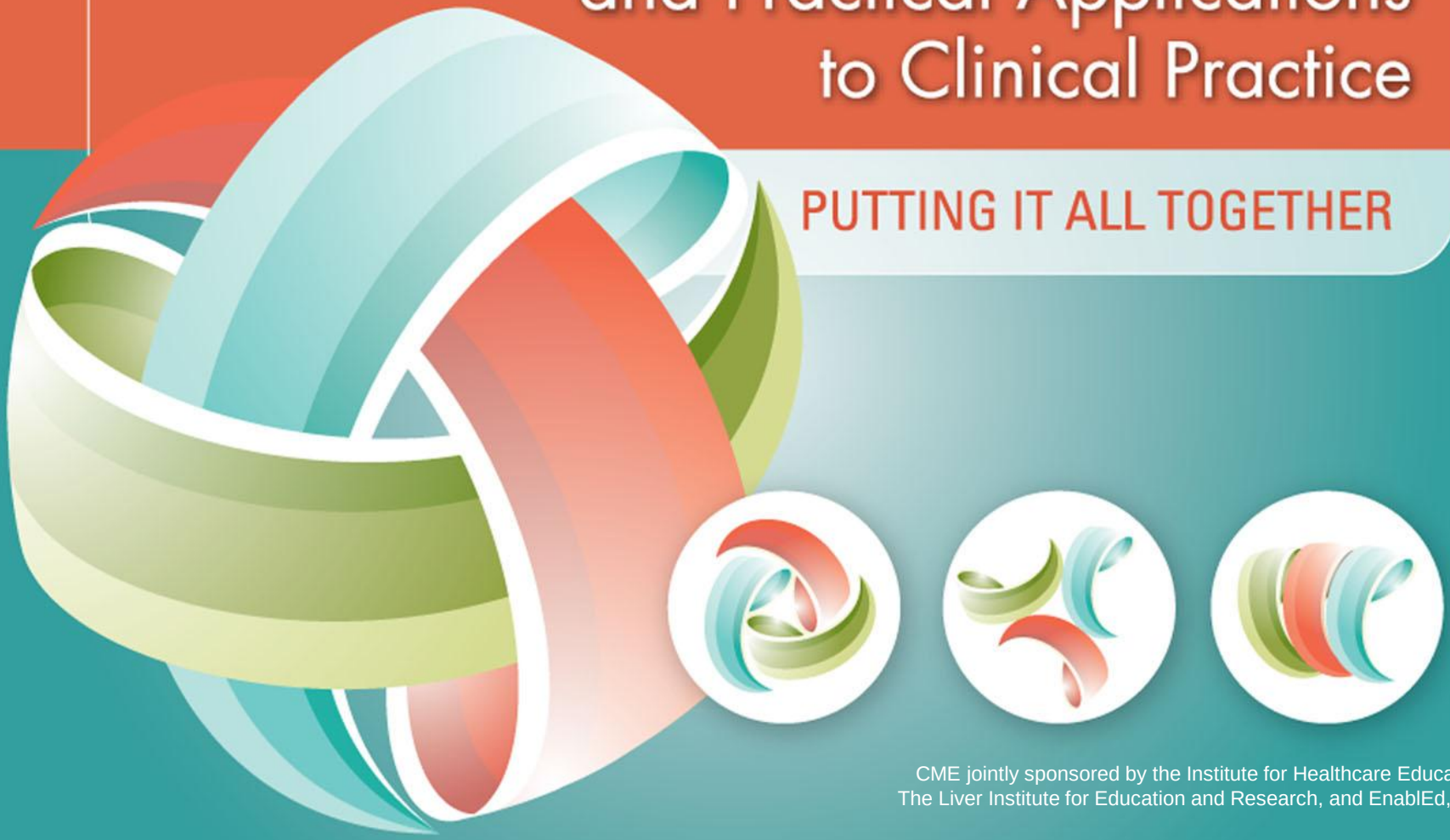
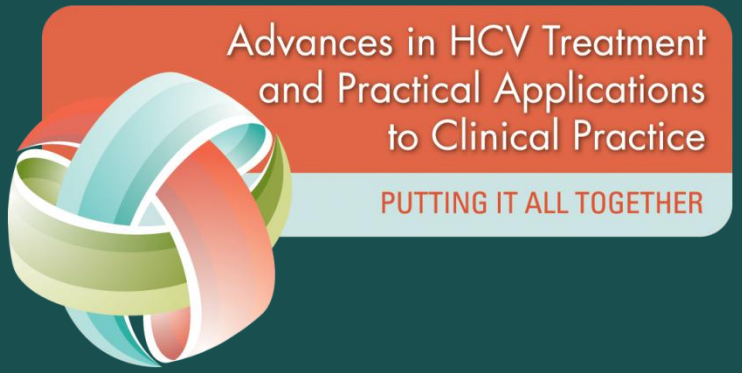
Advances in HCV Treatment and Practical Applications to Clinical Practice

PUTTING IT ALL TOGETHER



CME jointly sponsored by the Institute for Healthcare Education, The Liver Institute for Education and Research, and EnablEd, LLC



Case:
Viral Load Testing and Resistance

Case: Viral Load Testing and Resistance

- 57-year-old man with HCV genotype 1a infection for 35 years
- Course of PEG-IFN and ribavirin 6 years ago
  - Baseline HCV RNA: 3.1M IU/mL (6.49 $\log_{10}$)
  - 11,300 IU/mL at Week 12 (4.05 $\log_{10}$; a 2.44-$\log_{10}$ decrease from baseline), but not cleared by Week 24
- Medical history: diabetes mellitus, hypertension
- Medications: glimepiride, ramipril
- Physical examination: weight 91 kg; no evidence of advanced liver disease

HCV = hepatitis C virus; M = million; PEG-IFN = pegylated interferon.

