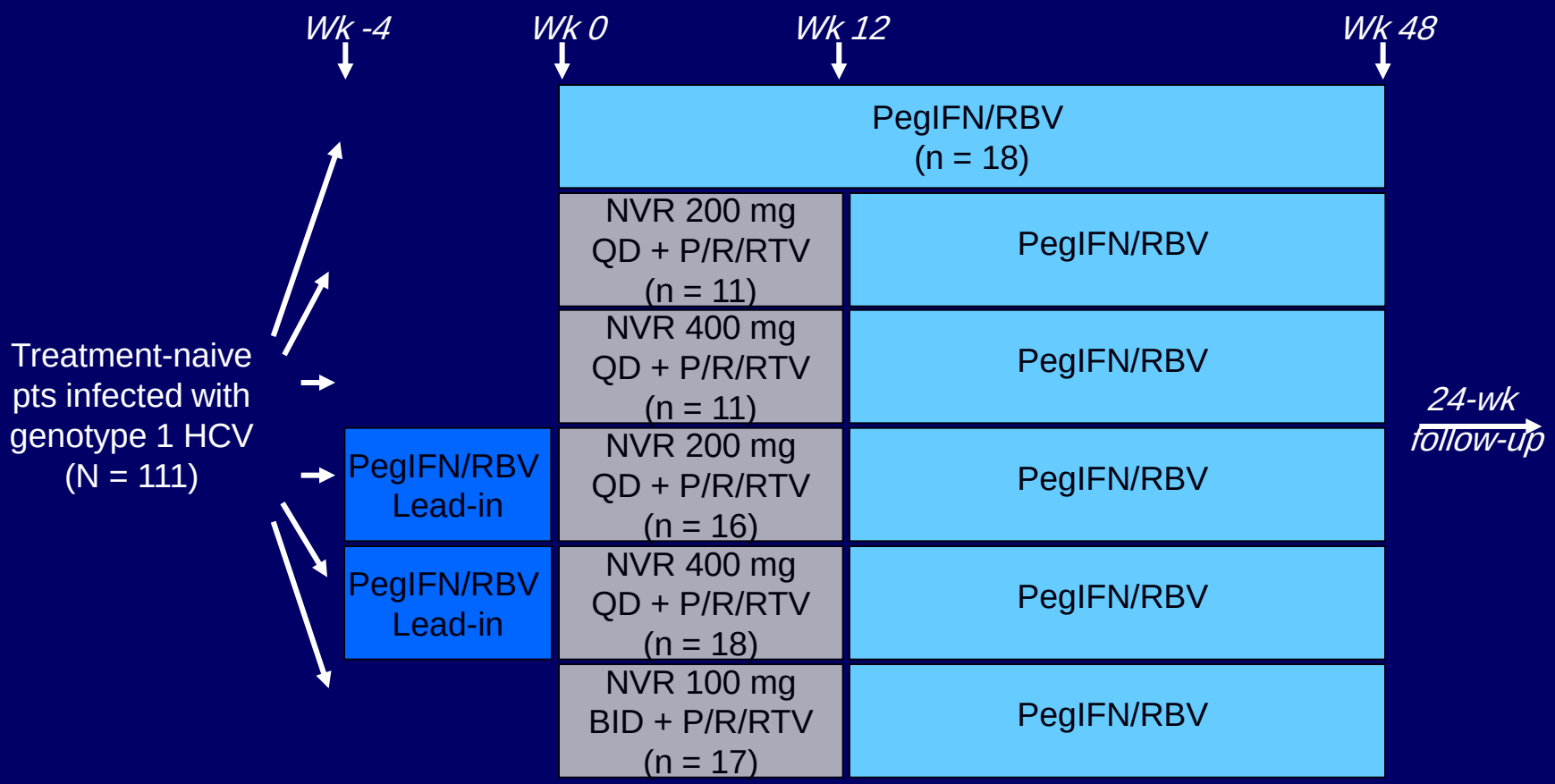
SVR Rates With BOC and TPV in GT1 Treatment-Naive and -Experienced Pts





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.

NEXT-1: HCV Protease Inhibitor Narlaprevir in Treatment-Naive G1 Pts

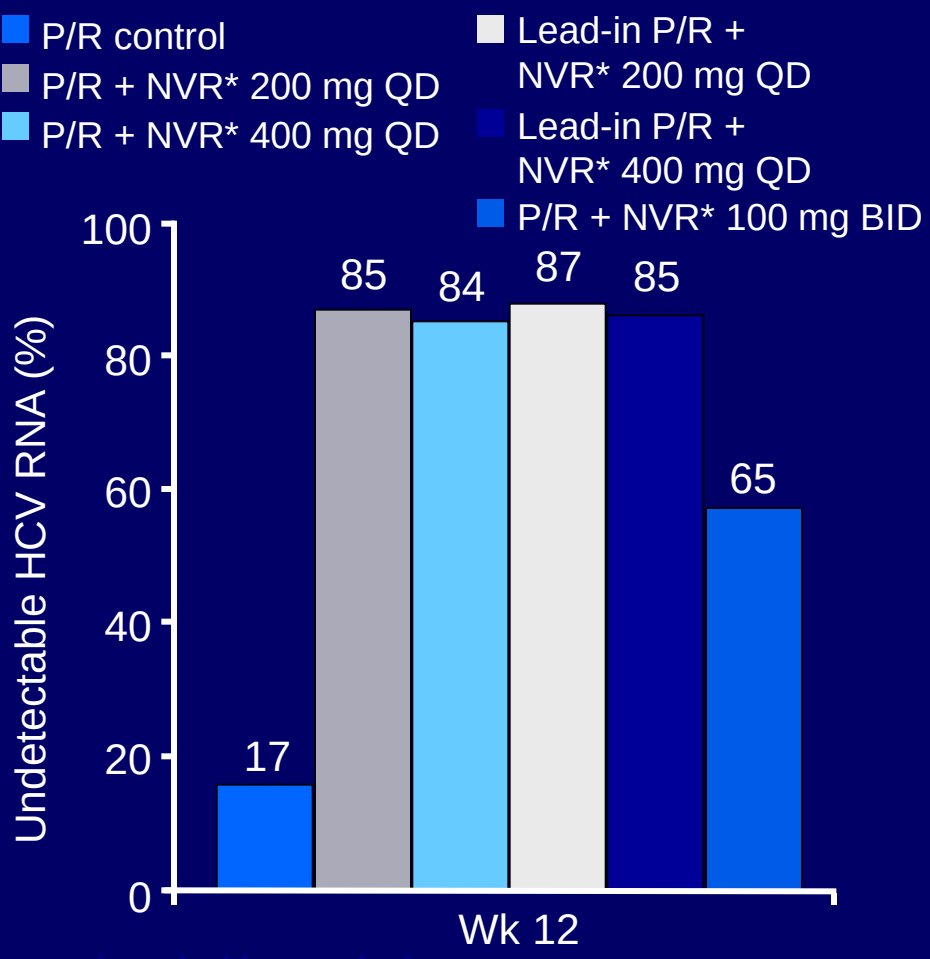


P, peginterferon alfa-2b 1.5 µg/kg/wk; R, ribavirin 600-1400 mg/day; RTV, ritonavir 100 mg.

Vierling JM, et al. AASLD 2009. Abstract LB4.

NEXT-1: NVR Potent in Treatment-Naive Pts, Wk 4 PegIFN/RBV Null Responders

- Rapid decline in HCV RNA upon initiation of NVR-based regimens vs pegIFN/RBV
- 11 null responders to pegIFN/RBV lead-in achieved HCV RNA below LLQ (< 25 IU/mL) at Wk 4 of NVR-based therapy
  - 9 maintained HCV RNA < 10 IU/mL through Wk 12 (NVR 200 mg and 400 mg QD dosing arms)
  - 2 pts experienced virologic breakthrough by Wk 8 (200 mg QD dosing arm only)