Case: Viral Load Testing and Resistance

- Current laboratory data:
  - ALT 78 IU/L
  - AST 56 IU/L
  - Albumin 3.8 g/dL
  - Platelets 160,000/μL
  - Hemoglobin 14.5 g/dL
  - White blood cells 7,100/μL
  - α-fetoprotein 7.8 ng/mL
  - HCV RNA 5.5M IU/mL (6.74 $\log_{10}$)
- FibroSure 0.47
- Ultrasound: spleen 12 cm, no focal liver lesions

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Case: Viral Load Testing and Resistance

- What proportion of patients have variants that are resistant to protease inhibitors (PI) at baseline?
- Would you do baseline resistance testing?

- Would you treat this patient?

Case: Viral Load Testing and Resistance

- The patient begins a course of boceprevir-based therapy
  - 4-week lead-in phase: PEG-IFN α-2b 1.5 μg/kg/week with ribavirin 1,200 mg/day
  - Body weight = 91 kg
- After 4 weeks, HCV RNA falls to 600,000 IU/mL (5.77 $\log_{10}$; a 0.97-$\log_{10}$ decrease from baseline)

Case: Viral Load Testing and Resistance

- What would you tell the patient his chances of achieving SVR are at this point?

SVR = sustained virologic response.

Case: Viral Load Testing and Resistance

- Patient starts boceprevir with continued PEG-IFN/ribavirin (PR) therapy
- Week 8: HCV RNA 1,780 IU/mL; hemoglobin 10.2 g/dL
- Week 12: HCV RNA 80 IU/mL; hemoglobin 9.1 g/dL
- Moderate fatigue, but activities are not limited

Case: Viral Load Testing and Resistance

- Would you continue therapy?
- How would you manage his anemia?

Futility Rules – When to Stop

BOCEPREVIR

If ≥100 IU/mL HCV RNA:

Stop PEG-IFN, ribavirin, and boceprevir

Week 24

Confirmed detectable HCV RNA

Stop PEG-IFN, ribavirin, and boceprevir

Boceprevir prescribing information.

Case: Viral Load Testing and Resistance

- Ribavirin dose reduced to 800 mg/day
- Week 20: HCV RNA 897 IU/mL; hemoglobin 9.4 g/dL
- Week 24: HCV RNA 6,590 IU/mL

Case: Viral Load Testing and Resistance

- What do you think has happened virologically?
- Would you stop therapy?
- What are the most likely resistant variants (RVs) that might have emerged?
- Would you do resistance testing at this time?

Case: Viral Load Testing and Resistance

- The patient asks about the long-term consequences of resistance
  - What would you tell him?

An Alternative Scenario

- What if the patient's viral level at Week 8 had been 145 IU/mL and negative from Weeks 12 to 24?
- How would you treat the patient?

Another Case

- A 54-year-old woman undergoes treatment of her chronic HCV infection for the first time
  - HCV genotype 1a
  - Baseline HCV RNA 3.5M IU/mL (6.54 $\log_{10}$)
  - Liver biopsy: F2 fibrosis
- Treated with PEG-IFN, ribavirin, and telaprevir
  - At Week 4, HCV RNA 2,200 IU/mL (3.34 $\log_{10}$)
  - Patient tolerating therapy relatively well
- What would you do?

Available HCV RNA Assays

Test	Lower limit of detection (IU/mL)	Upper limit of detection (IU/mL)
Roche HCV Amplicor 2.0	50	600–500,000
Roche COBAS TaqMan 2.0	10	$25–390 \times 10^{6}$*
Roche COBAS Taqman 2.0	10	$43–6.9 \times 10^{7}$**
Abbott Realtime	12	$12–100 \times 10^{6}$
Quest Diagnostics Heptimax	5	$5–69 \times 10^{6}$

**Manual extraction – used in pivotal trials.*
***Automated – used commercially (AmpliPrep).*

Jacobson IM et al. J Viral Hepat 2012;19(4):236-43; COBAS AmpliPrep/COBAS TaqMan HCV Test Package Insert, 2008.

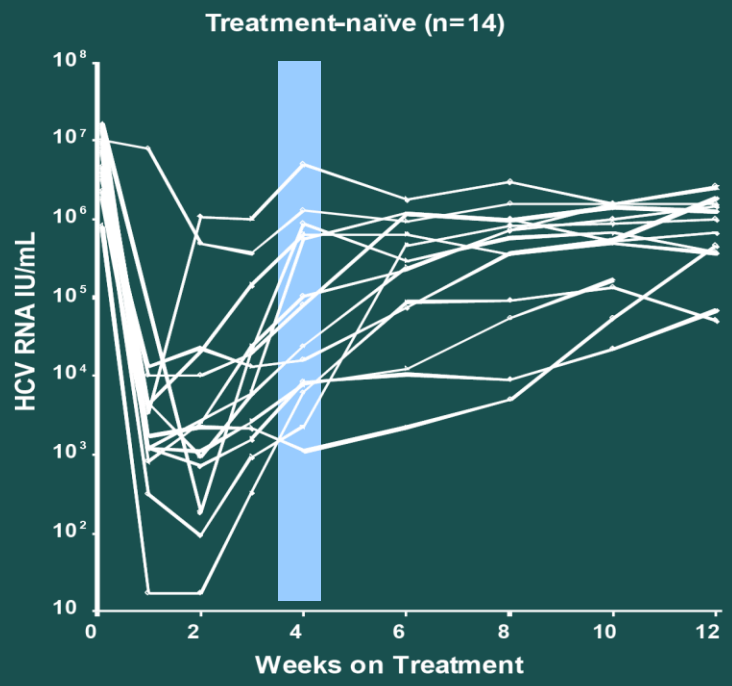
Futility Rules – When to Stop

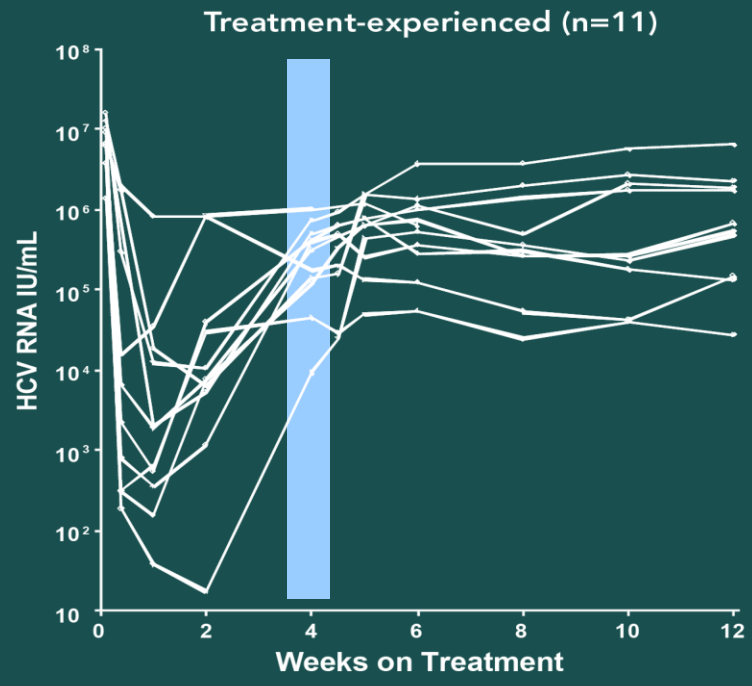
TELAPREVIR

If >1000 IU/mL HCV RNA:	Week 12 If >1000 IU/mL HCV RNA:	Week 24 Confirmed detectable HCV RNA
Stop PEG-IFN, ribavirin, and telaprevir	Stop PEG-IFN, ribavirin, and telaprevir	Stop PEG-IFN and ribavirin

Telaprevir prescribing information.

HCV RNA Profiles in Patients with HCV RNA >1000 IU/mL at Week 4 of Telaprevir Therapy





- 23 of 25 patients with HCV RNA level >1000 IU/mL at Week 4 reached nadir HCV RNA level at or before Week 4, typically by Week 2, with later increase in HCV RNA level by Week 4

Jacobson IM, et al. EASL 2012 Abstract 55.

Patients Exceeding HCV RNA Thresholds at Week 12 of Telaprevir Therapy

Patient Population/Futility Rule	Week 4, % (n/N)	Week 12*, % (n/N†)
Treatment-naïve (T12PR, ADVANCE/ILLUMINATE)		
HCV RNA >1000 IU/mL	1.7 (14/844)	1.5 (9/605)
HCV RNA >100 but ≤1000 IU/mL	1.9 (16/844)	1.2 (7/605)
Prior Relapser (T12PR48, REALIZE)		
HCV RNA >1000 IU/mL	0.7 (1/138)	0.8 (1/119)
HCV RNA >100 but ≤1000 IU/mL	0 (0/138)	0 (0/119)
Partial Responder (T12PR48, REALIZE)		
HCV RNA >1000 IU/mL	0 (0/46)	0 (0/39)
HCV RNA >100 but ≤1000 IU/mL	2.2 (1/46)	0 (0/39)
Null Responder (T12PR48, REALIZE)		
HCV RNA >1000 IU/mL	14 (10/70)	3.9 (2/51)
HCV RNA >100 but ≤1000 IU/mL	8.6 (6/70)	12 (6/51)

*For REALIZE: includes 7 patients who met Week 6 or Week 8 futility rules.
†Patients no longer receiving telaprevir or who lacked Week 12 HCV RNA level were excluded.

Jacobson IM, et al. EASL 2012 Abstract 55.

Resistance Profiles in Patients with HCV RNA >1000 IU/mL at Week 4 of Telaprevir Therapy

Variant	Level of resistance	Treatment-naïve (ADVANCE/ILLUMINATE) N=14	Treatment-experienced (REALIZE) N=11
V36M+R155K	High	12*	8
A156S/T/V	High	1	0
R155K	Low	0	2†
Wild-type	Wild-type	1	1

*Week 4 HCV RNA level and viral sequence unavailable for 1 patient, so Week 5 data used.

†R155K present at baseline in 1 patient.

Jacobson IM, et al. EASL 2012 Abstract 55.

Stopping Rules for BOC/PR Combination Therapy: Exploratory Analyses of SPRINT-2 and RESPOND-2

- Rationale for stopping rules with PI-based therapy includes desire to avoid emergence of resistant variants and unneeded exposure
- Stopping rules in Phase III BOC trials included:
  - Detectable HCV RNA Week 24
  - Detectable HCV RNA Week 12

Characteristics of Futility Rules Considered (SPRINT-2, both BOC arms)

Stopping Rule n (%)	Stopped by early rule (n=734)	Additional stopped by TW24 rule	Total stopped	SVR missed
TW8: <3 $\log_{10}$ decline	34 (5)	66 (9)	100 (14)	1
TW12: <2 $\log_{10}$ decline	24 (3)	71 (10)	95 (13)	0
TW12: ≥100 IU/mL	**65 (9)**	**49 (7)**	**114 (16)**	**0**
TW16: ≥25 IU/mL	73 (10)	32 (4)	105 (14)	1
TW24: detectable	NA	NA	79 (11)	0

Goals of Present Analysis:

1. Explore whether earlier stopping rule could be found for treatment-naïve patients
2. Explore whether TW8 stopping rule could apply to -naïves or experienced patients
3. Harmonize stopping rules between -naïves and experienced

Jacobson IM, et al. AASLD 2011 Abstract #954.