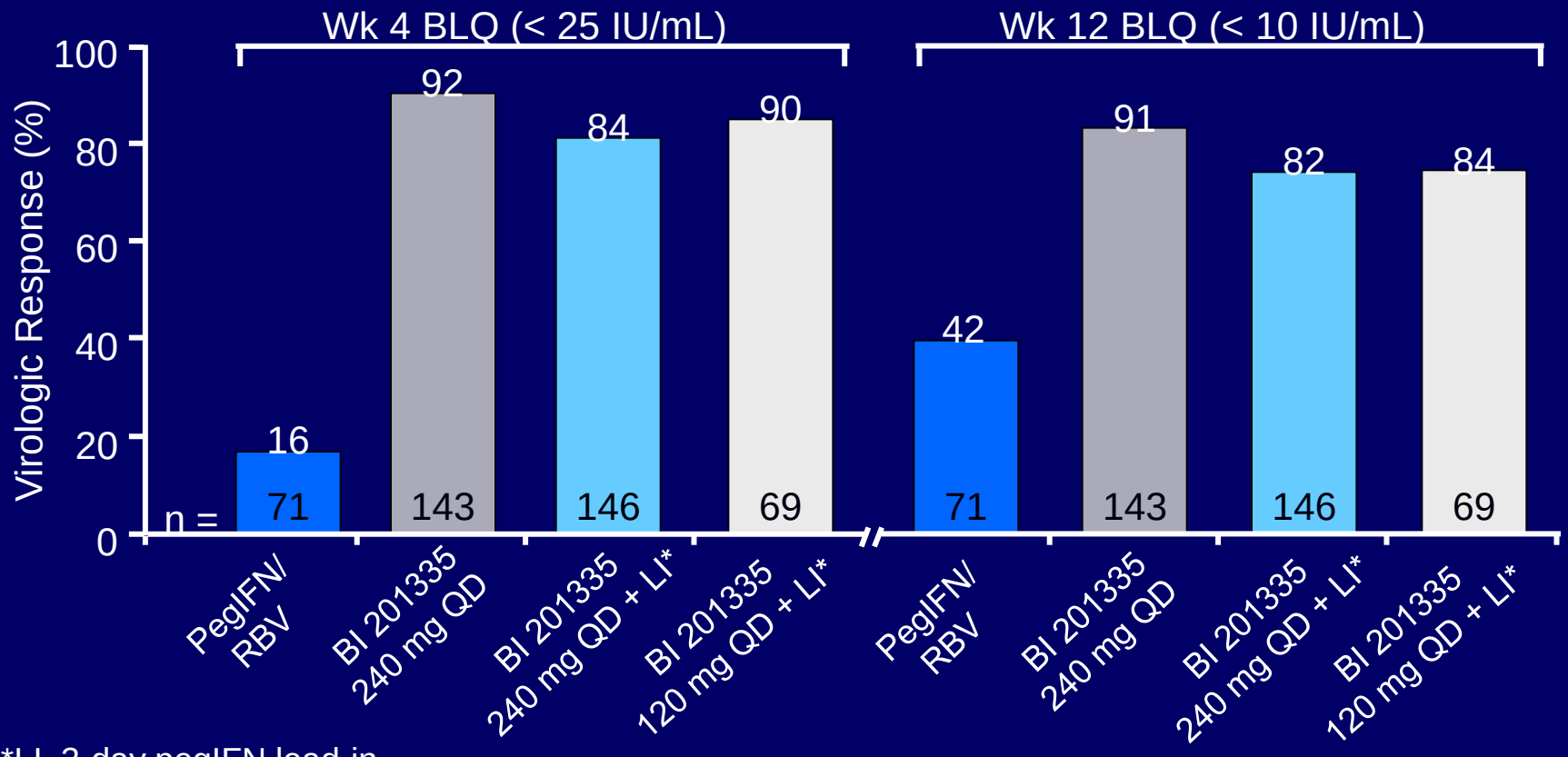


*Each dose of NVR administered with RTV 100 mg.

Vierling JM, et al. AASLD 2009. Abstract LB4. Figure reproduced with permission.

SILEN-C1: Rapid Virologic Response With Protease Inhibitor BI 201335 + PegIFN/RBV

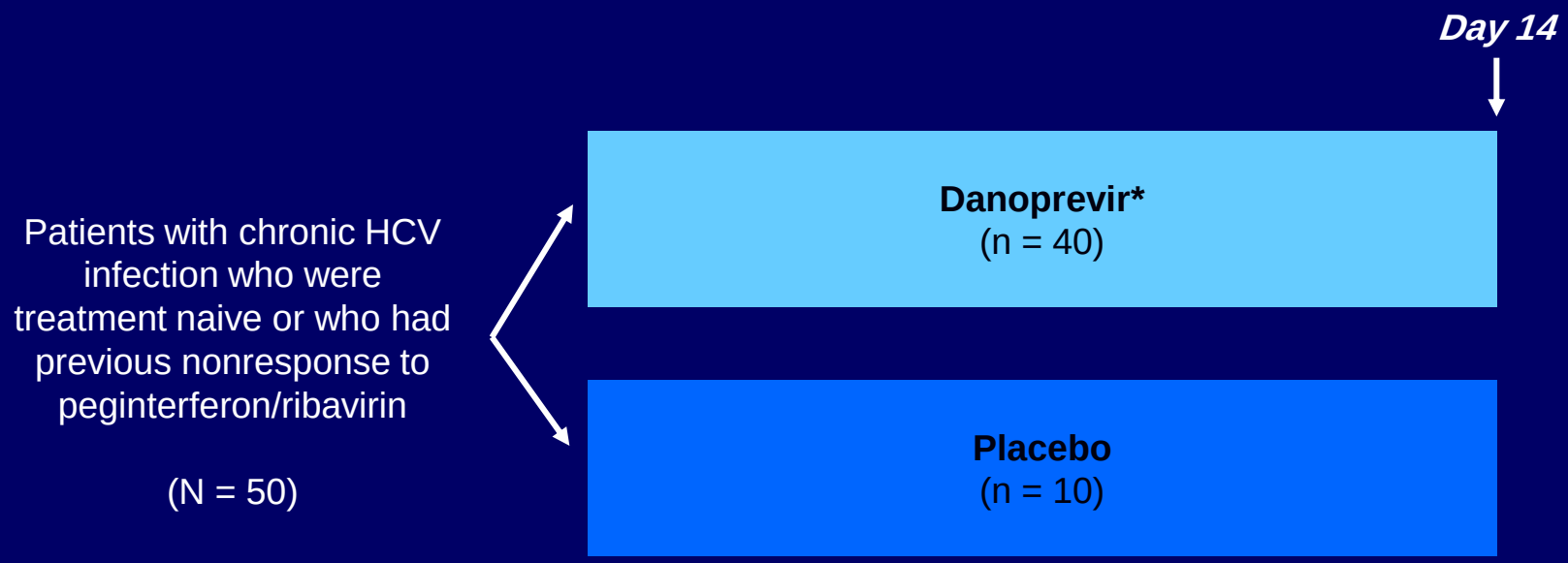
- Double-blind, placebo-controlled trial



*LI, 3-day pegIFN lead-in.

Sulkowski MS, et al. AASLD 2009. Abstract LB3. Figure reproduced with permission.

HCV NS3/4A Protease Inhibitor Danoprevir Improves Insulin Sensitivity and Suppresses HCV RNA in Patients Chronically Infected With Genotype 1 HCV



*Patients were grouped into 5 cohorts. Four cohorts of 10 treatment-naive patients were randomized to receive placebo or danoprevir every 12 hrs (100 mg, 200 mg) or every 8 hrs (100 mg, 200 mg). The fifth cohort of 10 previous nonresponders was randomized to receive placebo or danoprevir 300 mg every 12 hrs.

Moucari R, et al. Gut. 2010;59:1694-1698.

- Patients treated with danoprevir had significant changes in HCV RNA regardless of type of virologic response whereas HCV RNA unchanged among placebo-treated patients
- Baseline HCV RNA level only factor significantly correlated with decrease in HCV RNA (Spearman rho: 0.428; *P* = .009)

Patient Group	Mean Serum HCV RNA, log_{10} IU/mL				*P* Value
	Day 0	Day 7	Day 14	Day 15	
Danoprevir (n = 40)					
Continuous decline (n = 14) ▪	6.3	3.5	2.8	3.2	< .0001
Plateau (n = 12) ▪	6.1	4.2	4.2	4.9	< .0001
Rebound (n = 14) ▪	6.1	3.8	5.1	5.5	< .0001
Placebo (n = 10)	6.3	6.4	6.3	6.5	.906