TW = treatment week.

Stopping Rules for BOC/PR Combination Therapy: Exploratory Analyses of SPRINT-2 and RESPOND-2

- SPRINT-2: Further support for TW12 stopping rule
  - At TW12, 73 pts in BOC arms had detectable HCV RNA <100 IU/mL
  - 60% were undetectable at TW24
  - 21 achieved SVR
- 29% with detectable HCV RNA <100 IU/mL at TW12 achieved SVR
  - Represents a sufficient persistent chance of SVR to warrant continuation to TW24

Impact of TW12 Stopping Rules: SPRINT-2

Stopping Rule n (%)	Stopped by TW12 rule (n=734)	Additional stopped by TW24 rule	Total stopped	SVR missed
>LLD, 9.3 IU/mL	144 (20)	20	164 (22)	21
>LLQ, 25 IU/mL	83 (11)	41	124 (17)	5
≥50 IU/mL	78 (11)	43	121 (16)	4
≥100 IU/mL	**65 (9)**	**49**	**114 (16)**	**0**
≥1000 IU/mL	43 (6)	61	104 (14)	0
<2 $\log_{10}$ decline	24 (3)	71	95 (13)	0
<3 $\log_{10}$ decline	34 (5)	66	100 (14)	0

LLQ = lower limit of quantitation.

Jacobson IM, et al. AASLD 2011 Abstract #954.

Stopping Rules for BOC/PR Combination Therapy: Exploratory Analyses of SPRINT-2 and RESPOND-2

- RESPOND-2: Lessons learned from protocol deviations
- Protocol: patients with detectable HCV RNA (>LLD) at TW12 be stopped
  - 39 pts in BOC arms had detectable HCV RNA <100 IU/mL at TW12
  - Of these, 31 had detectable HCV RNA <25 IU/mL (LLQ)
    - 6 continued therapy
    - 5/6 achieved SVR

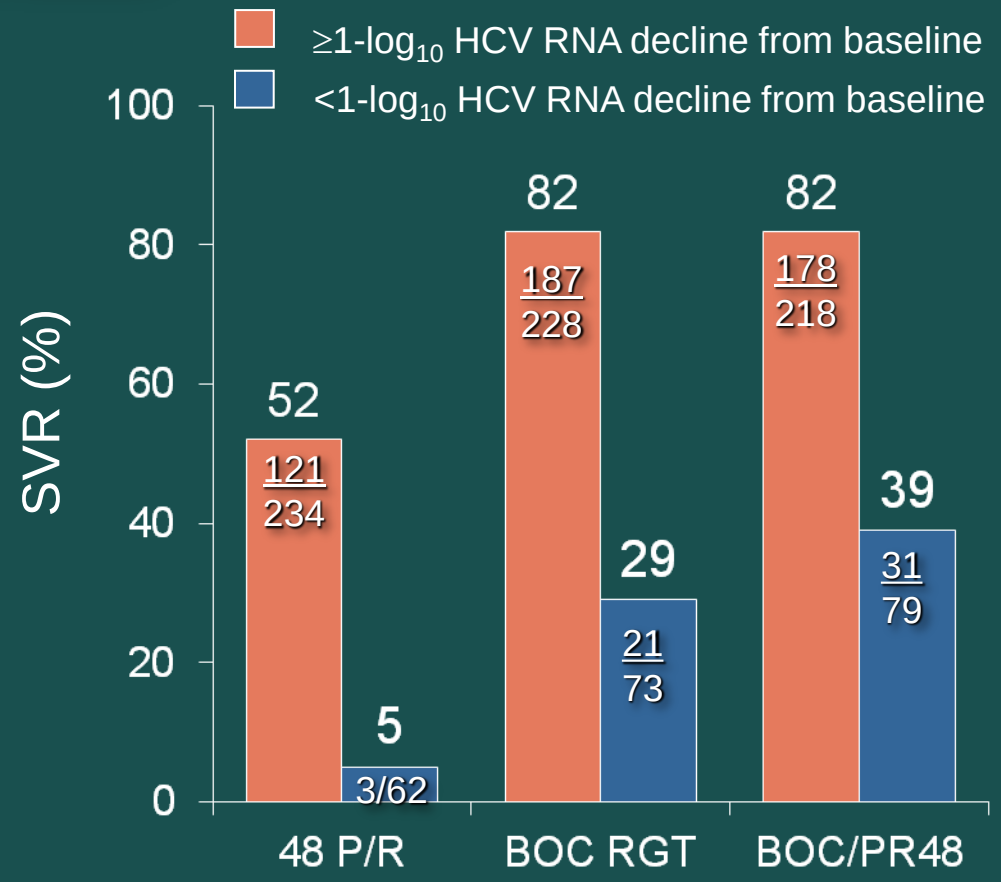
Jacobson IM, et al. AASLD 2011 Abstract #954.

Impact of TW8 Stopping Rules: RESPOND-2

Stopping Rule n (%)	Stopped by TW8 rule (n=323)	Additional stopped by TW12 rule	Total stopped	SVR missed
>LLD, 9.3 IU/mL	142 (44)	7	149 (46)	59
>LLQ, 25 IU/mL	79 (24)	14	93 (29)	14
≥50 IU/mL	70 (22)	15	85 (26)	11
≥100 IU/mL	57 (18)	24	81 (25)	8
≥1000 IU/mL	27 (8)	45	72 (22)	1
<2 $\log_{10}$ decline	3 (1)	69	72 (22)	0
<3 $\log_{10}$ decline	19 (6)	54	73 (23)	1

Stopping rules of HCV RNA ≥100 IU/mL at TW 12 and detectable HCV RNA at TW 24 enable early stopping for futility, prevent missed SVR, and harmonize rules between treatment-naïve and -experienced patients

SVR Rate by Response to 4-Week PR Lead-In Therapy in Non-Black Patients



Boceprevir resistance-associated variants*:

≥1-log_{10} decline:
- BOC RGT: 4% (10/232)
- BOC/PR48: 6% (13/231)

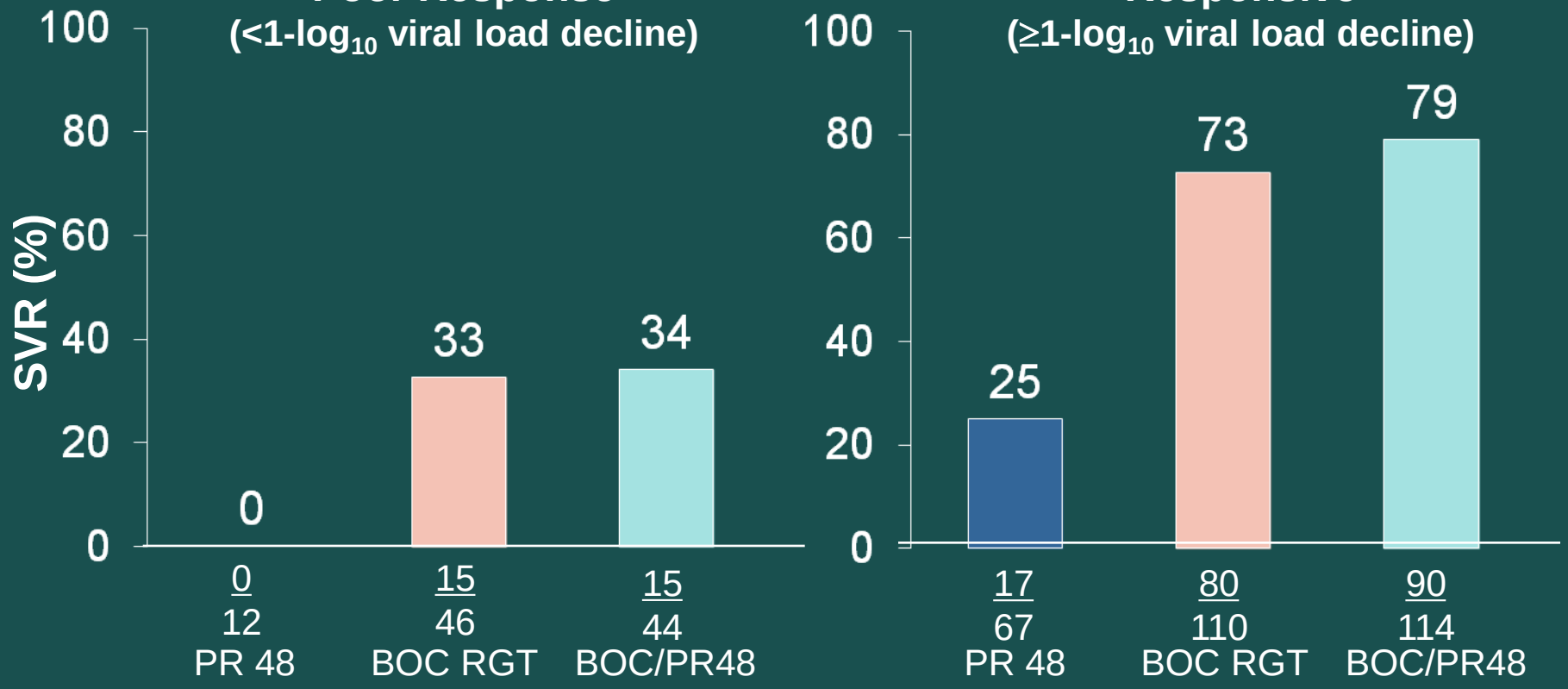
<1-log_{10} decline:
- BOC RGT: 52% (49/95)
- BOC/PR48: 40% (38/94)

* Boceprevir resistance-associated variants determined with population sequencing.

PR 48= pegylated interferon with ribavirin x 48 weeks;
RGT = response-guided therapy.

Poordad F, et al. N Engl J Med 2011;364(13):1195-206.

SVR Rate by Response to 4-Week PR Lead-In Therapy (RESPOND-2)



Bacon B, et al. N Engl J Med 2011;364(13):1207-17.

Telaprevir and Boceprevir Have Similar Resistant Variants (RVs)

Telaprevir	Boceprevir
V36A/M/C T54A R155K/T A156S/T/V	V36A/L/M F43C/S T54A R155K/Q/T/M A156S V170A/T

Kieffer TL, et al. J Antimicrob Chemother 2010;65:202-12.