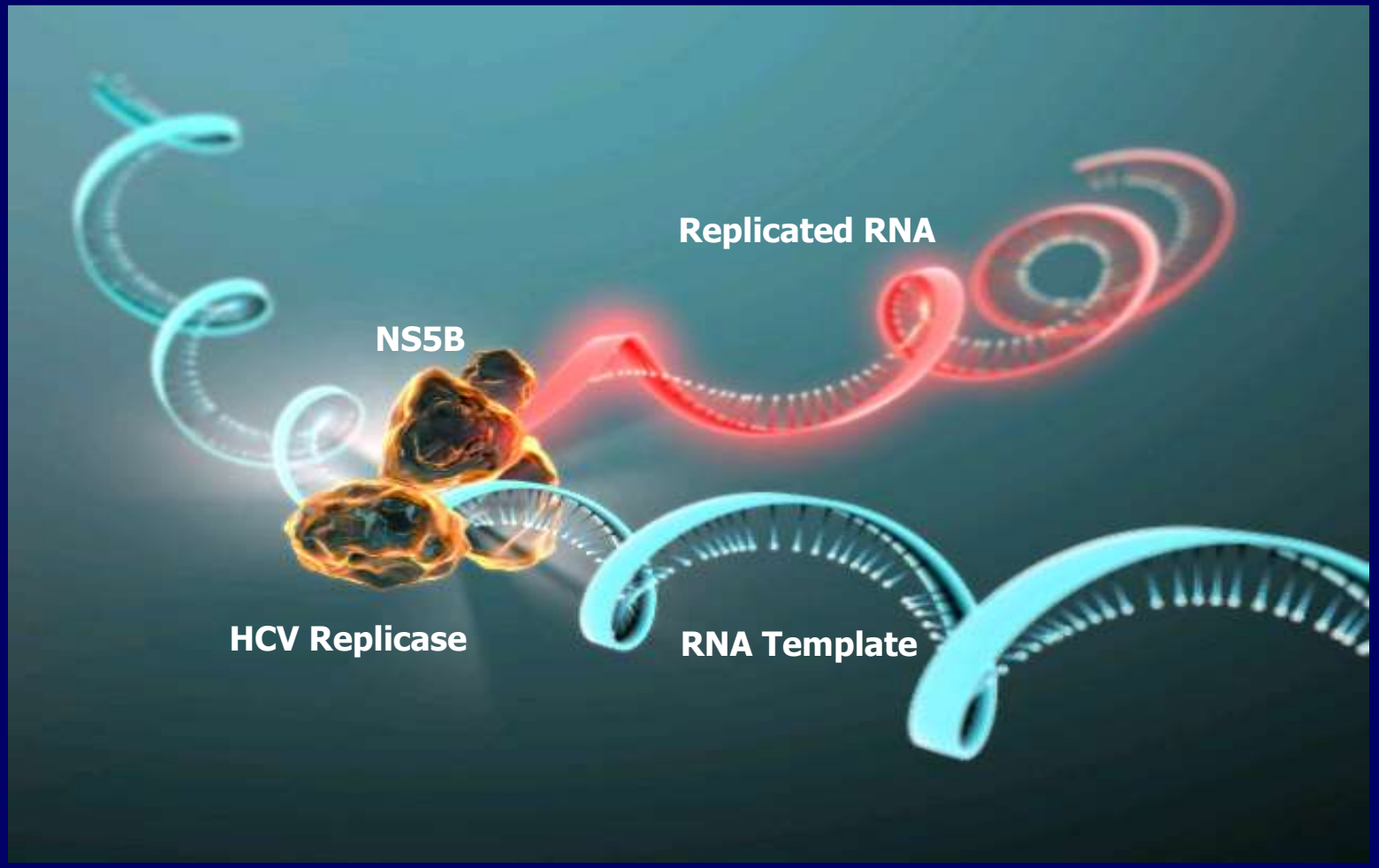
Moucari R, et al. Gut. 2010;59:1694-1698.

- Patients treated with danoprevir had significant changes in HOMA-IR regardless of type of virologic response whereas HOMA-IR unchanged among placebo-treated patients

Patient Group	Mean HOMA-IR Score				*P* Value
	Day 0	Day 7	Day 14	Day 15	
Danoprevir (n = 40)					
Continuous decline (n = 14) ▪	3.7	3.0	2.2	3.2	< .0001
Plateau (n = 12) ▪	3.7	2.1	1.9	2.9	< .0001
Rebound (n = 14) ▪	4.0	2.0	2.3	3.1	< .0001
Placebo (n = 10)	3.6	3.9	3.8	4.0	.945

Moucari R, et al. Gut. 2010;59:1694-1698.

NS5b Is Part of HCV Replicase—Critical to RNA Replication



Lindenbach BD, et al. *Nature*. 2005;436:933.
Graphic courtesy of Dr. M. Sulkowski.

NS5A inhibitors

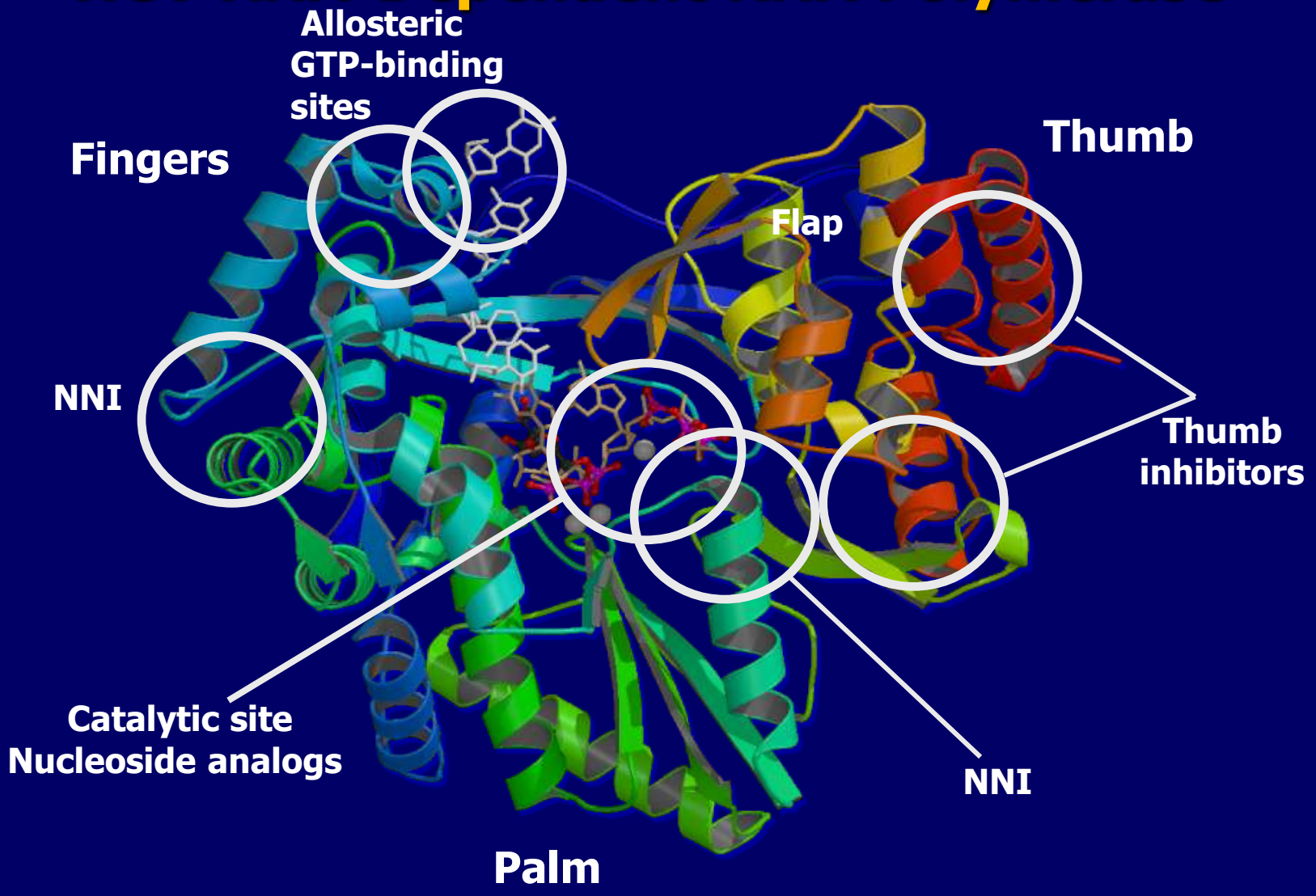
- It interfere with viral replication, assembly and release
- In combination with NS5B ⟶ Enhanced antiviral activity
- BMS-790052 as a mono therapy or in combination results in RVR and cEVR in over 80% of patient against most HCV genotypes

Activity of NS5A Inhibitors Combined With PR in Phase II Studies

Polymerase Inhibitor	Trial, Phase	Patients Meeting Efficacy Measure, % (SOC)
BMS-790052[1]	IIa	RVR: 42-92 (8) eRVR: 42-83 (8) cEVR: 58-83 (42)

1. Pol S, et al. EASL 2010. Abstract 1189.

HCV RNA-Dependent RNA Polymerase



Adapted from Butcher SJ, et al. *Nature*. 2001;410:235. Reprinted with permission.