HCV Genotype and Genetic Barriers to Resistance: Telaprevir and Boceprevir

HCV Genotype 1a

V36M+R155K variants observed clinically

R155K AGG → AAG

V36M GTG → ATG

2 Steps

HCV Genotype 1b

V36M, R155K variants not observed clinically

R155K CGG → AAG

R155 CGG → AGG

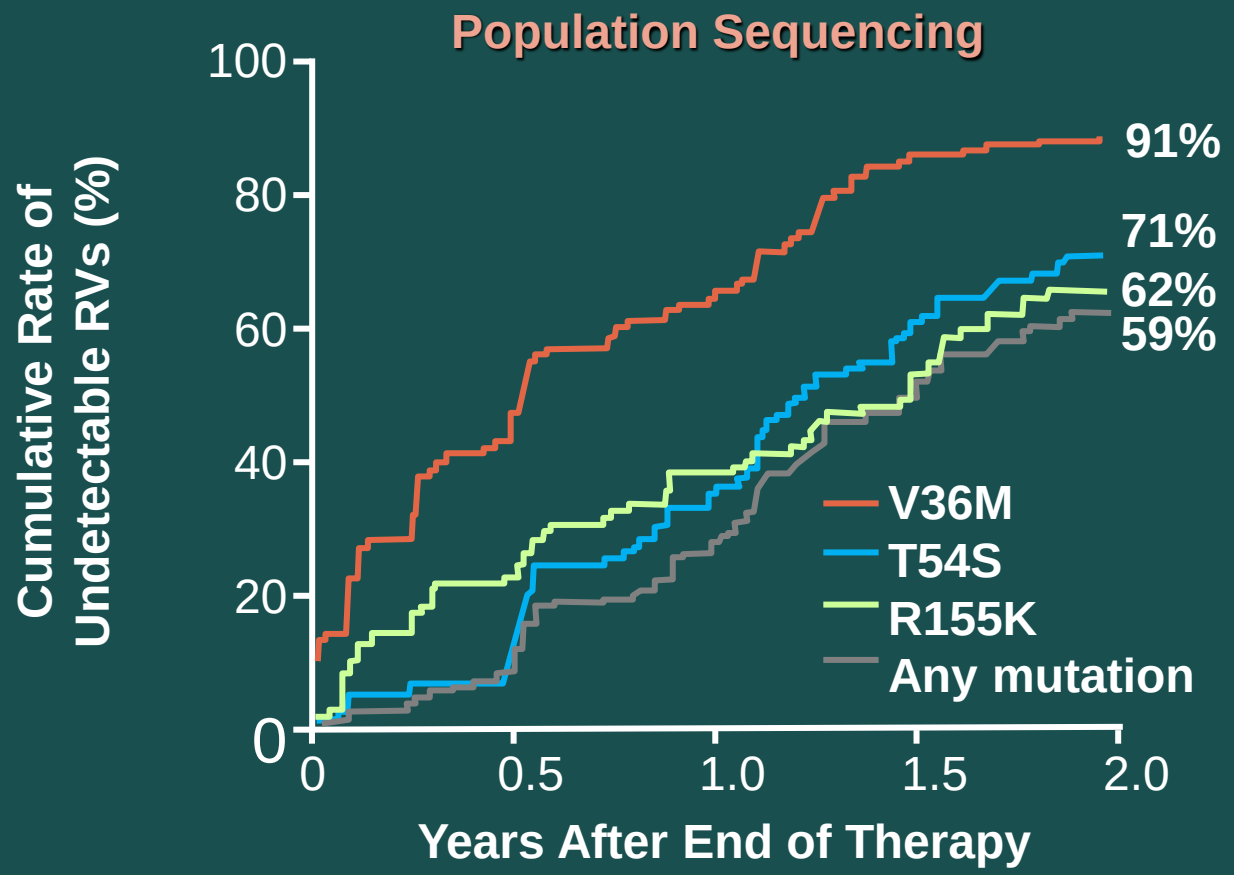
V36M GTC → ATG

V36 GTC → GTG

4 Steps = 2 nucleotide substitutions each required to create V36M and R155K/T mutations in genotype 1b

Sarrazin C, et al. Gastroenterol 2010;138:447-62; Susser S, et al. Hepatology 2009;50:1709-18; McHutchison JG, et al. N Engl J Med. 2009;360:1827-38; Hezode C, et al. N Engl J Med 2009;360:1839-50.

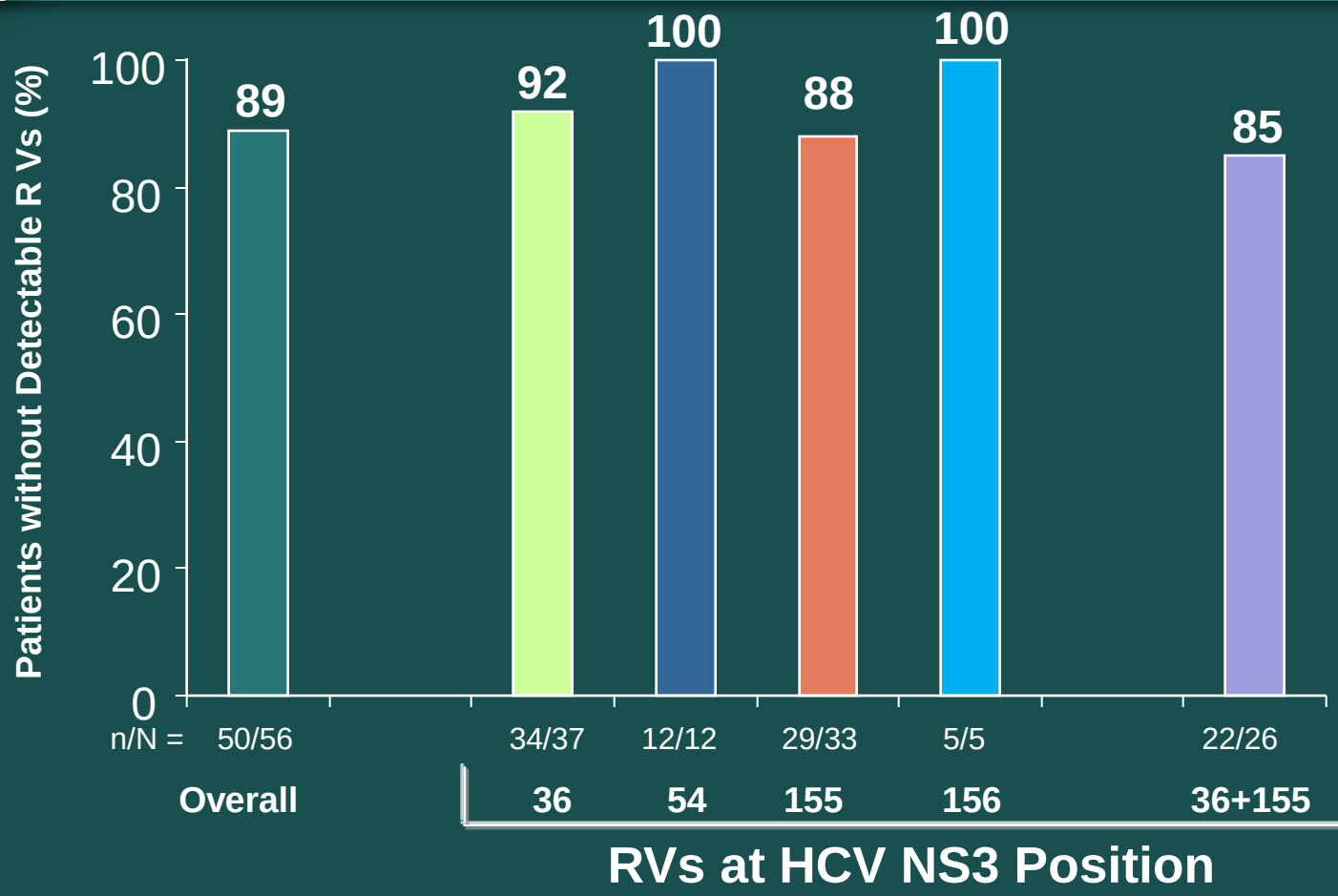
Long-Term Follow-Up of Resistant Mutations After Boceprevir/PR Therapy in HCV Genotype 1 Patients



7% of patients had RVs at baseline: no impact on SVR

Vierling JM, et al. EASL 2010. Abstract 2016.

EXTEND Study of Telaprevir: 89% of Patients No Longer Have Detectable Resistant Variants



Median follow-up time from end of prior study: 25 months (range 7–36).

Zeuzem S, et al. AASLD 2010 Oral 227.

Evaluation of Treatment-Emergent Resistant Variants in Phase III Trials of Telaprevir

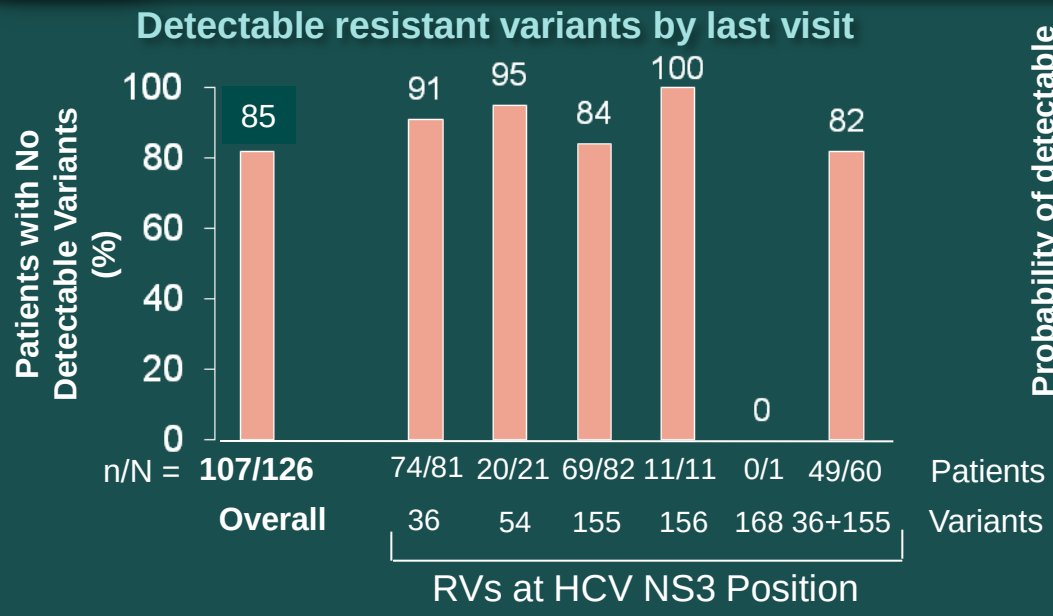
- 74% of treatment-failure pts had RVs
- 255 pts with RVs were followed from Phase III trials
  - ADVANCE/ILLUMINATE = 151
  - REALIZE = 104
- Population sequencing
- 60% lost RVs during median follow-up of 11 months
- RVs were different for genotype 1a vs. 1b, and cleared more rapidly for 1b

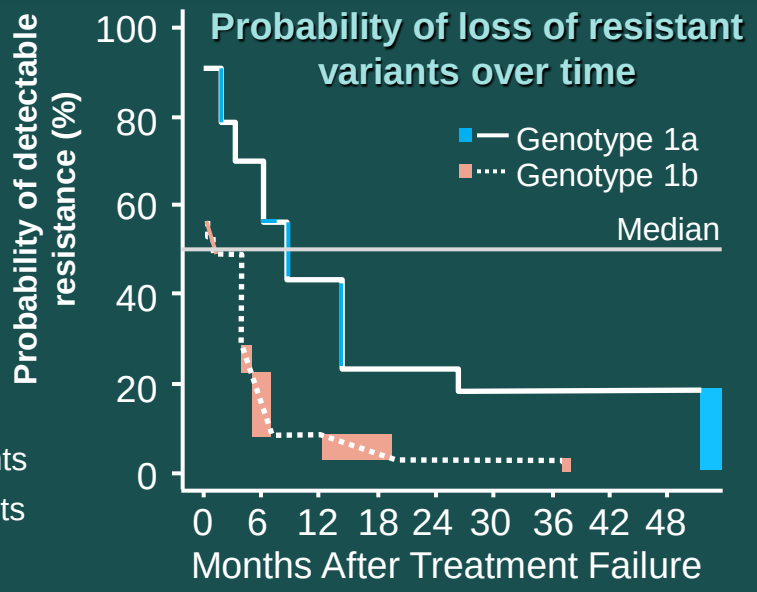
	Patients with No RVs	Median time after EOT, months
V36A/M	68% (115/169)	4/9
T54A/S	84% (27/32)	4
R155I/K/M/T	59% (100/170)	11
A156S/T/V	86% (19/22)	4
V36M + R155K	52% (65/124)	13