Compunds targeting HCV replication:

- NS5B polymerase inhibitors :
- NS5B polymerase inhibitors can be divided into 2 distinct categories

A-Nucleoside analogue inhibitors (NIS)

B-NON-Nucleoside analogue inhibitors (NNIS)

A-Nucleoside analogue inhibitors (NIS)

- NIS are potentially effective against different genotypes .
- Single amino acids subistitutions in every position of active center may result in loss of functions or impaired replicative fitness

- Mericitabine (R7128)
- R7128 + Peg –INF +RIBA ⟶

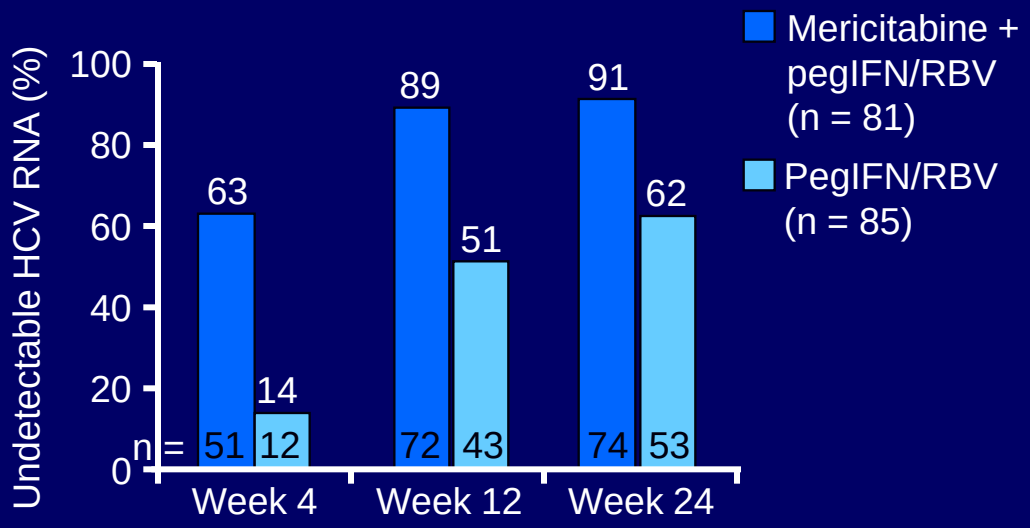
  EVR >80%
- R7128+Protease Inhibitors (R7227) for 14 Days ⟶ Synergistic antiviral activity .

B-NON-Nucleoside analogue inhibitors (NNIS)

- Achieves NS5B inhibition by binding to different allosteric enzyme sites, which result in conformational protein Change before the elongation complex is formed .
- They display low to medium antiviral activity and low genetic barrier to resistance.

JUMP-C Interim Analysis: Mericitabine + PegIFN/RBV in Tx-Naive GT 1/4 Patients

- Placebo-controlled, double-blind phase IIb trial
- Mericitabine (formerly RG7128) a nucleoside inhibitor of HCV NS5B RNA polymerase
- Week 36 interim analysis, patients randomized to 1 of 2 groups:
  - Mericitabine 1000 mg BID + pegIFN/RBV response-guided therapy (n = 81): triple therapy for 24 wks, then follow-up (if eRVR*) or 24 wks of pegIFN/RBV (if no eRVR)
  - PegIFN/RBV for 48 wks (n = 85)
- eRVR* 60% (n = 49) in mericitabine arm
  - SVR12 in 76% of these patients

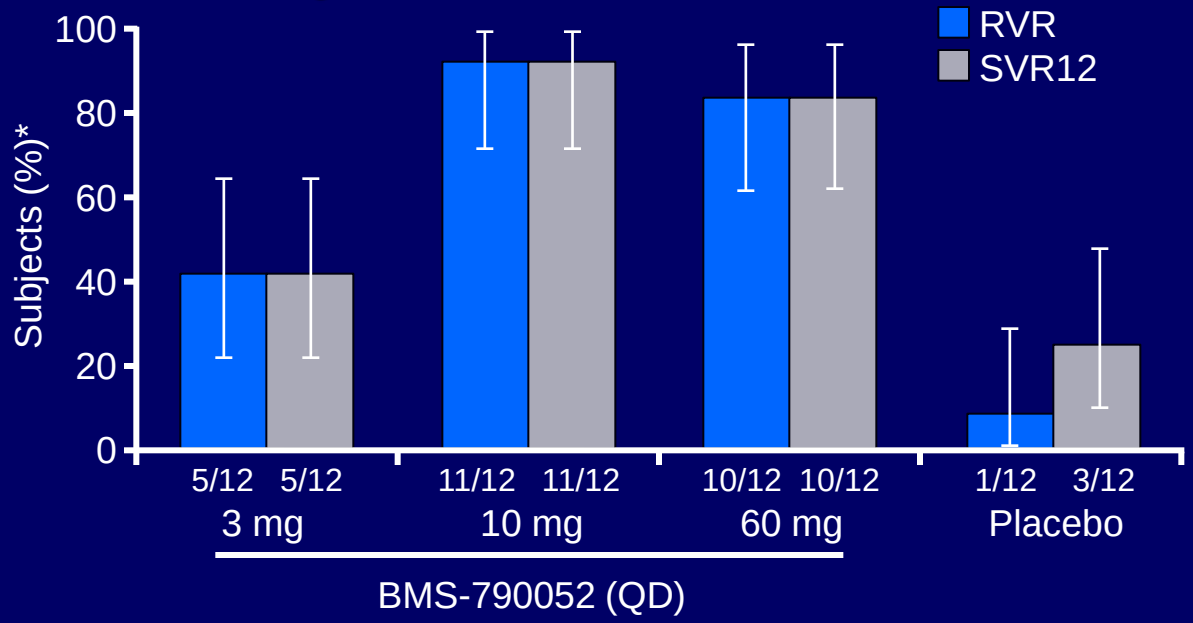


Pockros P, et al. EASL 2011. Abstract 1359.

*HCV RNA undetectable Weeks 4-22.

BMS-790052 in Tx-Naive GT1 Patients: 12-Wk Posttx Analysis of Phase IIa Trial

- BMS-790052: NS5A replication complex inhibitor
- BMS-790052 dosed at 3, 10, or 60 mg QD or placebo, each with pegIFN/RBV for 48 wks
  - High rates of SVR with BMS-790052 dosed at 10 or 60 mg QD



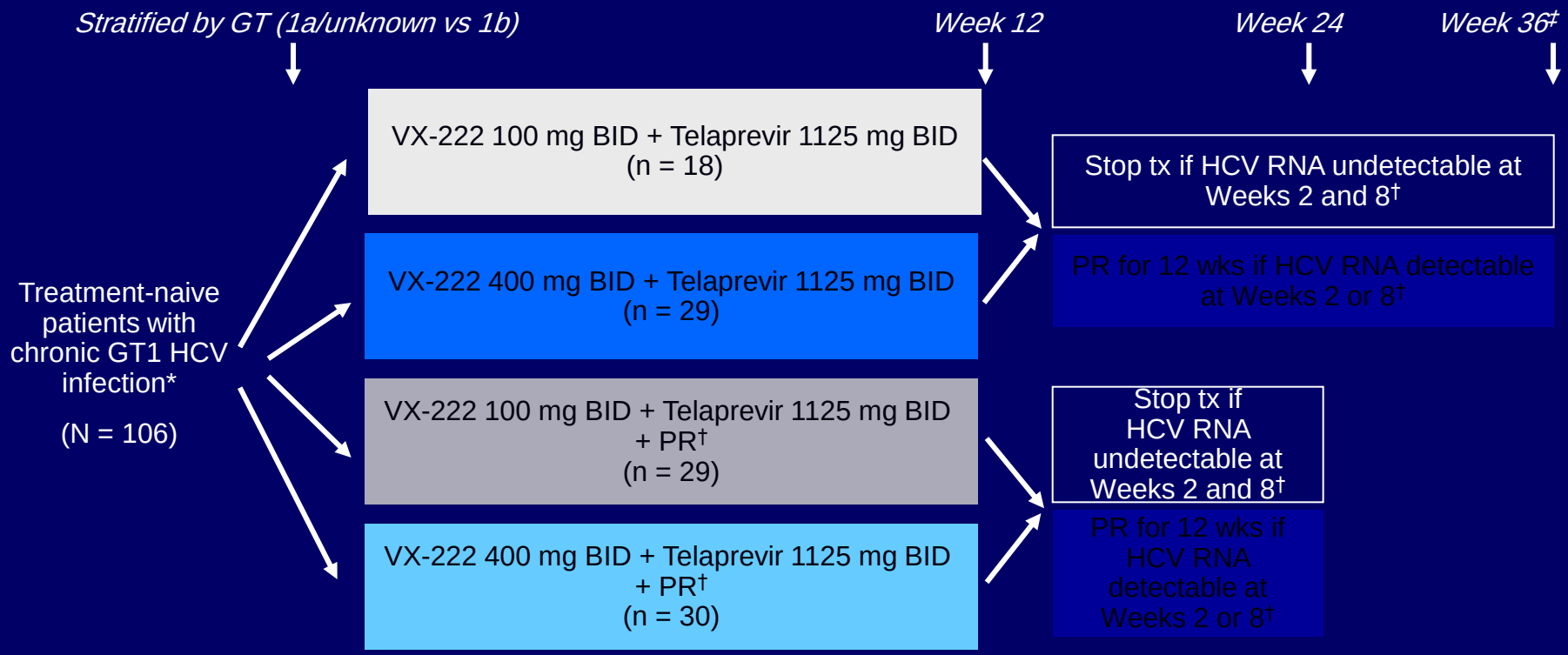
- Safety outcomes with BMS-790052 similar to pegIFN/RBV + placebo
  - No incremental hematologic, dermatologic, or hepatic toxicities