Long-term analysis of RV after PI failure provides encouragement that retreatment with PIs will be possible; reconstitution rates of wild-type virus are faster for genotype 1b vs. 1a. Retreatment studies will be needed for definitive assessment.

Sullivan J, et al. EASL 2011, Berlin, Oral 8.

Durability of SVR and Resistance After TVR-Based Therapy: Interim Analysis of the EXTEND Study





- >99% of patients who achieved SVR with telaprevir (TVR)-based therapy in Phase II/III studies had a durable response
- No liver-related complications in patients with SVR
- In non-SVR patients: 2 had hepatocellular carcinoma-associated liver transplant, 1 developed hepatic encephalopathy, 1 had ascites
- 85% of patients no longer had detectable RVs at a median 29 months from treatment failure

Sherman KE, et al. AASLD 2011, San Francisco, #248.

What Does Resistance to Direct-Acting Antiviral Agents Mean in Hepatitis C?

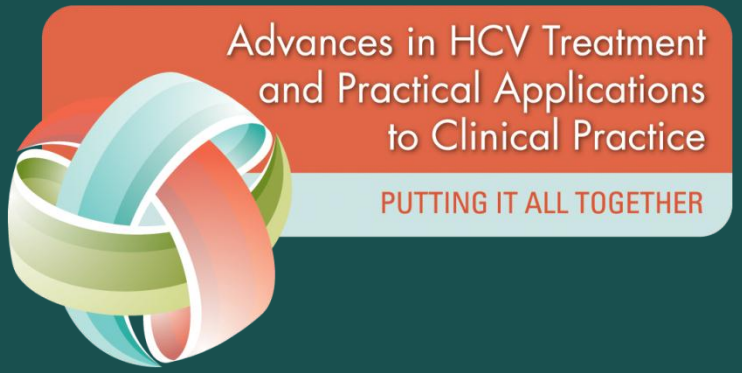
RESISTANCE
(V36, T54, R155, A156)

- Most patients with PI treatment failure are left with resistant variants
- Some HCV variants are "fit" and can persist in the long term
- Theoretical impact on future regimens that incorporate PIs

resistance

- HCV doesn't appear to be archived
- Encouraging data regarding clearance of variants from BOC + TVR studies
- Diverse pipeline decreases concern

Sullivan J, et al. EASL 2011, Berlin, Oral 8; Zeuzem S, et al. AASLD 2010 Oral 227; Vierling JM, et al. EASL 2010. Abstract 2016.



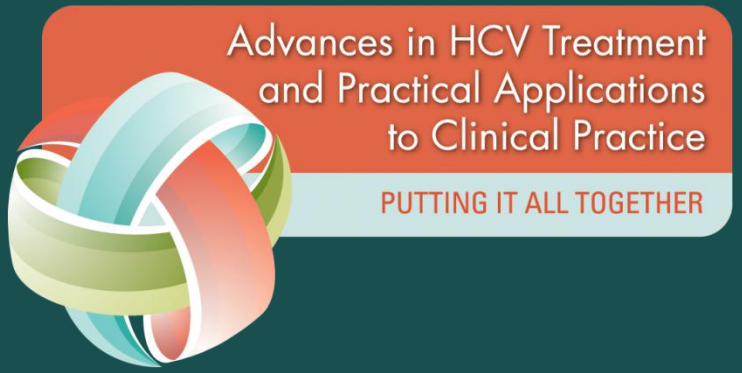
A Resistance Test Is Available Commercially: When Would You Use It?

Hypothetical Commercial Resistance Test

- Test uses population sequencing
- Requires 20%–25% of viral population to be the variant for detection

Potential Uses of Resistance Tests: No Published Guidelines at Present

- At baseline if effect on therapy can be shown; not recommended at present
- When patient meets a stopping rule
- When patient has virologic breakthrough
- When patient is being reconsidered for new treatment regimen
  - Present: Might apply to patients treated in past BOC or TVR trials with suboptimal regimens who want to try again
  - Future: For prior PI treatment failure, when another PI-containing regimen might be available



To What Extent Do You Discuss (or Think You Should Discuss) Resistant Variants with Your Patients?

Conclusions: Viral Load Testing and Resistance

- Sensitive real-time quantitative PCR assays that also specify detectability/undetectability (not just LLQ) should be used
- Response-guided therapy algorithms for TVR and BOC require complete undetectability at specified time points
- Clinicians must know and apply stopping rules
- In exceptional cases when clinicians continue beyond stopping rule (for HCV RNA level very close to cutoff), frequent monitoring is required

PCR = polymerase chain reaction.

Conclusions: Viral Load Testing and Resistance

- No role for baseline testing for resistance
- Most patients for whom PI therapy fails are left with resistant variants
- Resistant variants wane over time
- Clinicians should convey the concept of resistance to patients at an understandable level – especially for prior nonresponders