*Intent to treat analysis.
RVR, undetectable (< 10 IU/mL) HCV RNA at Week 4.

Pol S, et al. EASL 2011. Abstract 1373. Graphic used with permission.

ZENITH Week 12 Interim Analysis: VX-222 + Telaprevir ± PegIFN/RBV in GT1 Tx Naive

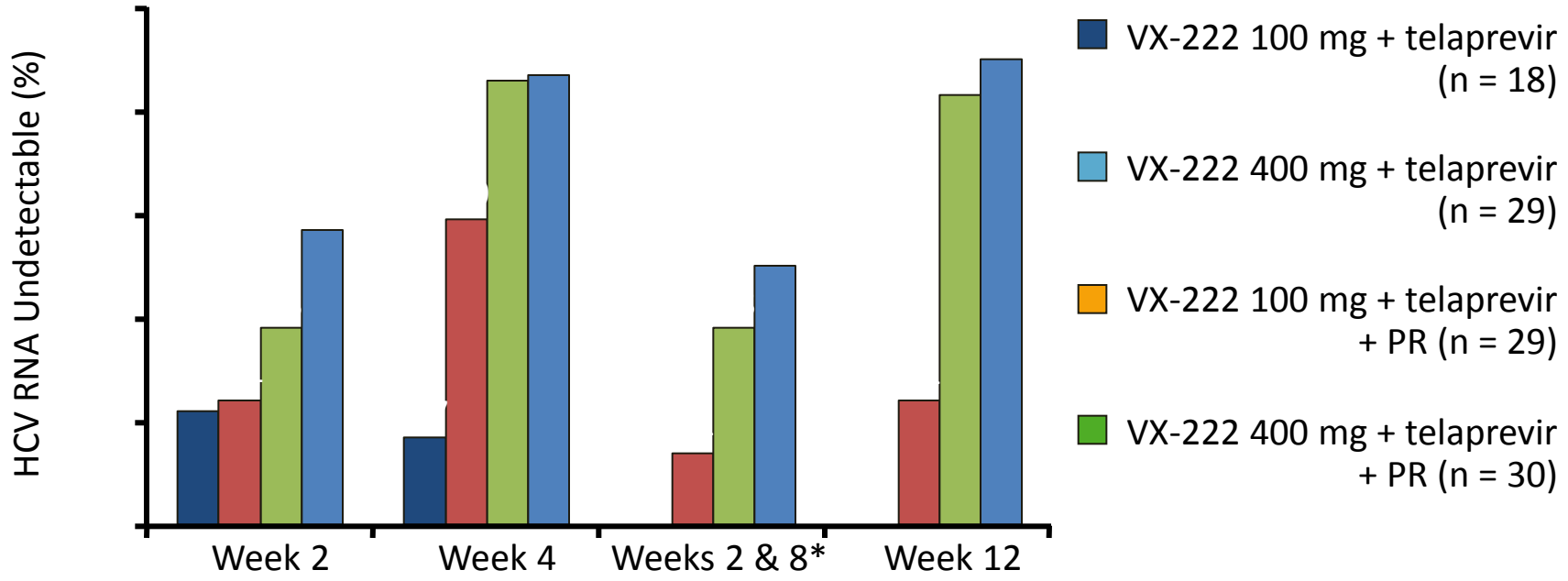
- Parallel-group, dose-ranging phase II study



*A fifth arm assessing VX-222 400 mg QD + telaprevir 1125 mg BID + RBV currently accruing.
†PegIFN 180 µg/wk + weight-based RBV 1000-1200 mg/day.

Di Bisceglie A, et al. EASL 2011. Abstract 1363.

ZENITH Week 12 Interim Analysis: VX-222 + Telaprevir ± PegIFN/RBV in GT1 Tx Naive

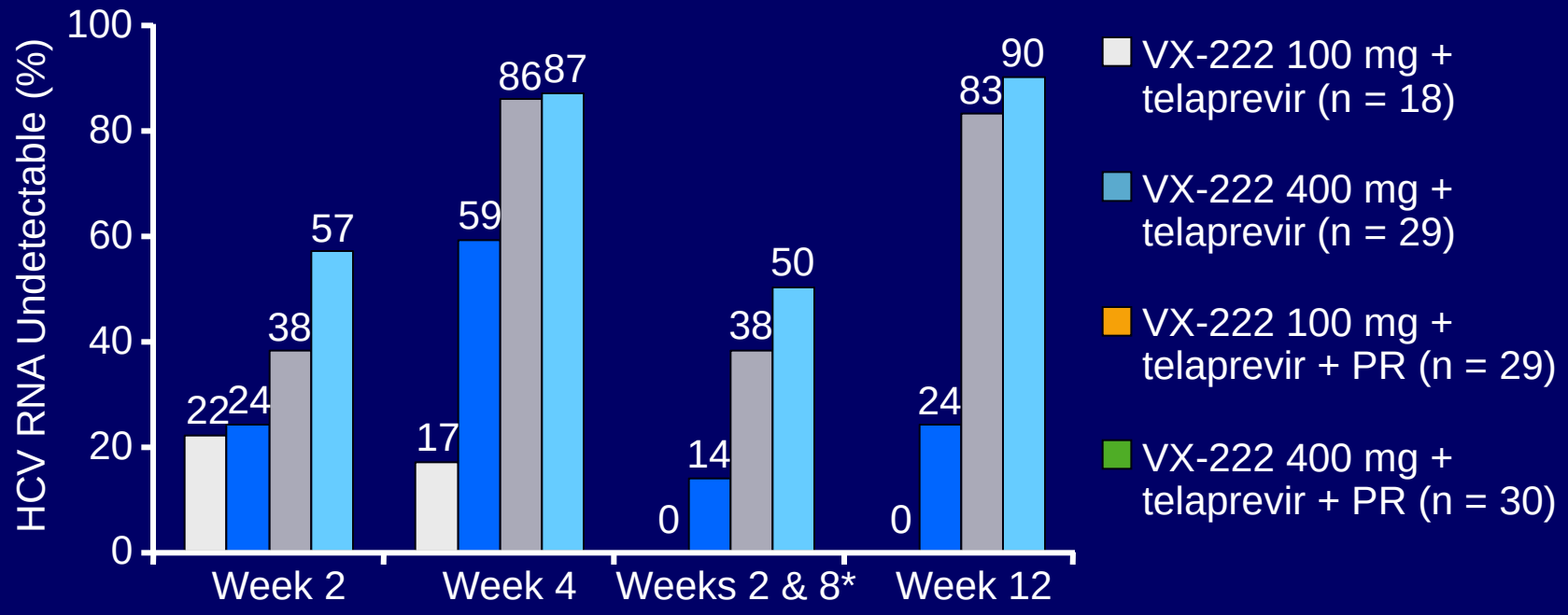


*Indicates patients eligible for shortened therapy.

- No virologic breakthrough in quad-therapy arms
- Virologic breakthrough common in VX-222/TVR dual-therapy arms (17% to 31%)
  - Both dual regimens stopped prematurely per protocol

Di Bisceglie A, et al. EASL 2011. Abstract 1363.

ZENITH Week 12 Interim Analysis: VX-222 + Telaprevir ± PegIFN/RBV in GT1 Tx Naive



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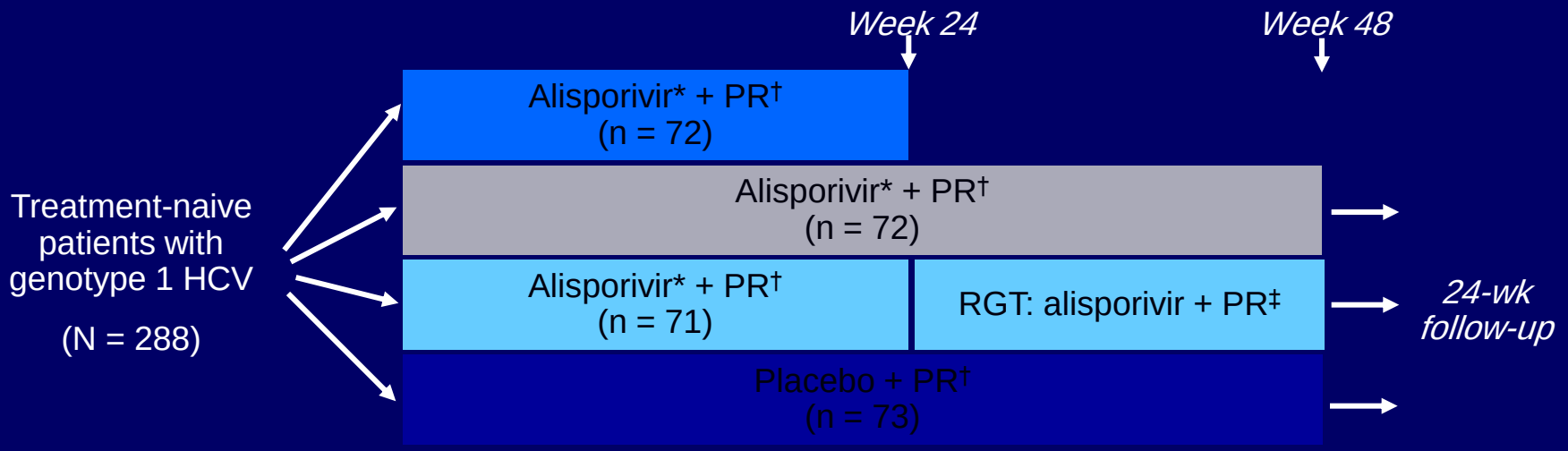
Di Bisceglie A, et al. EASL 2011. Abstract 1363.

Host protein as a target in treating HCV

- Cyclophilin B inhibitors decrease viral replication through modulation of NS5B activity
- Debio-025(alisporivir)
- In different studies as a mono therapy or in combination lead to good reduction in HCV RNA
- No difference in antiviral activity Between different genotypes

ESSENTIAL: Alisporivir + PegIFN/RBV in GT1 Treatment-Naive Patients

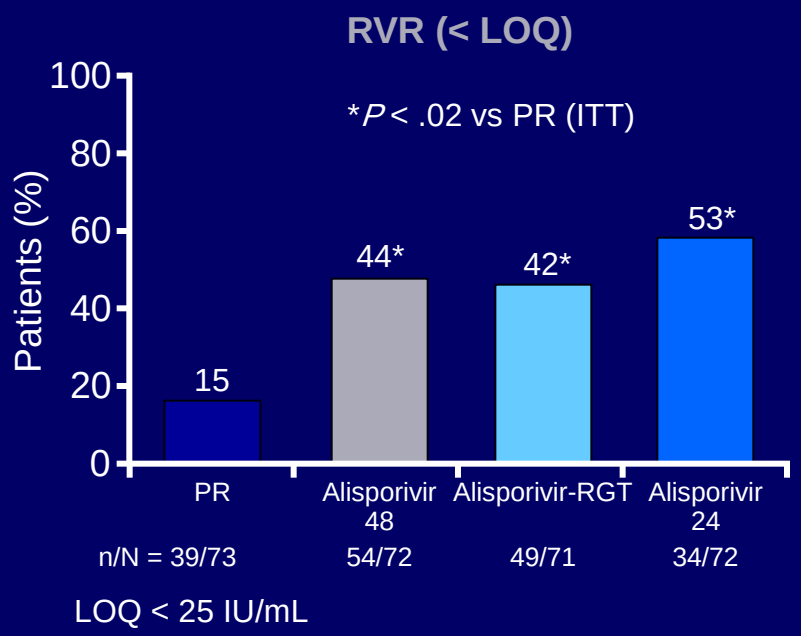
- Alisporivir: oral inhibitor of cyclophilin that acts as host-targeted antiviral
  - Modified form of cyclosporin A with enhanced cyclophilin binding but no immunosuppressive activity
  - Targets host cyclophilin A required for HCV replication
- Placebo-controlled, double-blind phase IIb trial

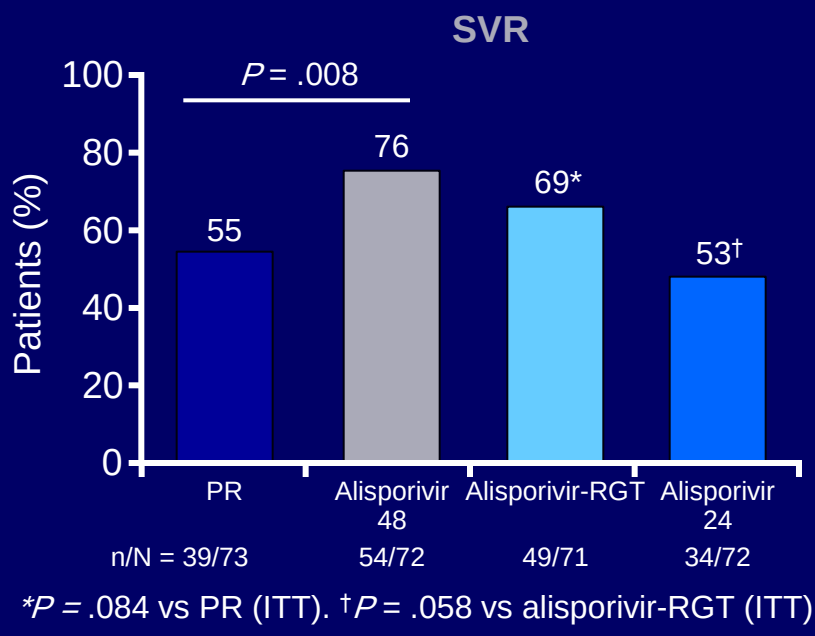


*Alisporivir dosed at 600 mg BID for first wk, then 600 mg QD thereafter. †PegIFN alfa-2a 180 µg/wk + RBV 1000-1200 mg/day. ‡Patients with RVR (ie, HCV RNA ≤ 10 IU/mL at Week 4) treated for 24 wks; patients without RVR treated for 48 wks.

Flisiak R, et al. EASL 2011. Abstract 4.

ESSENTIAL: Alisporivir + PegIFN/RBV in GT1 Treatment-Naive Patients





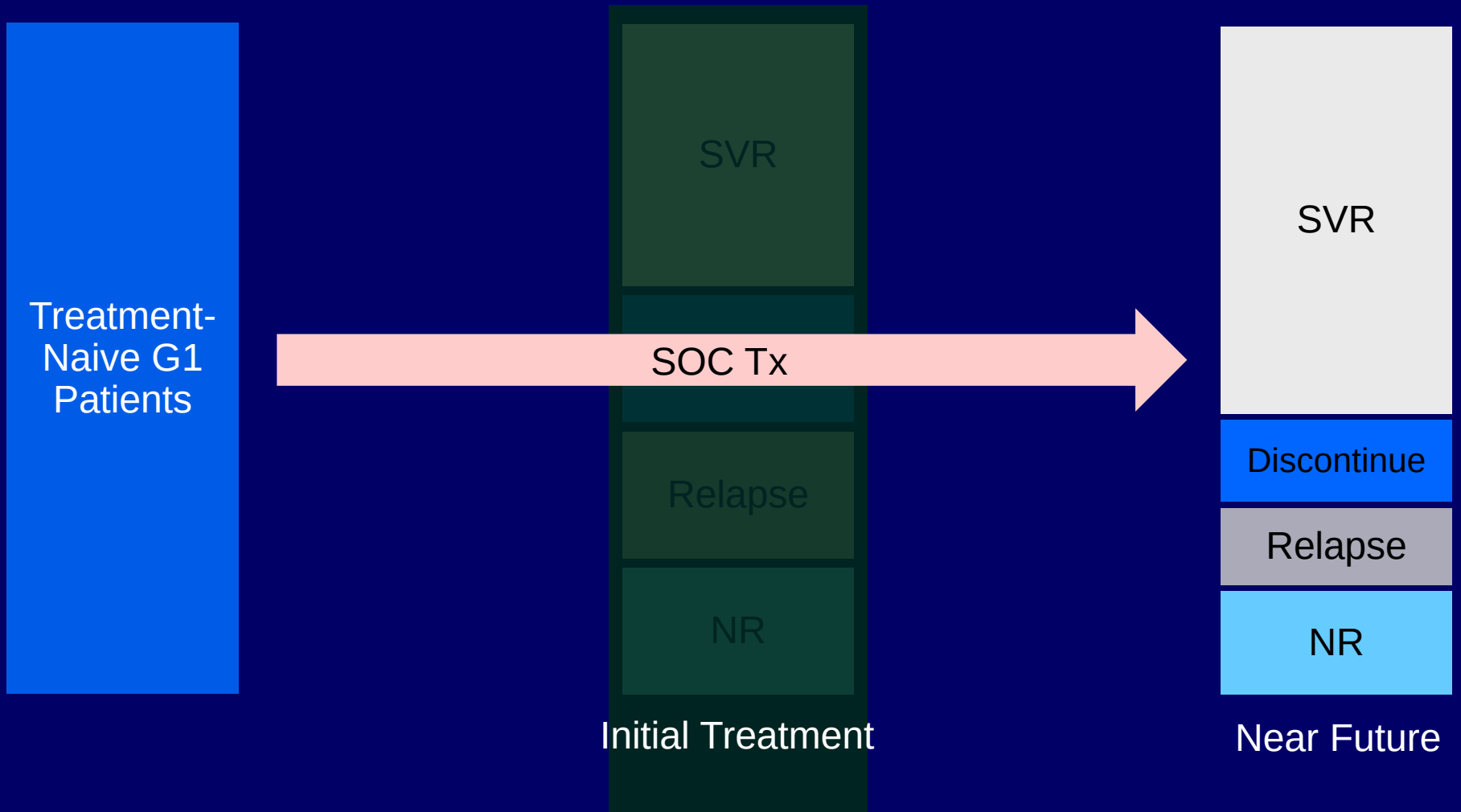
- Improved SVR rates with alisporivir vs pegIFN/RBV, regardless of *IL28B* GT
- Transient hyperbilirubinemia associated with initial loading dose of alisporivir
  - 4.2% had total bilirubin ≥ 5 x ULN; resolved to < 5 x ULN by Week 4

Flisiak R, et al. EASL 2011. Abstract 4. Graphic used with permission.

How Will We Use DAAs in the Future to Treat HCV Infection?

- Initial paradigm to be approved will be addition of DAA to pegIFN/RBV
  - Will substantially improve therapeutic possibilities for many GT1 patients
- However, challenging patient scenarios will remain, including
  - Previous null responders and other patients with adverse prognostic factors: is the improvement in SVR rate with telaprevir or boceprevir "good enough"?
  - Patients who cannot tolerate pegIFN, RBV, and/or the adverse events associated with telaprevir or boceprevir
  - Patients who cannot adhere to complex regimens for 6-12 mos; risk of resistance with suboptimal adherence
  - Others: Patients with end-stage renal disease, HCV/HIV coinfection, transplants
- For some of these patients, will future DAA regimens represent better options?

Evolving Therapies: Where Will We Be Soon?



Future treatment paradigm cont.

Response guided therapy

- We should move toward a response-guided therapy that can limit exposure and toxicity, and strive for higher response rates for some patients.

- Additionally, new methods of patient stratification prior to treatment not only will yield better prognostic information, but also are likely to alter therapeutic approaches regarding the potential benefits and risks of HCV therapy.

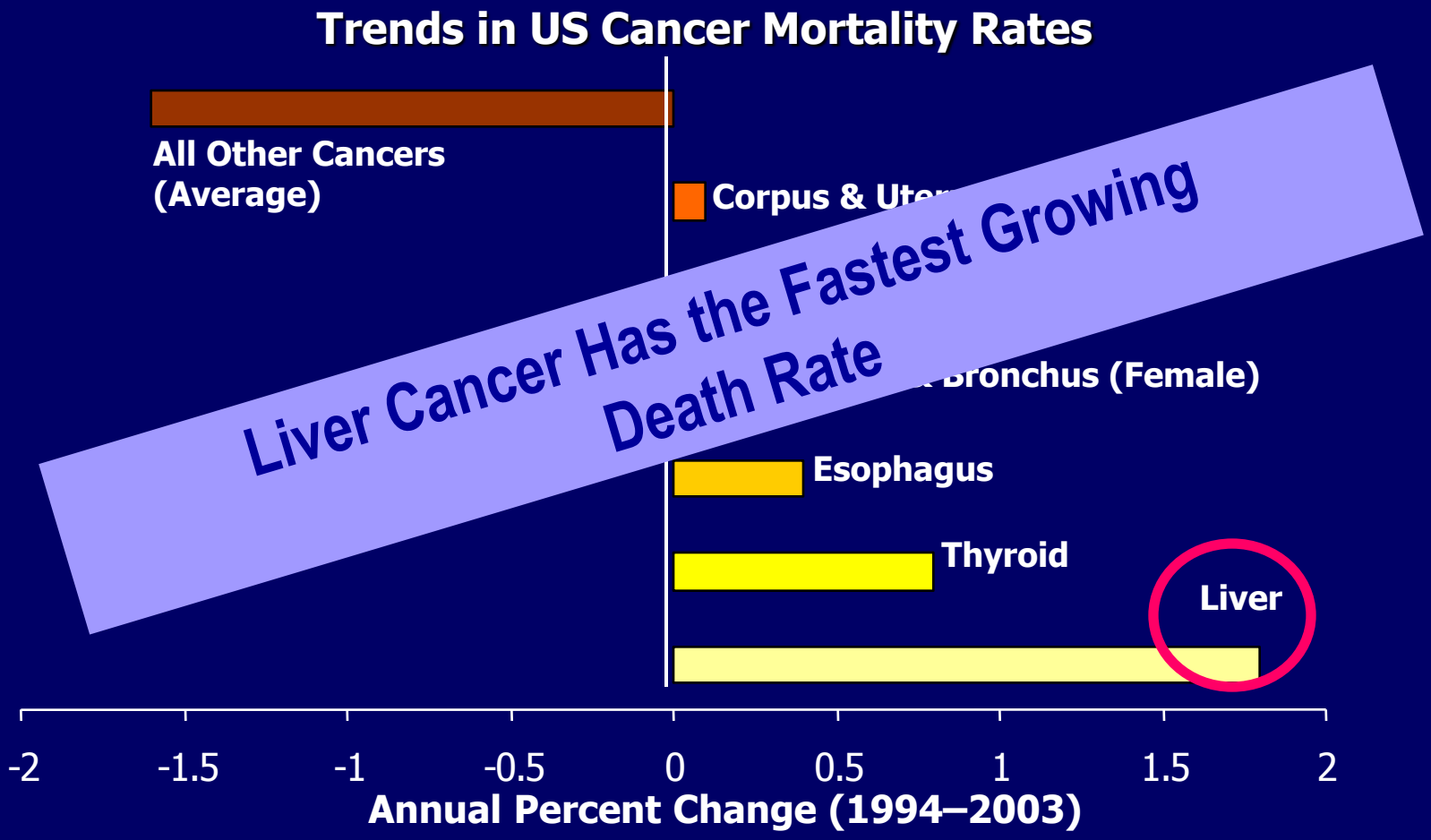
- Pharmacogenomics seems very promising in relation to the rational selection of different treatment strategies for each patient.
- In particular, data suggest that IL28B gene polymorphisms have an influence on viral kinetics, RVR, and SVR.

Personalized Medicine Becoming a Reality

- Treatment regimens for HCV are expected to become increasingly individualized.
- appropriate pre-treatment patient stratifications, Specifically, identifying the genotype 1 subtype, screening for inosine triphosphate pyrophosphatase (ITPA) deficiency and modifying therapy according to interleukin-28 (IL-28) polymorphisms have the potential to contribute to improved outcomes.

Conclusions

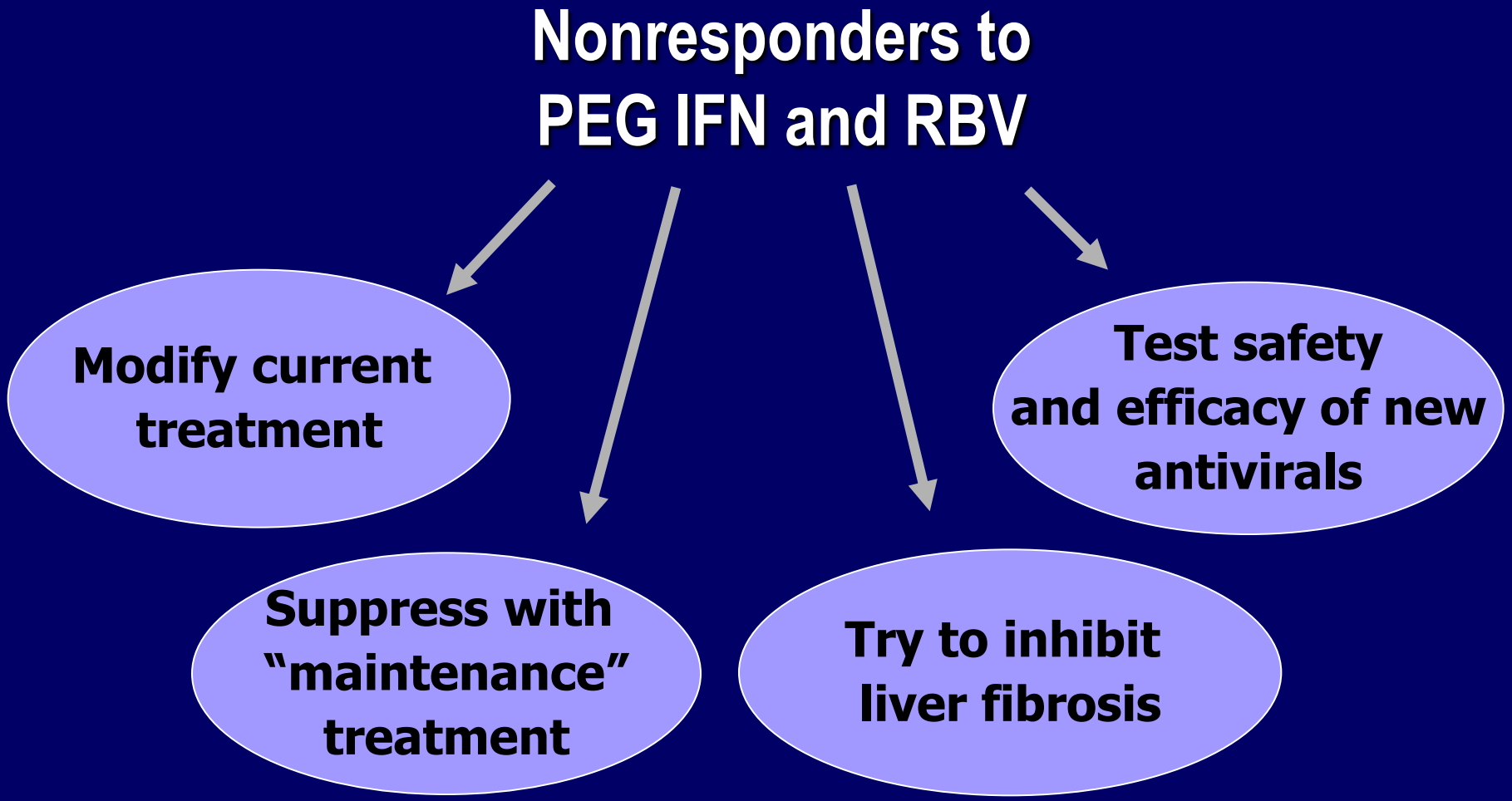
The Increasing Challenge of HCV Disease Burden



National Cancer Institute. Seer Summary Figures and Tables. Available at: http://seer.cancer.gov/csr/1975_2003/results_merged/topic_graph_trends.pdf. Accessed on March 27, 2007.

Reality Check

Assessing the Present to Anticipate the Future



Finding Our Way in the Maze

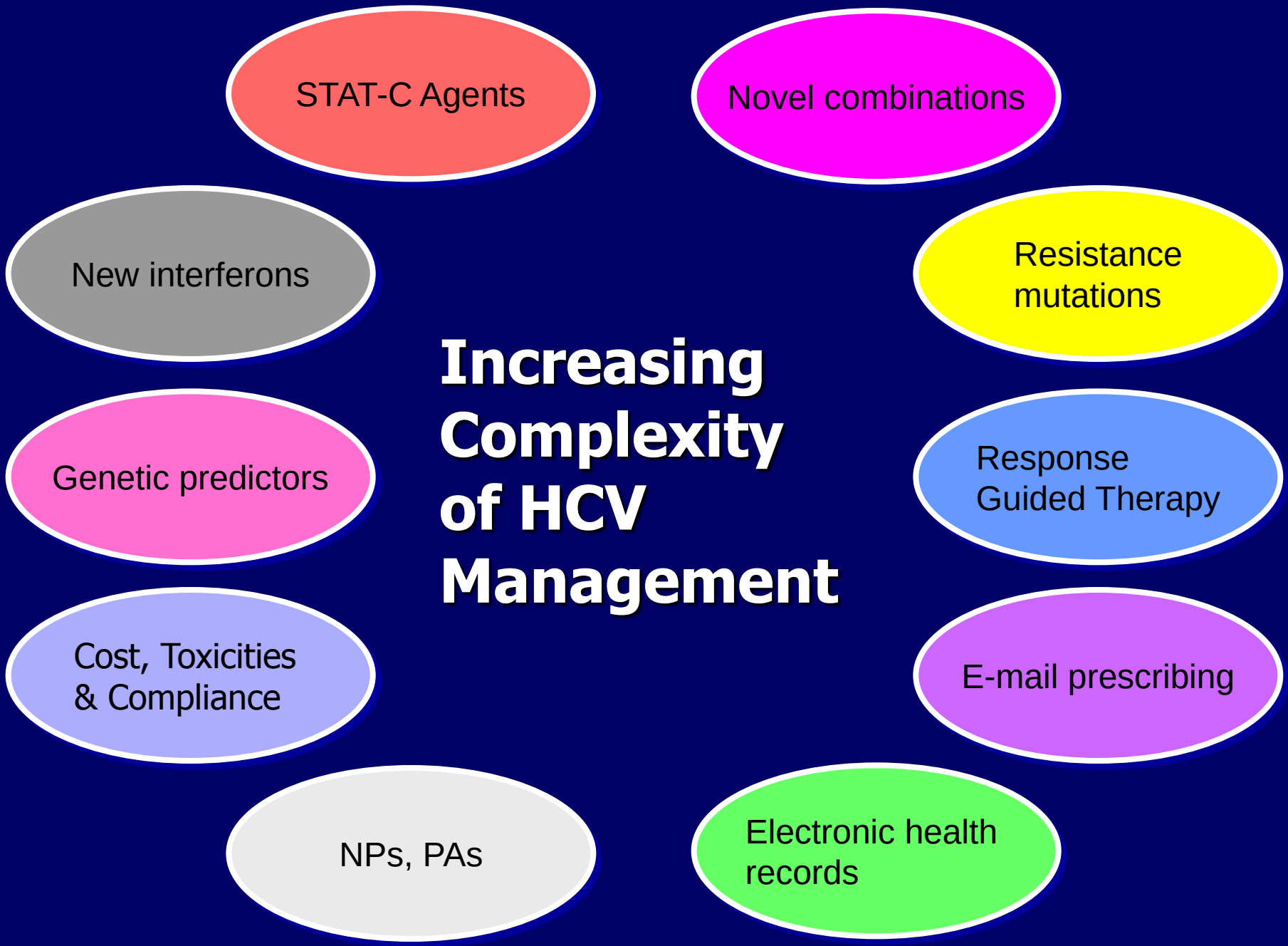
Changing Direction Toward More Effective Treatment

Addition of STAT-C Agents

IFN + **RBV** + **STAT-C**

Beyond IFN and RBV

Protease inhibitors + **Polymerase inhibitor** +/- **Additional STAT-C?**


STAT-C Agents
Novel combinations
New interferons
Resistance mutations
Increasing Complexity of HCV Management
Genetic predictors
Response Guided Therapy
Cost, Toxicities & Compliance
E-mail prescribing
NPs, PAs
Electronic health records

Take-Home Messages

- Current therapy is unlikely to significantly reduce HCC incidence
- Increased understanding of the hepatitis C virus increases the capacity to develop and assess new antivirals
- STAT-C agents require us to think more like virologists than hepatologists or gastroenterologists
- Change is inevitable
  - Anticipate it
  - Be prepared

Thank you